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Development of a New Exercise-Based Approach to Target Fatigue in Multiple Sclerosis

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“Als wäre so eine schwere Decke über einem“

”As if there’s a heavy blanket upon you”

(a study participant describing her fatigue experience)

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Abbreviations

BMCT = balance and motor control training

CNS = central nervous system

COSMIN = Consensus Standards for Measurement Instruments

EBV= Epstein-Barr Virus

EDSS = Expanded Disability Status Scale

FIS = Fatigue Impact Scale

FSMC = Fatigue Scale for Motor and Cognitive Functions

FSS = Fatigue Severity Scale

HIIT = high intensity interval training

HRmax = maximum heart rate

MAT = multimodal agility-based exercise training

MCT = moderate continuous training

MFIS = Modified Fatigue Impact Scale

MS = multiple sclerosis

NRC = Neurological Rehabilitation Center Godeshoehe

PICOTS = population, intervention, comparator, outcome, timing, and setting

PmMS = Personen mit Multiple Sklerose

PRO = patient-reported outcomes

PROMIS = Patient-Reported Outcome Measurement Information System

pwMS = persons with multiple sclerosis

RCV = Rehabilitation Center Valens

ReFEx = Rehabilitation, Fatigue, and Exercise

RCT = randomized-controlled trial

RQ= research question

SET = strength and endurance training

VO_{2peak} = peak oxygen uptake

WEIMuS = Würzburg Fatigue Inventory for Multiple Sclerosis

6MWT = 6-minute walk test

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Abstract

This research endeavor continued along several stages. In a joint decision between stakeholders from research (TU Dortmund University) and clinical practice (Neurological Rehabilitation Center Godeshoehe (NRC)), and considering evidence from the literature, fatigue was identified as a serious and common symptom in persons with multiple sclerosis (pwMS), where exercise might be applied as an efficacious intervention. Therefore, research efforts were directed at the development of an exercise-based fatigue intervention.

Appraising the current evidence for fatigue reduction via exercise, aerobic training was recognized as an exercise type frequently studied in the context of multiple sclerosis (MS) fatigue, but recent meta-analysis had pointed towards limited effects. Therefore, publication 1 reinvestigated the relationship between aerobic capacity and fatigue in a secondary analysis of data from two randomized-controlled trials (RCT), previously conducted at the Rehabilitation Center Valens (RCV), Switzerland. The data showed that the aerobic capacity - fatigue relationship was not reproducible in this relatively large sample of 131 pwMS - even when analyzing subgroups that should benefit the most (e.g., those with severe fatigue).

Other types of exercise, namely, balance and motor control training, were associated with larger effect sizes in some of the recently performed meta-analyses, but less frequently studied. Different authors have hypothesized working mechanisms for fatigue reduction regarding this type of exercise, including (I) balance training for making “navigating the environment” less effortful (Moss-Morris et al., 2021, p. 14), (II) “coordination of eye, head, and whole-body movements” to “reduce the cognitive load associated with conscious compensatory strategies in dynamic environments” (Hebert et al., 2018, p. 2), and (III) “improvement of sensory integration with a subsequent reduction of the cognitive load associated with motor processing” (Callesen et al., 2020, p. 2). As part of this thesis, these working mechanisms were integrated into a new exercise framework in publication 2, centered on an existing group-based framework for fall prevention in the elderly, which already included many of the mentioned aspects (Donath et al., 2016). The new framework was termed ‘multimodal agility-based exercise training’ (MAT).

Next, a study was designed to compare MAT with ‘traditional’ strength and endurance training (SET) regarding the effects on fatigue and related symptoms (study acronym: ReFEx; Rehabilitation, Fatigue, and Exercise). The setting of the study was the NRC in Bonn, Germany. In line with described stage models for the development of new behavioral interventions, before comparing efficacy, evaluation of the study protocol feasibility was the main objective of the remaining publications. This was based on MAT not being previously studied in pwMS and the setting of the study being a clinical inpatient rehabilitation center (i.e., a complex setting). The feasibility study protocol was described in publication 3 and included a mixed-methods methodology, i.e., a quantitative, and qualitative evaluation.

Quantitative feasibility results were reported in publication 4. These concluded that an adaptation of eligibility criteria to increase recruitment will be necessary, and that the primary outcome measure should be able to measure change in perceived fatigue more robustly. A multicenter RCT focused only on gym-based MAT was articulated as an option to assess the effect of MAT.

These results were supplemented by the qualitative evaluation of participants’ experiences during the trial in publication 5. Qualitative results concluded that MAT content was appreciated by pwMS and that fatigued pwMS were able to adhere to high frequency exercise, without an overall accumulation of fatigue. Nevertheless, social comparison and negative self-evaluation should be monitored.

In summary, publication 1 supported that aerobic training is not the most efficacious exercise type to reduce fatigue in pwMS. Publications 2-5 then developed a new group-based exercise framework based on described working mechanisms regarding exercise and fatigue, and quantitatively and qualitatively evaluated the feasibility of conducting a randomized-controlled trial in a clinical inpatient rehabilitation setting to compare the new framework with traditional strength and endurance training. Results showed that several changes need to be applied before the evaluation of the study protocol can be continued. Consequently, research can build on these early stage, but important results in the future.

Zusammenfassung

Vielfach wurde in der Literatur beschrieben, dass Fatigue eine relevante und für von Multiple Sklerose betroffene Personen, stark beeinträchtigende Symptomatik darstellt. Dies führte zu Beginn dieser Forschungsarbeit zur gemeinsamen Entscheidung von Klinikerinnen und Klinikern des Neurologischen Rehabilitationszentrums Godeshöhe und Forschenden der TU Dortmund (den Autor dieser Arbeit eingeschlossen), eine Trainingsintervention zu entwickeln und zu evaluieren, mit der diese Situation verbessert werden könnte. Es wurde ein schrittweises Vorgehen zur Entwicklung eines robusten Studiendesigns gewählt.

Zunächst zeigte sich aerobes Ausdauertraining bei der Evaluierung der Studienlage als häufig untersuchte Trainingsform. Allerdings wiesen aktuelle Meta-Analysen darauf hin, dass diese Trainingsform nur einen geringen Effekt haben könnte. Daher wurde in Publikation 1 eine sekundäre Analyse aus gepoolten Daten zweier randomisiert-kontrollierter Studien durchgeführt, welche beide in den Rehabilitationskliniken Valens (Schweiz) durchgeführt worden waren. Die Datenanalyse zeigte, dass die Verbindung zwischen aerober Kapazität und Fatigue in dieser relativ großen Stichprobe von 131 PmMS nicht reproduziert werden konnte - selbst bei der Analyse von Subgruppen, welche nach bestehenden Hypothesen am meisten profitieren sollten (z. B. Personen mit schwerer Fatigue).

Andere Formen körperlichen Trainings, insbesondere Gleichgewichtstraining sowie Training der motorischen Kontrolle, wurden in einigen kürzlich durchgeführten Meta-Analysen mit größeren Effektstärken in Verbindung gebracht. Die geringe Studienzahl schränkte jedoch deren Aussagekraft ein. Zudem hatten unterschiedliche Autorinnen und Autoren Hypothesen dazu aufgestellt aufgrund welcher Mechanismen diese Trainingsformen auf Fatigue wirken könnten, darunter: (I) Gleichgewichtstraining, um “navigating the environment” weniger anstrengend zu gestalten (Moss-Morris et al., 2021, S. 14), (II) “coordination of eye, head, and whole-body movements”, um die kognitive Belastung durch „conscious compensatory strategies in dynamic environments” zu verringern (Hebert et al., 2018, S. 2), und (III) “improvement of sensory integration with a subsequent reduction of the cognitive load associated with motor processing” (Callesen et al., 2020, S. 2). In Publikation 2 wurden diese Mechanismen in ein neues Trainingskonzept integriert, das auf einem bereits bestehenden Trainingskonzept zur Sturzprävention bei älteren Menschen basierte

und bereits viele der genannten Aspekte enthielt (Donath et al., 2016). Das neue Trainingskonzept wurde als 'multimodal agility-based exercise training' (MAT) bezeichnet.

Anschließend wurde ein Studienprotokoll entworfen, um MAT mit ‚traditionellem' Kraft- und Ausdauertraining hinsichtlich der Auswirkungen auf Fatigue und verwandte Symptome zu vergleichen (Studienakronym: ReFEx; Rehabilitation, Fatigue, and Exercise). Ort der Studie war das Neurologische Rehabilitationszentrum Godeshöhe in Bonn (Deutschland). In Übereinstimmung mit beschriebenen Stufenmodellen für die Entwicklung neuer verhaltensbasierter Interventionen, war die Bewertung der Machbarkeit des Studienprotokolls das Hauptziel der verbleibenden Publikationen, da MAT zuvor nicht bei PmMS untersucht worden war und der Studienort als stationäres Rehabilitationszentrum eine komplexe Umgebung darstellte. Dieses Machbarkeitsstudienprotokoll wurde in Publikation 3 beschrieben und beinhaltete einen Mixed-Methods-Ansatz, d. h. eine quantitative und qualitative Bewertung.

Die quantitativen Machbarkeitsergebnisse wurden daraufhin in Publikation 4 berichtet. Diese kamen zum Schluss, dass eine Anpassung der Einschlusskriterien zur Steigerung der Probandenrekrutierung notwendig sein würde und dass der primäre Ergebnisparameter in der Lage sein sollte, Veränderungen in der wahrgenommenen Fatigue robuster zu messen. Eine multizentrische, randomisiert-kontrollierte Studie, die sich ausschließlich auf das MAT ‚an Land' konzentriert, könnte als zukünftige Option hinsichtlich der Bewertung des MAT Effekts angewandt werden.

Die qualitativen Ergebnisse in Publikation 5 zeigten, dass das MAT von PmMS positiv bewertet wurde und dass PmMS und Fatigue in der Lage sind, ein Training in hoher Frequenz durchzuführen, ohne dass es zu einer Akkumulation von Fatigue kommt. Dennoch müssen soziale Vergleiche und negative Selbstbewertung von Therapeutinnen und Therapeuten im Blick behalten werden.

Somit stützte Publikation 1 die These, dass aerobes Training nicht die wirksamste Trainingsform zur Reduzierung von Fatigue bei PmMS ist. Die quantitative und qualitative Evaluierung der Machbarkeitsstudie (Publikationen 3-5) zur Untersuchung eines neuen Trainingskonzeptes (Publikation 2) in einem stationären Rehabilitationsumfeld fiel gleichwohl negativ aus, sodass Änderungen am Studienprotokoll notwendig sind. Die Forschung kann nun auf diesen zwar frühen, aber wichtigen Ergebnissen aufbauen.

1 Introduction

In many countries, multiple sclerosis (MS) is the leading cause of non-traumatic, neurological disorder among young adults. According to the Atlas of MS, in Germany, the average age at diagnosis is 33 years and 72% of patients are women. There are currently about 280,000 persons living with MS in Germany and every month about 1,200 persons are diagnosed with the disease (Multiple Sclerosis International Federation, 2020).

MS is characterized as a chronic inflammatory and degenerative disease of the central nervous system (CNS), with heritable and environmental factors being discussed as causes (Thompson et al., 2018). Among environmental factors, infection with a virus has been investigated as a leading cause for MS, and recently an infection with Epstein-Barr Virus (EBV) was established as a necessary factor to develop MS, as MS risk increased 32-fold after EBV infection in formerly negative subjects (Bjornevik et al., 2022). As more than 90% of the population worldwide experiences EBV infection, usually during the first two decades of life, MS is currently conceptualized as a rare complication of EBV infection, with other environmental factors (e.g., low Vitamin D, smoking, obesity during childhood or adolescence) possibly modulating the risk to develop MS (Bjornevik et al., 2023). All these modulating factors are associated with inflammation. The pathways through which EBV infection might lead to MS include molecular mimicry (i.e., similarities between foreign and self-peptides activating autoreactive immune cells) and an altered immune response to EBV infection, eventually resulting in an inflammatory attack against the myelin sheath that insulates axons in the brain and injury of neurons themselves, all contributing to a loss of neurologic function (Bjornevik et al., 2023; Robinson & Steinman, 2022).

A common symptom of diseases involving dysregulation of the immune system such as autoimmune diseases, cancer, chronic infections, and MS is fatigue (Dantzer et al., 2014; Rouault et al., 2023). However, debilitating fatigue can also be present in neurologic conditions such as traumatic brain injury or stroke, which are less associated with long-term inflammation (Kuppuswamy, 2022; Penner & Paul, 2017). One definition of fatigue from the Patient-Reported Outcome Measurement Information System (PROMIS) - among many that have been proposed - states that fatigue includes “a range of self-reported symptoms, from mild subjective feelings of

tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles" (Riley et al., 2010, p. 1318).

While fatigue was reported as the most common symptom (58%) among 35,000 persons with MS (pwMS) from the German multiple sclerosis register (Rommer et al., 2019), it is also reported as one of the most disabling symptoms (Barin et al., 2018) with high socioeconomic relevance, as 25% of pwMS have impaired working capacity because of 'invisible symptoms' such as fatigue or impaired cognition (Kobelt et al., 2019).

Similar to other diseases, no clear pathomechanism currently exists for fatigue in MS, but several guiding theories have been described (Dantzer et al., 2014; Kuppuswamy, 2022; Manjaly et al., 2019; Penner & Paul, 2017). For example, one pathway involves inflammation triggering a cascade of molecular and cellular events in the brain and the periphery, resulting in so called 'sickness behavior' (i.e., a syndrome of fatigue, social withdrawal and lowered mood), which usually resolves when an illness subsides, but might turn chronic in cases with chronic inflammation (Dantzer et al., 2014; Hanken et al., 2014; Kuppuswamy, 2022; Manjaly et al., 2019). Another perspective is given by the theory of allostatic self-efficacy, emphasizing the importance of interoception and metacognition (Manjaly et al., 2019; Rouault et al., 2023; Stephan et al., 2016). Essentially, this theory proposes that "the subjective experience of fatigue arises when, in a situation of persistent dyshomeostasis, the brain arrives at the metacognitive diagnosis that its control over bodily states is failing" (Rouault et al., 2023, p. 2).

Adding to the complexity of fatigue in MS, is the compartmentalization of fatigue into several subcategories including (I) primary (i.e., resulting from the disease itself) and secondary fatigue (i.e., resulting from other concomitant circumstances or diseases such as anemia, thyroid dysfunction, or sleep disorders) (Penner & Paul, 2017), (II) state fatigue (i.e., a motor or cognitive task-induced "psychophysiological condition characterized by a decrease in motor or cognitive performance and/or an increased perception of fatigue" (Behrens et al., 2023, p. 8)) and trait fatigue (i.e., fatigue experienced by an individual over weeks to months, usually quantified via self-report questionnaires) (Behrens et al., 2023), or (III) fatigability (i.e., the objectively measurable decrease in performance during a motor or cognitive task) and fatigue

(i.e., the perceptual dimension, which is inherently subjective) (Kluger et al., 2013; Manjaly et al., 2019), among other dichotomies.

Exercise, “a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness” (Caspersen et al., 1985, p. 126), has been studied as a symptomatic, and recently also as a preventive and disease-modifying treatment for pwMS (Dalgas et al., 2019). Especially regarding symptomatic treatment, substantial evidence exists concerning the effects of exercise on balance/falls, walking, or health-related quality of life, among others (Dalgas et al., 2019; Motl et al., 2017).

Exercise has also attracted considerable interest as a treatment option for fatigue in MS. While Langeskov-Christensen et al. (2017) provided a first scoping review on potential pathophysiological pathways that could explain the effects of exercise on fatigue, seven meta-analyses and network meta-analyses have now summarized the evidence regarding different types of exercise (Andreu-Caravaca et al., 2021; Chen et al., 2021; Harrison et al., 2021; Heine et al., 2015; Moss-Morris et al., 2021; Taul-Madsen et al., 2021; Torres-Costoso et al., 2022). Even though these meta-analyses have provided some indications of what the most beneficial type of exercise might be - as will be shown later - several inconsistencies exist.

Consequently, the guiding question for this thesis centered on: what is the most effective type of exercise for reducing fatigue in pwMS? Rather than giving a definitive answer, the thesis focused on the initial phase of handling this question, i.e., scanning the literature for pathways and types of exercise that had been described as beneficial (in the meta-analyses already mentioned) to then develop a new exercise framework and design and evaluate a feasibility study in a specific setting (a neurologic rehabilitation center). Evaluating feasibility is important if research on behavioral health interventions is conceptualized to occur within a stage model that includes the scale up of interventions. For example, the UK Medical Research Council’s framework for developing and evaluating complex interventions describes four phases: development or identification of the intervention, feasibility, evaluation, and implementation (Skivington et al., 2021). Consequently, the feasibility study had the primary goal of making an informed decision about whether to progress to the next stage of evaluation by answering whether the planned study “can be done, should be done, and, if so, how” (Eldridge et al., 2016, p. 2).

2 Background

2.1 Getting the Language Right – Fatigue Definitions and Taxonomies

Lauren Krupp, one of the early investigators of fatigue in MS, wrote in 2004 that the word ‘fatigue’ is “laden with ambiguity” (p. 6), which stems in part from the fact that (at least in the English language) ‘fatigue’ is a lay term and “there can be a wide variation in the way patients understand it, as well as in the way they understand related terms such as depression, weakness, deconditioning, tiredness, pain, and motivation” (p. 6). Around the same time, Chaudhuri and Behan (2004) also made this point. They wrote that an “overlap between the lay notion of tiredness and the clinically relevant symptom of fatigue“ (p. 978) prevents an exact definition. This is a hallmark of why studying treatments for fatigue in pwMS has been slow-going, conflicting, and complex; if it is not exactly clear what is to be studied, this gets hard to measure, and even more challenging to measure change resulting from any intervention. Accordingly, Kluger et al. (2013) wrote that “current treatments are nonspecifically targeted to a vaguely defined symptom with unsatisfactory outcomes“ (p. 409). Table 1 gives an overview on various currently existing definitions of fatigue, related to MS or neurological conditions in general. Many include the subjective nature of the symptom and make a distinction between motor and cognitive fatigue. The definition by Mills and Young (2008) is especially comprehensive and has been established based on interviews with pwMS.

Recently, there has even been an effort to abandon the term ‘fatigue’ and begin a renaming discussion (some propositions were: ‘central neurophysiological dys-/de-innervation‘, or ‘transitory multi-focal CNS denervation‘ (Hubbard et al., 2021)). This was based on the dissent, that the original meaning (in French and Latin) and current usage of the word ‘fatigue’ refers to “tiredness which occurs after engaging in some type of activity“ (Hubbard et al. (2021, p. 984). The authors argued that this has led to a wrongly established causal link between activity type and type of fatigue, i.e., motor fatigue arising from physical activities. But this does not necessarily exist in pwMS. For example, a patient might experience walking problems after cognitive work. Instead, they emphasized five phenomena consistently described by clinicians and patients, some of them similar to components of the definition by Mills and Young (2008): (I) a transitory state of limited predictability, (II) a group of co-occurring symptoms, (III) undetermined by preceding activity, (IV) triggered by heat. Other

authors have also questioned the adequacy of the term fatigue (Krieger & Sumowski, 2020).

Table 1

Definitions of Fatigue Related to MS or Neurological Conditions

Reference	Definition
Multiple Sclerosis Council (1998)	“A subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities” (p. 2)
Chaudhuri and Behan (2004)	“difficulty in initiation of or sustaining voluntary activities“ (p. 978)
Mills and Young (2008)	“reversible, motor and cognitive impairment with reduced motivation and desire to rest, either appearing spontaneously or brought on by mental or physical activity, humidity, acute infection and food ingestion. It is relieved by daytime sleep or rest without sleep. It can occur at any time but is usually worse in the afternoon. In MS, fatigue can be daily, has usually been present for years and has greater severity than any premorbid fatigue“ (p. 57)
Dantzer et al. (2014)	“feeling that relates to the lack of motivation to deploy resources and engage in high-effort performance to cope with their situation” (p. 39)
Sander et al. (2017)	“a subjective sensation of lack of energy and exhaustion” (p. E79)
Marchesi et al. (2022)	“the subjective feeling of physical, cognitive or psychosocial exhaustion and tiredness, which can occur and be perceived by patients also at rest” (p. 682)

Note. Definitions are in chronological order according to year of publication.

As mentioned in the introduction, several dichotomies have been established in the literature regarding fatigue (Table 2). Overall, these have led to the existence of many fatigue-related terms, which themselves have been variously defined. Some have argued that the compartmentalization into different scientific fields, which study fatigue (e.g., psychology, exercise science, neuroscience, medical fields) might be a reason for this (Behrens et al., 2023). Several researchers have tried to provide a unifying taxonomy to make studies comparable and speed up meaningful discoveries (Behrens et al., 2021; Behrens et al., 2023; Enoka et al., 2021; Enoka & Duchateau, 2016; Kluger et al., 2013).

The following paragraphs provide an overview on existing taxonomies, which have been relevant for the field of MS. It will be shown that these taxonomies have not necessarily led to a more homogenous landscape of fatigue-related terms, and that the respective field (e.g., medical vs. non-medical) still influences the aspects of fatigue under study and terms in use.

Table 2

Fatigue Dichotomies

Terms
Fatigue - fatigability
Perceived - performance fatigability
Trait - state fatigue
Central - peripheral fatigue
Motor - cognitive fatigue
Primary - secondary fatigue

In the already mentioned taxonomy on fatigue in neurologic illnesses, Kluger et al. (2013) start with a basic distinction between *fatigue* and *fatigability* (Figure 1). According to the authors, *fatigue* refers to subjective sensations and *fatigability* refers to objective changes in performance and these two constructs are not only distinct but might also be independent (see Table 3 for an overview on terms and definitions used in the respective taxonomy papers). To emphasize this distinction, they also use the

terms *perceived fatigue* and *performance fatigability*. They introduce several factors, which modulate the amount of *perceived fatigue* (*homeostatic* and *psychological factors*) and *performance fatigability* (*peripheral* and *central factors*). Regarding the application of their taxonomy to measurement, Kluger et al. (2013) mention that *perceptions of fatigue* are quantifiable via self-report scales, which either focus on momentary *state* perceptions, or chronic characteristics (*trait* perceptions). Lastly, they describe *fatigability* to be quantifiable in the *motor*, as well as in the *cognitive* domain.

In a following influential paper on the effect of fatigue on human performance, Enoka and Duchateau (2016) (Roger Enoka, was also among the three authors of the Kluger et al. (2013) taxonomy paper) proposed another taxonomy primarily differentiating between *perceived fatigability* and *performance fatigability*, which in combination lead to the symptom of *fatigue* (see Table 3 for the respective definitions). Notably, this taxonomy was not confined to neurological illnesses, but included examples from older adults, and athletes, and was more geared towards fatigue resulting from the performance of certain tasks. The term *perceived fatigability* contradicted Kluger et al. (2013), who defined *fatigability* as objective changes in performance, not related to perception. However, Enoka and Duchateau (2016) similarly suggested several *modulating factors* for *perceived fatigability* (*homeostasis* and *psychological state*) and *performance fatigability* (*contractile function* and *muscle activation*). They also emphasized fatigue to be a symptom, which can only be quantified via self-report, either as a *trait* characteristic or a *state* variable. Enoka and Duchateau (2016) wrote that:

> the trait level of fatigue represents the average amount of fatigue experienced during the preceding several days and depends on the absolute values of the modulating factors that contribute to perceived fatigability. In contrast, the state level of fatigue reflects the rate of change in the modulating factors that contribute to both performance and perceived fatigability during ongoing activity. (p. 2234)

Despite some differences, both taxonomies had three levels: the lowest describing *modulating factors*, affecting the second level, *perceived fatigue/fatigability* or *performance fatigability*, which on the highest level determine *trait* or *state* measures of fatigue (Figure 1). However, Kluger et al. (2013) emphasized that

perceptions of fatigue and *performance fatigability* are potentially independent, and that it has proven difficult to find associations between the two in previous studies, while Enoka and Duchateau (2016) explicitly stressed that *perceived fatigability* and *performance fatigability* are two interdependent attributes. A reason for this might be, that the first statement concerned the association between *trait fatigue* and *performance fatigability*, the second concerned the association between (activity-induced) *state fatigue* and *performance fatigability*. This illustrates the importance of this distinction. Arguably, *trait fatigue* might play a more prominent role as a symptom of diseases, while (activity-induced) *state fatigue* is a core interest in the exercise sciences (Behrens et al., 2023; Venhorst et al., 2018).

Enoka et al. (2021) published a third taxonomy paper focused on pwMS. It included several key differences to the past taxonomies. As cited, Enoka and Duchateau (2016) proposed *state fatigue* to be connected to the rate of change in *modulating factors* of *perceived*, as well as *performance fatigability,* but only quantifiable via self-report. However, in Enoka et al. (2021), *state fatigue* is no longer connected to performance, as the authors describe it to be the exclusive result of *interoceptive feedback* and the *psychological state* (see figure 1 in their paper and Table 3). Similarly, the term *trait fatigue* is defined differently from all other taxonomies: “A characteristic that can be quantified with measures of either objective or perceived fatigability” (p. 961), while all other taxonomies relate to *trait fatigue* as based on experience or perception, not quantifiable with objective measures.

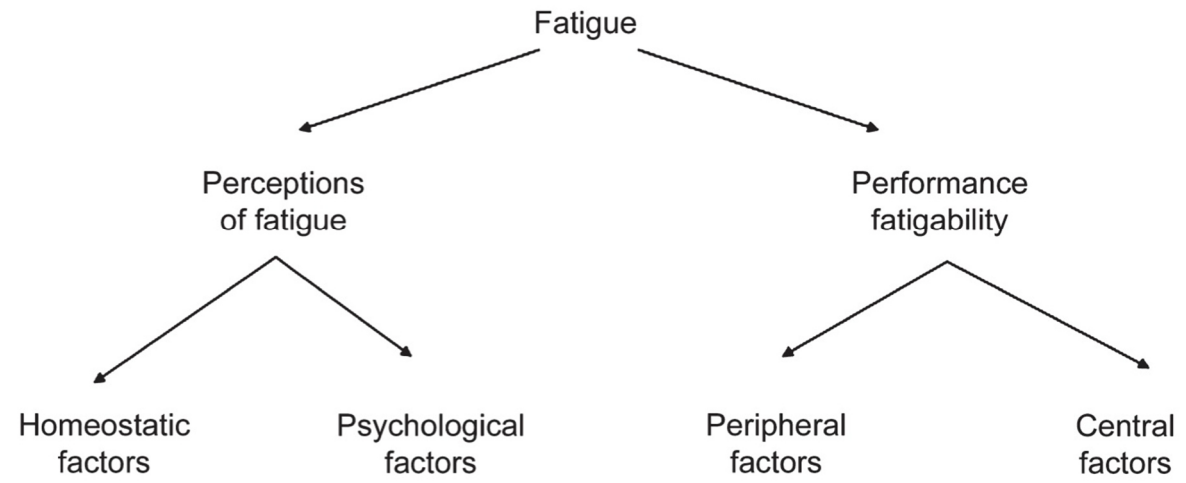
Lastly, the group of Behrens et al. (2023) published an update on the taxonomy by Enoka and Duchateau (2016), which primarily considers fatigue that is task-related. The authors also differentiate between *trait* and *state fatigue*. Additionally, they specifically emphasize cognitive aspects of *state fatigue*, introducing the terms *cognitive performance fatigue* and *perceived cognitive fatigue,* besides *motor performance fatigue* and *perceived motor fatigue*. According to Enoka and Duchateau (2016), *state fatigue* can only be quantified via self-report. However, according to Behrens et al. (2023) this introduces the problem that *state fatigue* is essentially the same as *perceived fatigability*. Furthermore, they argue that performance may decrease without a corresponding increase in fatigue perception (and vice versa). Consequentially, the authors state: “since we do not refer to state fatigue as a self-reported disabling symptom, the term fatigability does not seem to be necessary as it does not contribute any benefit compared to the term fatigue“.

This summary exemplifies how the terms fatigue and fatigability have been on a journey for more than a decade. Starting with fatigue representing subjective sensations, and fatigability objectively measurable changes, continuing with the conflict in the term perceived fatigability, and then abandoning the term fatigability all together.

For this thesis, the taxonomy by Kluger et al. (2013) will be applied, primarily because of its ease of use and wide application in the MS literature, including recent topical reviews and experimental studies (Bertoli & Tecchio, 2020; Marchesi et al., 2022; Rouault et al., 2023). Accordingly, *fatigue* will refer to subjective perceptions, quantified via self-report, and, in the current context, these usually relate to *trait* aspects. *Fatigability* will refer to objectively quantified performance decrements during motor or cognitive tasks. *State fatigue* will be considered as momentary fatigue perceptions but was less relevant in the present research.

Figure 1

The Fatigue Taxonomy for Neurologic Illnesses



Note. Figure adapted from "Fatigue and Fatigability in Neurologic Illnesses: Proposal for a Unified Taxonomy", by B. M. Kluger et al., 2013, *Neurology, 80(4),* p. 412 (https://doi.org/10.1212/WNL.0b013e31827f07be) Copyright 2013 by the American Academy of Neurology.

Table 3

Definitions from Selected Fatigue Taxonomy Papers

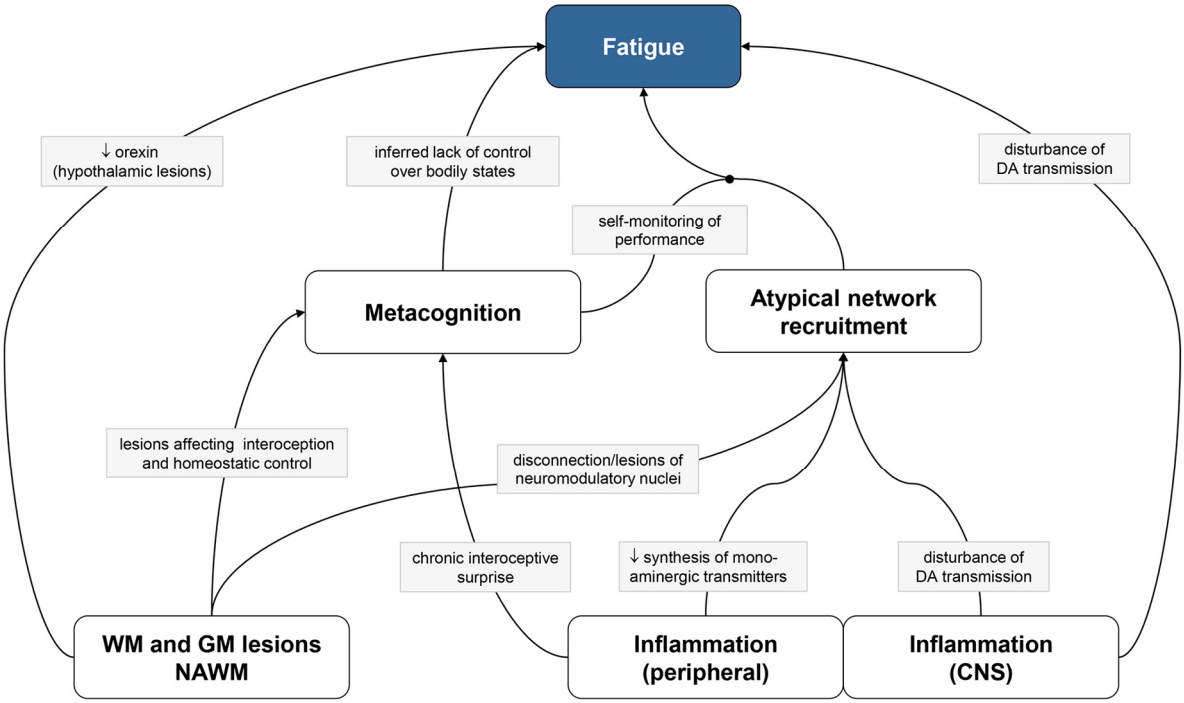
Term	Kluger et al. (2013)	Enoka and Duchateau (2016)	Enoka et al. (2021)	Behrens et al. (2023)
Perceived fatigue / fatigability	Perceived fatigue “subjective sensations of weariness, increasing sense of effort, mismatch between effort expended and actual performance, or exhaustion” (p. 411)	Perceived fatigability “changes in the sensations that regulate the integrity of the performer” (p. 2229)	Perceived fatigability “Subjective estimate of past or future work capacity” (p. 961)	Perceived (motor/cognitive) fatigue “motor and cognitive task-induced modulation of the perception of fatigue” (p. 9)
Performance / objective fatigability / fatigue	Performance fatigability “magnitude or rate of change in a performance criterion relative to a reference value over a given time of task performance or measure of mechanical output” (p. 411)	Performance fatigability “decline in an objective measure of performance over a discrete period” (p. 2229)	Objective fatigability “Magnitude of change in a performance metric after completing a prescribed task” (p.961)	(Motor/cognitive) performance fatigue “acute reduction in motor and cognitive performance” (p. 9)
State fatigue	State fatigue “momentary (state) perceptions” (p. 413)	State fatigue “rate of change in key adjustments during a fatiguing task” (p. 2234)	State fatigue “instantaneous estimate of the level of fatigue (feelings)” (p. 961)	(Task-induced) state fatigue “psychophysiological condition that is characterized by a decrease in motor or cognitive performance and/or an increased perception of fatigue“ (p. 9)
Trait fatigue	Trait fatigue “chronic characteristics” (p. 413) of perceptions of fatigue	Trait fatigue “average amount of fatigue experienced during the preceding several days” (p. 2236)	Trait fatigue “characteristic that can be quantified with measures of either objective or perceived fatigability” (p. 961)	Trait fatigue “fatigue experienced by an individual over a longer period of time (weeks and months)” (p. 8)

2.2 Pathophysiological Framework of (Primary) Fatigue in MS

Fatigue resulting directly from MS disease processes has been termed primary fatigue, while fatigue arising from other sources (e.g., sleep, depression, medication, deconditioning) has been named secondary fatigue (Kos et al., 2008; Langeskov-Christensen et al., 2017; Multiple Sclerosis Council, 1998). As mentioned in the introduction, several theories have emerged to explain primary fatigue in MS and other diseases (for a discussion of three recent theories, including post-stroke fatigue see Kuppuswamy (2022)). Figure 2, taken from the article by Manjaly et al. (2019), depicts pathophysiological mechanisms discussed for primary fatigue in pwMS. Its elements will be reviewed and one fatigue theory – the metacognitive theory of allostatic self-efficacy - will be shortly introduced.

Figure 2

Pathophysiological Pathways for Primary Fatigue in MS



Note. Figure from "Pathophysiological and Cognitive Mechanisms of Fatigue in Multiple Sclerosis", by Z. M. Manjaly et al., 2019, *Journal of Neurology, Neurosurgery and Psychiatry*, *90*(6), p. 643 (https://doi.org/10.1136/jnnp-2018-320050) Copyright 2019 by the Authors. CNS = central nervous system; DA = dopamine; GM = grey matter; NAWM = normally appearing white matter; WM = white matter.

As MS results in damage to the brain and spinal cord, imaging studies have tried to find an association between various pathological markers on brain scans and the symptom of fatigue, starting with associations between structural parameters and fatigue. These included lesional, volumetric and microstructural parameters assessed in the white matter and/or grey matter of the CNS (displayed on the lower level in Figure 2). As summarized by Paul (2023), these studies have predominantly been inconclusive, as some studies found certain associations, while others did not. Findings might depend on whether regional or whole brain aspects are studied (regional aspects seem to find more consistent associations (Bertoli & Tecchio, 2020; Manjaly et al., 2019; Marchesi et al., 2022)), the methods used to quantify lesions or volume, patient selection, and use of questionnaire (Paul, 2023). Palotai et al. (2020) showed that refinement of study methodology can increase correlation of fatigue measures with structural imaging parameters and might improve study replicability. For example, they included a temporal component by performing more than one fatigue evaluation and a refined stratification of patients by establishing subgroups of patients labeled as ‘sustained’, ‘reversible’, or ‘never fatigued’. Some consistent findings, that did emerge regarding (regional) structural abnormalities and fatigue are damage to the thalamus, striatum, and certain cerebral cortices (frontal, temporal, and parietal), which has led several researchers to hypothesize that damage to the so-called ‘cortico-striato-thalamo-cortical loop’ is involved in MS-related fatigue (Bertoli & Tecchio, 2020; Marchesi et al., 2022; Palotai & Guttmann, 2020; Paul, 2023; Pinarello et al., 2023). Furthermore, it has been suggested that structural damage to brain regions, which are important for vigilance, arousal, motivation (e.g., hypothalamus), or interoception (e.g., insular and anterior cerebral cortex) is associated with fatigue, and that these brain regions are frequently affected by MS pathology (Manjaly et al., 2019). On a larger scale, lesions in the CNS might disturb coordinated network activity important for motor and cognitive processes, leading to compensatory activity, which might be detected by metacognitive processes (see paragraph below on the metacognitive theory and Figure 2) (Manjaly et al., 2019).

As studies on structural changes and fatigue have provided mixed results, several authors argued, that the role of functional changes in the CNS is more prominent regarding fatigue (Bertoli & Tecchio, 2020; Rocca et al., 2021). This aspect is displayed as ‘atypical network recruitment’ in Figure 2. In studies investigating structural and functional alterations in the same patients, according to Bertoli and

Tecchio (2020), results strongly support the fact that functional alterations prevail over structural alterations. Functional alterations can be studied with neuroimaging techniques during motor or cognitive tasks, where pwMS frequently show an increase of brain activity, which has been interpreted as a compensatory mechanism or an increased effort to maintain normal function (Manjaly et al., 2019; Paul, 2023). This increased effort might also be detected by metacognitive processes, explaining the emergence of feelings of fatigue (see paragraph below on the metacognitive theory and Figure 2).

Bertoli and Tecchio (2020) summarized several functional alterations related to fatigue, which are of particular relevance for the present work as these concern alterations in the sensorimotor network, which might, in principle, be responsive to exercise. These include: hyperexcitability at rest and hyperactivation during motor execution of the primary motor cortex, increased activation in brain areas that are involved in motor planning and motor adaptation, as well as altered brain–body cortico-muscular synchronization. The authors further noted that these findings were obtained from pwMS with minimal disability, which indicates “early involvement of sensorimotor communication impairment in the fatigue symptom“ (Bertoli & Tecchio, 2020, p. 1813).

Peripheral immunological and inflammatory processes acting on the CNS through immune-to-brain interfaces are additional pathophysiological pathways, which are discussed in the context of fatigue (lower level in Figure 2) (Manjaly et al., 2019). As stated in the introduction, during common infections, inflammation triggers a cascade of molecular and cellular events in the brain and the periphery, resulting in so called ‘sickness behavior’ (i.e., a syndrome of fatigue, social withdrawal and lowered mood), which usually resolves when an illness subsides, but might turn chronic in cases with chronic inflammation (Dantzer et al., 2014; Kuppuswamy, 2022).

Direct and indirect pathways of peripheral inflammation affecting the brain have been investigated. Direct pathways include cytokines acting on brain endothelial cells, trafficking of peripheral immune cells into the brain, or activation of vagal afferents by pro-inflammatory mediators leading to insular responses (Manjaly et al., 2019). Possible indirect pathways consist of a reduction in synthesis of monoaminergic neurotransmitters, important for motivation, arousal, and mood, due to a dysregulation of the kynurenine pathway and decreased availability of necessary enzymes, both resulting from peripheral inflammation (Manjaly et al., 2019). Furthermore, inside the brain, inflammation can trigger the activation of microglia, which also impacts

dopaminergic transmission, possibly resulting in decreased motivation. However, the question of how exactly inflammation in the brain leads to fatigue in MS has not yet been answered and the association between fatigue and levels of inflammatory markers has been equivocal (Kuppuswamy, 2022; Marchesi et al., 2022).

Regarding pathophysiological mechanisms for fatigue in MS, one question persists: how does the subjective experience of fatigue arise? This question is addressed by the metacognitive theory of allostatic self-efficacy, described by Stephan et al. (2016) and applied to fatigue in pwMS by Manjaly et al. (2019). The theory emphasizes the two cognitive constructs of interoception and metacognition (Rouault et al., 2023). Interoception indicates the perception of bodily states such as blood oxygenation, or heart rate, while metacognition concerns cognition about cognition, e.g., reflecting on singular perceptual decisions, but also global beliefs about abilities and skills (Seow et al., 2021). In this way, it builds a crucial bridge between pathological findings and the subjective feeling of fatigue in MS. In brief, the theory postulates that:

> fatigue reflects the metacognitive diagnosis that the brain is failing to exert control over bodily states and does not have any action at its disposal to overcome a state of dyshomeostasis. Given this inferred helplessness or low 'allostatic self-efficacy', fatigue would correspond to a feeling state that signals the futility of any further actions. (Manjaly et al., 2019, p. 5)

The only other option at the brain's disposal would be rest (Manjaly et al., 2019; Rouault et al., 2023; Stephan et al., 2016). As briefly described above, there is initial evidence that interoception is altered in pwMS and might be associated with fatigue (Gonzalez Campo et al., 2019; Manjaly et al., 2019). For example, Gonzalez Campo et al. (2019) showed that behavioral, structural, and functional interoceptive alterations are signs of fatigued pwMS. Specifically, a cardiac interoceptive pathway (following one's own heartbeat) was associated with (trait) fatigue (Gonzalez Campo et al., 2019). However, a first experimental study was not able to verify an association of fatigue with metacognition (Rouault et al., 2023).

As stated by Kuppuswamy (2022) in her review on fatigue theories, there currently only exists fragmented evidence for proposed fatigue theories including the

just mentioned metacognitive theory, across diseases, and future studies will have to further test their hypotheses.

2.3 Assessment

Based on the taxonomy by Kluger et al. (2013) the following section provides details on how perceptions of fatigue and performance fatigability can be measured in pwMS.

2.3.1 Fatigue

Trait fatigue is usually quantified via self-report questionnaires (also described as patient-reported outcomes (PRO)), which assess the amount of fatigue experienced in the preceding weeks (the exact timespan varies between 1 to 4 weeks, but can also be unspecified) (Block et al., 2022). Frequently, these PROs were designed to capture fatigue in the motor domain as well as in the cognitive domain (even though it has been questioned whether this is truly the case (Patejdl & Zettl, 2022; Pust et al., 2019)). State fatigue is typically quantified with questions regarding momentary perceptions including visual analog scales (Block et al., 2022). Studies evaluating the effect of pharmacologic and non-pharmacologic treatments have predominantly relied on questionnaires assessing trait fatigue, therefore assessment of state fatigue will not be discussed in this section.

Close et al. (2023) recently identified 87 different PROs (until October 2021, available in English) to measure fatigue, of which 18 were MS-specific or non-disease-specific questionnaires. Notably, only three of the 18 PROs have been highly used in clinical trials, while the others were only seldomly or never adopted. The most highly adopted fatigue PROs in pwMS were the Fatigue Severity Scale (FSS) (Krupp et al., 1989), Fatigue Impact Scale (FIS) (Fisk et al., 1994), and Modified Fatigue Impact Scale (MFIS) (Ritvo et al., 1997).

Another systematic review performed by the MS Outcome Measures Task Force of the Academy of Neurologic Physical Therapy, located in the USA, has recently summarized the evidence and clinical utility of 17 fatigue PROs (until January 2020) (Cohen et al., 2023). Specifically, they performed a methodologic quality assessment of PROs focusing on test-retest reliability, responsiveness, content validity, interpretability, and generalizability. According to their assessment, only two

PROs (MFIS and FSS) had high reliability, no notable ceiling/floor effects, and high clinical utility. Furthermore, responsiveness data was present for these two measures. Other measures had either weak or missing data for certain psychometric properties. Missing responsiveness data of fatigue measures has been a problem for researchers studying fatigue interventions, as it indicates a measure's ability to detect change (Sander et al., 2017). This problem is especially pressing when short-term fluctuations are to be studied (Krieger & Sumowski, 2020; Sander et al., 2017). In the review by Cohen et al. (2023), only three measures had excellent reliability and provided responsiveness data (MFIS, FSS, and MFIS-5 (shortened MFIS)). Based on the review, the MS Outcome Measures Task Force suggested to use the MFIS as a comprehensive (the questionnaire assesses the dimensions of physical, cognitive, and psychosocial fatigue) measure for research and practice purposes, and the FSS as a quick screening tool for physical fatigue only.

As a recent, but probably important development, remote monitoring of fatigue in MS should be briefly mentioned (Block et al., 2022; Pinarello et al., 2023). First, PROs can be administered online in any setting, as applied in Publications 3-5. Second, smartphone-based assessment enables frequent, momentary measurements of fatigue in daily life, which might reduce the recall bias inherent in traditional PROs and allows to quantify day-to-day and time-of-day fluctuations (Block et al., 2022). Indeed, fatigue fluctuations during the day have been described in healthy persons and pwMS (Powell et al., 2017).

Despite improved quality and availability of psychometric data for fatigue PROs, Close et al. (2023) have highlighted the issue of insufficient content validity. Content validity of PROs depends on the developer's conceptualization of fatigue and the respondent's interpretation of the questions (Block et al., 2022), as it pertains to "the extent to which PROs adequately reflect a defined measurement content" (Close et al., 2023, pp. 1650-1651). It can be viewed as the most important PRO quality, and a prerequisite for psychometric evaluation (Close et al., 2023). However, the comprehensive analysis of content validity performed by Close et al. (2023) showed that none of the existing questionnaires fulfilled all criteria of the Consensus Standards for Measurement Instruments (COSMIN) (Terwee et al., 2018). Notably, the MFIS and FSS, suggested for use by Cohen et al. (2023), were not among the five most highly rated measures (although part of their review, content analysis was much less comprehensively investigated in Cohen et al. (2023)). Indeed, particularly the FSS

received one of the lowest ratings. This is especially concerning as the MFIS and FSS are among the most highly used PROs in fatigue studies, which let Close et al. (2023) to conclude that, so far, PRO quality may not have driven use in studies nor selection for clinical trials. Overall, consistent weaknesses of existing questionnaires were “construct definitions, qualitative work, use of development samples representative of the target population, and use of literature reviews” (Close et al., 2023, p. 1661). Of note, one of the two highest scoring PROs regarding content validity was the Neurological Fatigue Index – Multiple Sclerosis (Mills et al., 2010), which is based on the interview study by Mills and Young (2008), mentioned in the definitions section (2.1).

In summary, most existing studies, which have investigated a pharmacologic or non-pharmacologic treatment for MS-fatigue, have used a PRO measurement for which it is unclear (I) how much change in its score is necessary to be deemed important, (II) whether the tool is ‘granular’ enough to detect an effect of the intervention (i.e., missing responsiveness), and (III) what kind of construct is assessed and whether the questionnaire resembles the symptom of fatigue as experienced by pwMS (i.e., missing content validity). Close et al. (2023) highlighted the importance of these aspects: “This means that studies influencing the care of PLwMS [people living with MS] and our research directions have almost certainly been misleading, with potentially damaging implications for the quality of life for PLwMS“ (p. 1662).

2.3.2 Fatigability

Fatigability is usually quantified via performance decrements in motor or cognitive tasks (Block et al., 2022; Kluger et al., 2013). In the motor domain, these include declines in peak force, power, speed, or accuracy, while in the cognitive domain declines in reaction time, or accuracy over time can be investigated (Kluger et al., 2013). As described in chapter 2.1, the increase in fatigue perception in response to a motor or cognitive task can be measured as well. This was defined by some authors as perceived fatigability (Broscheid et al., 2023). Table 4 gives an overview on different study designs for the assessment of fatigue and fatigability.

Regarding motor fatigability, several studies investigated repeated voluntary contractions of hand or leg muscles over defined periods, but this was criticized as “at

best fragments of meaningful, intention-guided motor sequences“ (Patejdl & Zettl, 2022, p. 3) and correlation with PRO scores was weak.

Other studies tried to use more ecologically valid tasks - most frequently, tasks of walking endurance (Abasıyanık et al., 2022; Patejdl & Zettl, 2022). For example, a simple metric of functional walking fatigability is the decline of meters walked in the first and the last minute of a 6-minute walk test (6MWT) (Van Geel, Veldkamp, et al., 2020). Several studies also combined tests of walking endurance with simultaneous measurements of gait kinematics and kinetics, as well as oxygen consumption to quantify the underlying factors of walking fatigability (Broscheid et al., 2022; Ibrahim et al., 2020; Rooney et al., 2022; Theunissen et al., 2023). The 6MWT can also be applied as a fatiguing task to study its effects on muscle strength, gait, balance, or reaction time after finishing the test (Abasıyanık et al., 2022) (see Table 2). Interestingly, in a systematic review on these two strategies, changes in gait kinematics (i.e., walking speed, step length, step time, step width, and double support phase) were more prominent when gait was assessed prior to and immediately after the 6MWT compared with studies assessing gait during the 6MWT (Abasıyanık et al., 2022). Increased oxygen consumption during walking tests is hypothesized to be a consequence of the aforementioned alterations in biomechanical variables, as these lead to reduced efficiency of movement (Rooney et al., 2022). Indeed, evidence from a recent meta-analysis pointed towards oxygen cost of walking being significantly higher in individuals with MS compared to healthy controls (Rooney et al., 2022).

An increasing number of studies have tried to find associations between various measures of motor performance fatigability and (state and trait) fatigue. While there were a number of interesting results (Drebinger et al., 2020; Ibrahim et al., 2022; Ibrahim et al., 2020), such as the level of state fatigue during a 6MWT being predictable from kinematic gait parameters obtained from an inertial measurement unit system on the subject’s feet (Ibrahim et al., 2020), a recent study reported no associations between changes in state fatigue (during a 6MWT) and changes in cost of walking, gait characteristics, or electromyography of the lower leg muscles (Theunissen et al., 2023). Moreover, technologies for gait analysis allow for a vast number of parameters to be collected and analyzed, and walking protocols can differ between studies, which could introduce a high amount of heterogeneity (Abasıyanık et al., 2022).

Table 4

Study Designs for the Assessment of Fatigue and Fatigability

Study design	Related taxonomy term
A person (at rest) is asked to rate their fatigue over the last days to weeks.	Trait fatigue
A person (at rest) is asked to rate their fatigue in the moment.	State fatigue
A person performs a motor or cognitive task and performance decrements are analyzed over time.	Performance fatigability
Before and after performing a motor or cognitive task, a person performs a motor or cognitive test, and alterations between the two tests are analyzed.	Performance fatigability
While performing a motor or cognitive task, a person is asked to rate their fatigue in the moment.	Perceived fatigability / state fatigue
Before and after performing a motor or cognitive task, a person is asked to rate their fatigue in the moment.	Perceived fatigability / state fatigue

Cognitive fatigability has been studied less extensively, but the general study designs are similar to the assessment of motor fatigability (Table 4). Measures of attention have been central to the study of cognitive fatigability (Harrison et al., 2017; Kuppuswamy, 2023; Penner et al., 2023), as attention is a basic function involved in almost any task and relatively independent of control strategies that might be used to compensate for fatigue (Penner et al., 2023). Moreover, attention can be categorized into separate dimensions and domains, and according to Penner et al. (2023) especially domains of attention intensity (i.e., alertness, sustained attention, vigilance) can be used to study cognitive fatigability. Some studies found an association between measures of cognitive fatigability (alertness) and trait (cognitive) fatigue (Penner et al., 2023). Circadian changes in alertness measures have been used to study cognitive fatigability and it was hypothesized that these might be able to objectively detect the subjectively reported worsening of fatigue symptoms during the day. This assessment procedure has especially been applied in the context of inpatient rehabilitation in

Germany (Claros-Salinas et al., 2010; Dettmers et al., 2021; Neumann et al., 2014; Penner et al., 2023) and a similar design was applied in Publications 3 and 4. Emphasizing the importance of the function of attention for fatigue in neurological cohorts, in her review, Kuppuswamy (2023) concluded that in MS, stroke, traumatic brain injury, and Parkinson's disease, there was evidence of poor selective attention that explained levels of chronic fatigue.

2.4 Evidence for the Effects of Exercise on Fatigue

Several publications have discouraged the use of medications to treat MS-related fatigue (Marchesi et al., 2022; Nourbakhsh, 2021; Nourbakhsh et al., 2021). Instead, non-pharmacological interventions have been recommended, especially exercise interventions (Marchesi et al., 2022).

Current meta-analyses have identified more than 50 RCTs, that investigated an exercise intervention and a fatigue outcome (Harrison et al., 2021) (for a complete overview on meta-analyses providing results for specific exercise categories see Table 5). However, many of these were 'non-targeted' interventions, meaning that fatigue was one outcome among several, and that the intervention was not specifically designed to target fatigue. Typically, in this case, studies will not prescreen participants for the presence of fatigue symptoms, resulting in a higher probability of detecting no effects of the intervention (Moss-Morris et al., 2021). This is also connected to the fact, that only very rarely have exercise studies considered the effect on a potential pathophysiological pathway of fatigue (Langeskov-Christensen et al., 2017; Moss-Morris et al., 2021) (Figure 3). The following two sections will present pre-existing evidence regarding the two main types of exercise that were investigated in this thesis (endurance training and balance and motor control training or multimodal exercise), while also trying to give some perspective on pathophysiological pathways (Figure 3).

Table 5

Overview of Meta-Analytic Reviews on Exercise and Fatigue in MS

Reference	Reviewed until	Exercise categories (*n* studies)	Homogenous? (I^2)	Total *n* of studies	Inclusion criteria	SMD
Heine et al. (2015)	October 2014	1. Mixed training[a] (6) 2. Other[b] (9) 3. Endurance training (11) 4. Task-oriented training[c] (2) 5. Muscle power training (4)	1. No (82%) 2. Yes (45%) 3. Yes (28%) 4. Yes (0%) 5. No (70%)	36	RCTs, targeted[#] & non-targeted	**1. -0.73** **2. -0.54** **3. -0.43** 4. -0.34 5. 0.03
Moss-Morris et al. (2021)	August 2018	1. Balance[d] (2) 2. General exercise[e] (aquatic) (5) 3. General exercise[e] (2) 4. Combined exercise[f] (1) 5. Aerobic (3)	1. Yes (0%) 2. No (74%) 3. No (91%) 4. N.a. 5. Yes (26%)	13	RCTs, only targeted	**1. -1.26** **2. -1.02** 3. -1.22 4. -0.49 5. -0.29
Harrison et al. (2021)	August 2018	1. Balance[d] (5) 2. General exercise[e] (16) 3. Resistive exercise (5) 4. Combined exercise[f] (15) 5. Aerobic (22)	1. Yes (0%) 2. Yes (33%) 3. Yes (0%) 4. No (68%) 5. Yes (19%)	51	RCTs, targeted & non-targeted	NMA **1. -0.84** **2. -0.52** **3. -0.42** **4. -0.39** **5. -0.38** Pairwise **1. -0.87** **2. -0.47** **3. -0.46**

						4. -0.35 **5. -0.41**
Andreu-Caravaca et al. (2021)	March 2020	1. Aerobic training (11)	1. Yes (6%)	11	RCTs & uncontrolled trials, targeted & non-targeted, only AT, only FSS	1. -0.17
Taul-Madsen et al. (2021)	April 2020	1. Aerobic training (9) 2. Resistance training (3)	1. No (58%) 2. Yes (0%)	12	RCTs, only AT and RT, Targeted & non-targeted	**1. -0.61** **2. -0.41**
Torres-Costoso et al. (2022)	February 2021	1. Resistance (4) 2. Combined exercise[g] (25) 3. Mind-body exercise[h] (15) 4. Aerobic (14) 5. Balance[i] (2) 6. Aerobic with resistance (6)	1. No (87%) 2. No (82%) 3. No (74%) 4. Yes 5. Yes 6. Yes	58	RCTs, targeted & non-targeted	NMA **1. -1.15** **2. -1.00** **3. -0.83** **4. -0.62** 5. -0.72 6. -0.47 Pairwise **1. -1.09** **2. -0.74** **3. -0.70** **4. -0.32** 5. -0.48 6. -0.18
Chen et al. (2021)	April 2021[+]	1. Aquatic (2) 2. Aerobic (13) 3. Dance (1) 4. Resistance (4) 5. Yoga (5)	1. Yes (19%) 2. No (62%) 3. N.a. 4. Yes (0%) 5. No (59%)	27	RCTs, targeted and non-targeted	NMA **1. -1.73** **2. -0.49** 3. -0.54 4. -0.35

	6. Endurance (5) 7. Resistance and endurance (1) 8. Aerobic and resistance (2) 9. Climbing (1)	6. Yes (45%) 7. N.a. 8. Yes (0%) 9. N.a.	5. -0.33 6. -0.23 7. -0.21 8. -0.13 9. 0.54

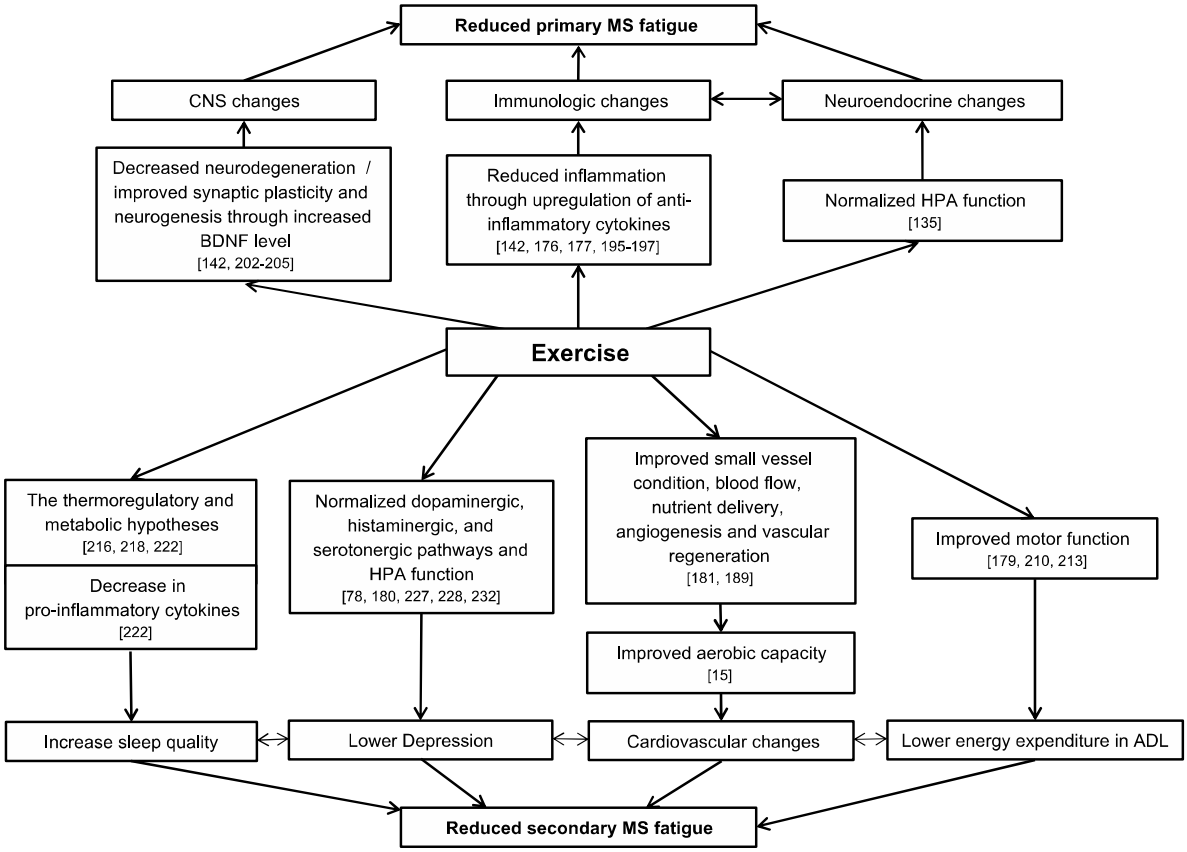
Note. The order of the table follows the column 'Reviewed until'. All data refer to comparisons versus a control condition. I^2 values above 50% are interpreted as designating homogeneity. If provided in the respective papers, definitions of, or examples for exercise categories other than aerobic or resistance training are given in the specific notes below. AT = aerobic training; FSS = Fatigue Severity Scale; N.a. = not applicable; NMA = network meta-analysis; RCT = randomized-controlled trial; RT = resistance training; SMD = standardized mean difference.

[+] Last article included was published in 2019. [a] "exercise interventions that incorporated both endurance and muscle power components" (p. 17), three of those were (in part) aquatic. [b] hippotherapy, balance training, yoga, inspiratory muscle training, motor learning, sports climbing, robot-assisted gait training. [c] "aim of the intervention […] to improve performance at a certain task such as walking" (p. 7) [d] "main fitness component in static and dynamic exercises that are designed to improve individuals' ability to withstand challenges from postural sway or destabilizing stimuli caused by self-motion, the environment, or other objects" (p. 9). [e] "exercise involving combination of two or more" of exercise components (aerobic, resistive, flexibility, and balance) "no dominant fitness component focus provided" (p. 9). [f] "exercise explicitly aimed at more than one of the exercise components […], often using a progressive overload principle" (p. 9). [g] "interventions that involved 2 or more components of exercise during the same session, often using coordination, balance, and strength exercise" (p. 3). [h] "balance-bases [*sic*] exercises focused on breathing and postural control, such as Pilates or yoga; this intervention could add strength exercises" (p. 3). [i] "static or dynamic exercises aimed to improve postural and neuro-muscular control" (p. 3) [#] primary focus of the intervention explicitly stated as reducing fatigue.

Bold = significant SMD

Figure 3

Hypothetical Effects of Exercise on Mechanisms Underlying MS Fatigue



Note. Figure from "Potential Pathophysiological Pathways That Can Explain the Positive Effects of Exercise on Fatigue in Multiple Sclerosis: A Scoping Review", by M. Langeskov-Christensen et al., 2017, *Journal of the Neurological Sciences,* 373, p. 314 (https://doi.org/10.1016/j.jns.2017.01.002) Copyright 2017 by Elsevier B.V. ADL = activities of daily living; BDNF = brain-derived neurotrophic factor; CNS = central nervous system; HPA = hypothalamic-pituitary-adrenal axis; MS = multiple sclerosis.

2.4.1 Evidence for the Aerobic Capacity - Fatigue Relationship

Deconditioning, described as reduced cardiorespiratory fitness and reduced tolerance to exercise, is regarded as a pathway leading to secondary fatigue in pwMS (Langeskov-Christensen et al., 2017) (Figure 3). For example, peak oxygen uptake (VO_{2peak}) relative to bodyweight, a main indicator of aerobic capacity, is significantly lower in ambulatory pwMS, compared to matched healthy controls (Klaren et al., 2016). Furthermore, it was hypothesized, that increasing aerobic capacity may

contribute to expending energy at a lower percentage of maximal energy expenditure during functional tasks, which would subsequently attenuate fatigue (Rooney et al., 2022; Rooney et al., 2019).

Consequentially, the improvement of aerobic capacity, mainly via endurance training, was among the first exercise-based approaches to target fatigue - already investigated in the late nineties (Mostert & Kesselring, 2002; Petajan et al., 1996). Today, the ‘aerobic capacity – fatigue hypothesis‘ is still prominent in the literature (Langeskov-Christensen et al., 2017; Rooney et al., 2019; Taul-Madsen et al., 2021). However, one recent review and meta-analysis, which analyzed interventions specifically designed to improve fatigue, quantified only small effects of endurance training on fatigue and high drop-out rates (Moss-Morris et al., 2021). Additionally, in a RCT powered and designed to study the effectiveness of aerobic training on fatigue in severely fatigued pwMS, even one year of aerobic training did not lead to a clinically meaningful fatigue reduction when compared to a low-intensity control intervention (Heine et al., 2017). Furthermore, these authors questioned the trainability of pwMS as the training response after one year of endurance training was marginal. The amount of improvement in aerobic capacity was discussed as a relevant factor for fatigue reduction and a prerequisite for a translational effect (Heine et al., 2017; Taul-Madsen et al., 2021). Yet, a VO_{2peak}-responder analysis has not been performed in the existing literature regarding fatigue reduction.

The meta-analysis by Harrison et al. (2021) included fatigue-targeted as well as non-targeted exercise interventions and was performed by the same working group as Moss-Morris et al. (2021), for the same timeframe (Table 5). It additionally applied a network meta-analysis approach. Despite the highest number of studies (n=22), aerobic training was least effective among the five exercise subtypes studied in the network meta-analysis.

Andreu-Caravaca et al. (2021) focused their meta-analysis solely on aerobic training studies (targeted- and non-targeted regarding fatigue), and only the ones that applied the FSS as an outcome measure, thereby acquiring a homogenous sample of 11 studies. This resulted in an even smaller effect size (Table 5).

Contrary to these results showing that the effect of aerobic training on fatigue is small or inferior to other types of exercise, other research has also shown the opposite. Taul-Madsen et al. (2021) performed a meta-analysis on studies applying only aerobic or resistance training (targeted and non-targeted regarding fatigue) and

reported a large, significant effect size, which was superior to resistance training. However, the effect of the 12 aerobic training studies was quantified to be heterogeneous (Table 5).

Rooney et al. (2019) performed a cross-sectional (therefore not listed in Table 5) meta-analytic review showing that cardiorespiratory fitness and fatigue were moderately associated with each other in the five studies analyzed. They concluded that higher levels of aerobic capacity are associated with lower fatigue.

2.4.2 Evidence for Balance and Multimodal Exercise

In the context of reducing energy expenditure to reduce fatigue, it might not only be necessary to improve aerobic capacity, but also to improve motor function (e.g., muscle strength, gait kinematics) (Langeskov-Christensen et al., 2017) (Figure 3). This notion would also imply other training modalities than endurance training, e.g., specific balance and motor control training to reduce energy cost and consequentially reduce fatigue. Apart from improving energy expenditure, recent work has introduced other pathways for fatigue reduction, emphasizing cognitive and sensory elements present in motor control (Prosperini & Castelli, 2018). These included (I) balance training for making "navigating the environment" (Moss-Morris et al., 2021, p. 14) less effortful, (II) "coordination of eye, head, and whole-body movements" to "reduce the cognitive load associated with conscious compensatory strategies in dynamic environments" (Hebert et al., 2018, p. 2), and (III) "improvement of sensory integration with a subsequent reduction of the cognitive load associated with motor processing" (Callesen et al., 2020, p. 2).

The study of interventions specifically incorporating the abovementioned elements for fatigue reduction is more recent than the study of aerobic training, with the first studies emerging in the 2010s (Hebert & Corboy, 2013; Hebert et al., 2011). As there potentially exist multiple pathways for fatigue reduction via exercise and different exercise subtypes are more geared towards certain pathways than others (Harrison et al., 2021), a case can be made for multimodal exercise. Indeed, multimodal exercise has been studied frequently in pwMS and has also been regularly considered as an exercise category on its own in several of the mentioned meta-analyses (although termed inconsistently). As the framework that was described in

Publication 2 is based on multimodal exercise as well as balance and motor control training, evidence for both types will be briefly summarized.

In contrast to aerobic training, the characterization of balance and motor control training, or multimodal training is extremely heterogeneous in the currently existing meta-analyses. For example, the first meta-analysis that provided effect estimates for exercise subtypes regarding fatigue (Heine et al., 2015), introduced the category of 'task-oriented training', which included two studies with a small effect size. One was a home-walking program (Geddes et al., 2009), the other a task-oriented circuit training, complemented with training of walking endurance (Straudi et al., 2014). Notably, both studies were small pilot/feasibility studies, not designed to study the effectiveness of the interventions. Despite being in the same category, both studies differed substantially in training content (i.e., one intervention included no specific balance and motor control training, while the other one did). The same meta-analysis also defined the exercise categories of 'mixed training' and 'other training'. While 'mixed training' focused on interventions incorporating only strength and endurance training, 'other training' included a vast array of interventions, among them 'balance training' and 'motor learning', but also hippotherapy, yoga, or robot-assisted gait training. 'Mixed training' attained the highest effect size in this meta-analysis (but was highly heterogeneous).

Subsequently, the meta-analysis of Moss-Morris et al. (2021), defined a sole category for 'balance' training, incorporating two studies specifically targeted at fatigue, showing a very large, homogenous, and significant effect size (Table 5). However, both studies were performed by the same group (Hebert et al., 2011; Hebert et al., 2018). 'General exercise (aquatic)', defined in the meta-analysis as "exercise involving a combination of two or more" (Moss-Morris et al., 2021, p. 9) exercise components (aerobic, resistive, flexibility, and balance) performed in the water, exhibited a moderate to large effect, but again, was heterogeneous. This was also the case for general exercise performed on land, with just two studies included, and therefore a non-significant result.

In the ensuing network meta-analysis (Harrison et al., 2021), 'balance' training remained as the top exercise subcategory with a large, homogenous, and significant effect size, now incorporating five studies performing vestibular rehabilitation, training on a Wii balance board, personalized balance rehabilitation, sensory integration balance training, robotic-assisted gait training, and hippotherapy. A recent RCT (n =

71), published after the meta-analyses, performed balance and motor control training in pwMS with impaired mobility for 10 weeks (including cognitive tasks) and quantified significant fatigue reductions (although staying below a clinically relevant threshold on group-level) (Callesen et al., 2020). This study design profoundly influenced the framework described in Publication 2 and the feasibility study described in Publications 3-5.

2.5 Development and Feasibility Testing of Rehabilitation Interventions

As the present work describes the results of a feasibility study, background on the importance of feasibility studies in the continuum of intervention development will be given in this section.

Scaling of interventions can be defined as “processes occurring during intervention development where initial early-stage pilot/feasibility studies are conducted to inform a subsequent larger trial of a behavioral intervention“ (Beets et al., 2021, p. 2). Several stage models for behavioral interventions currently exist (Czajkowski et al., 2015). One stage model is included in the UK Medical Research Council’s framework for developing and evaluating complex interventions, which describes four phases: (I) development or identification of the intervention, (II) feasibility, (III) evaluation, and (IV) implementation (Skivington et al., 2021). The stage of research has implications for hypothesis generation, interpretation, and contextualization of study results (Motl et al., 2022) and feasibility studies are specifically designed to generate sufficient evidence to make informed decisions whether a larger, more well-powered trial “can be done, should be done, and, if so, how” (Eldridge et al., 2016, p. 2). At best, a feasibility study enhances the probability for success of a subsequent large-scale, resource-intensive RCT (Leon et al., 2011). Despite often being used interchangeably, a distinction between pilot and feasibility studies can be made, in that pilot studies have the same aforementioned goals, but are a subset of feasibility studies, which conduct a future definitive RCT, or part of it, on a smaller scale (Eldridge et al., 2016). According to Thabane et al. (2010) reasons to conduct a pilot study exist in several domains. For example, studying the feasibility of trial ‘processes’ includes determining recruitment, and retention rates, while in the ‘resources’ domain, time and budget problems are evaluated. In the ‘management’ domain, data management can be scrutinized, and the ‘scientific’ domain deals with

safety issues, among others. As a result of feasibility testing, researchers might adapt the study intervention and evaluation procedures, or refrain from conducting a large-scale study altogether, thereby avoiding the waste of resources. Besides quantitative feasibility measures, qualitative methods have been increasingly adopted in feasibility studies on interventions for a complex patient group or situated in a complex environment (O'Cathain et al., 2015). Qualitative research might answer how to make an intervention more acceptable to the target group or more relevant and useful in specific contexts (among many other potential research questions).

The need to follow stages of development and methods of feasibility testing in the specific field of exercise and rehabilitation for pwMS is profound. Learmonth and Motl (2018) have argued, that a reason for ongoing debate about the strength of evidence for exercise in pwMS is related to limitations of previous RCTs. For example, they mentioned high attrition rates in exercise intervention studies, a decrease of effects after an exercise program is terminated, and a generally poor degree of physical activity in pwMS. They stated: “We believe that one major limitation of previous research that ultimately undermines efficacy, effectiveness and translation is that the majority of studies on physical activity and its benefits have not undergone initial and systematic feasibility testing“ (Learmonth & Motl, 2018, p. 2). In this context, it is important to note that the issue is not necessarily that feasibility studies do not exist in the field. Quite contrary, other authors have criticized that most MS rehabilitation trials belong to the lower stages of the UK Medical Research Council’s framework and large-scale effectiveness and implementation research is lacking (Dalgas et al., 2020; das Nair et al., 2019). The issues with pilot and feasibility trials rather pertain to a wrongly placed emphasis on assessing statistical significance - in a sample that is too small (Leon et al., 2011; Sim, 2019) - instead of feasibility measures, and that many feasibility studies “tend to exist in isolation” (Thabane et al., 2010, p. 11), meaning that promising interventions are not developed further on the continuum (Sandroff & DeLuca, 2020). In a separate publication Learmonth et al. (2019) further described how patient and public involvement in feasibility research, i.e. qualitative methods, might help to explain why pwMS are not physically active despite the existing evidence for exercise, and how it might identify ways to increase recruitment and retention. Most recently, Motl et al. (2022) have shared their guidance on improving the quality of research in the exercise and MS field, advising researchers to clearly identify the stage of research, as they judged many studies to “straddle the

stages of research" (p. 5). They advocated feasibility studies as learning lessons for a subsequent larger trial. These ideas were incorporated into the present work.

3 Research Questions

RQ1 Can previously described associations between aerobic capacity and fatigue be reproduced on a cross-sectional and interventional level?

RQ2 Is it feasible to conduct a randomized controlled trial including a newly developed multimodal agility-based exercise training framework to improve fatigue and fatigability in an inpatient rehabilitation setting?

RQ3 How do pwMS experience the multimodal agility-based exercise training and what are the demands of the study protocol from a patient perspective?

4 Methods and Results (Abstracts)

Publication 1

Wolf, F.*, Rademacher, A.*, Joisten, N., Proschinger, S., Schlagheck, M. L., Bloch, W., Gonzenbach, R., Kool, J., Bansi, J., & Zimmer, P. (2022). The aerobic capacity – fatigue relationship in persons with Multiple Sclerosis is not reproducible in a pooled analysis of two randomized controlled trials. *Multiple Sclerosis and Related Disorders*, *58*, 103476. https://doi.org/https://doi.org/10.1016/j.msard.2021.103476

*shared first authorship

Background: Fatigue is one of the most frequent symptoms of pwMS but has limited treatment options. Aerobic capacity and endurance training have been discussed as relevant factors to improve fatigue. However, over the last decades, results have been equivocal. This secondary analysis of two pooled parallel group RCTs of three weeks of endurance training (high intensity interval training (HIIT) and moderate continuous training (MCT)) for pwMS aimed to (I) reproduce reported associations between aerobic capacity and fatigue on a cross-sectional and interventional level. The analysis further aimed to (II) investigate intervention effects on fatigue in a severely fatigued subgroup and (III) analyze differences in changes of fatigue between VO_{2peak}-responders and non-responders.

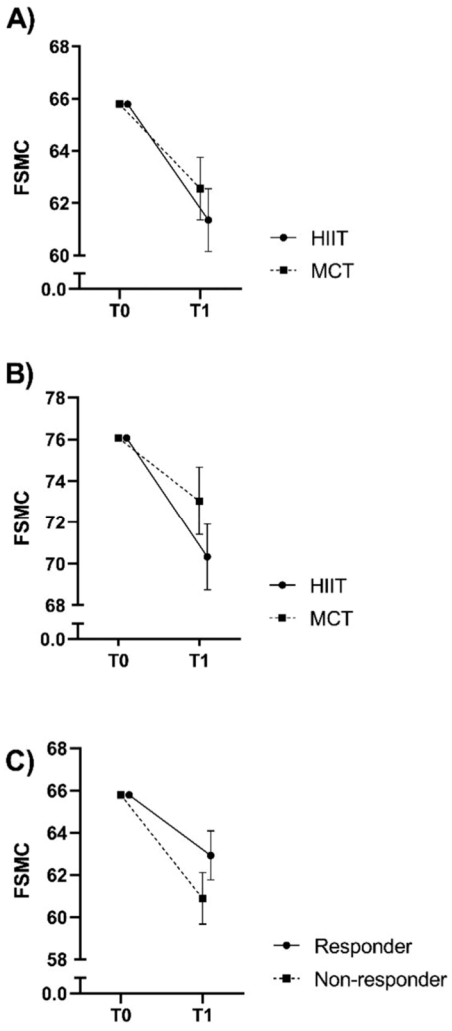
Methods: Both RCTs were conducted in the same inpatient rehabilitation clinic in Valens, Switzerland. Original primary outcomes were cognitive function (RCT1) and change in proportion of circulating regulatory T-cells (RCT2). PwMS (*n* = 131) with a relapsing-remitting or secondary progressive MS phenotype and Expanded Disability Status Scale (EDSS) score between 1 - 6.5 were eligible. Over the two studies participants exercised 3 - 5 times per week on cycle ergometers at intensities of 65 - 70% of maximum heart rate (HRmax) for 30 min (MCT groups) or three times per week with five 90 – 180 s intervals at intensities of 85% – 100% of HRmax and 90 s rest intervals (HIIT groups). Main outcome measures for the present secondary analysis were VO_{2peak} measured during a cardiopulmonary exercise test and the Fatigue Scale for Motor and Cognitive Functions (FSMC), both assessed at the start and end of inpatient rehabilitation.

Results: Baseline correlations did not reveal a significant association between VO_{2peak} and FSMC. There were no significant improvements in fatigue after the HIIT and MCT in the overall sample or the subsample of severely fatigued pwMS and no significant differences in fatigue changes between VO2peak-responders and non-responders.

Conclusions: Our analysis did not confirm the aerobic capacity - fatigue relationship on a cross-sectional and experimental level, even when analyzing subgroups that should benefit the most according to proposed hypotheses.

Figure 4

Baseline-Adjusted Analysis of Covariance Results for Patient-Reported Fatigue



Note. (A) HIIT versus MCT within the total sample (*n* = 130); (B) severely fatigued subgroup (*n* = 76); (C) VO_{2peak} responders vs. non-responders (*n* = 130). Figure from "The Aerobic Capacity – Fatigue Relationship in Persons With Multiple Sclerosis is not

Reproducible in a Pooled Analysis of two Randomized Controlled Trials", by F. Wolf, A. Rademacher, et al., 2022, *Multiple Sclerosis and Related Disorders*, *58*, p. 4 (https://doi.org/10.1016/j.msard.2021.103476) Copyright 2021 by Elsevier B.V. T0 = baseline; T1 = post exercise intervention; FSMC = Fatigue Scale for Motor and Cognitive Functions; HIIT = High-Intensity Interval Training; MCT = Moderate Continuous Training.

Publication 2

Wolf, F., Eschweiler, M., Rademacher, A., & Zimmer, P. (2022). Multimodal Agility-Based Exercise Training for Persons with Multiple Sclerosis: A New Framework. *Neurorehabilitation and Neural Repair*, *36*(12), 777-787. https://doi.org/10.1177/15459683221131789

Introduction: Multimodal agility-based exercise training (MAT) has been described as a framework for fall prevention in the elderly but might also be a valuable concept for exercise training in pwMS.

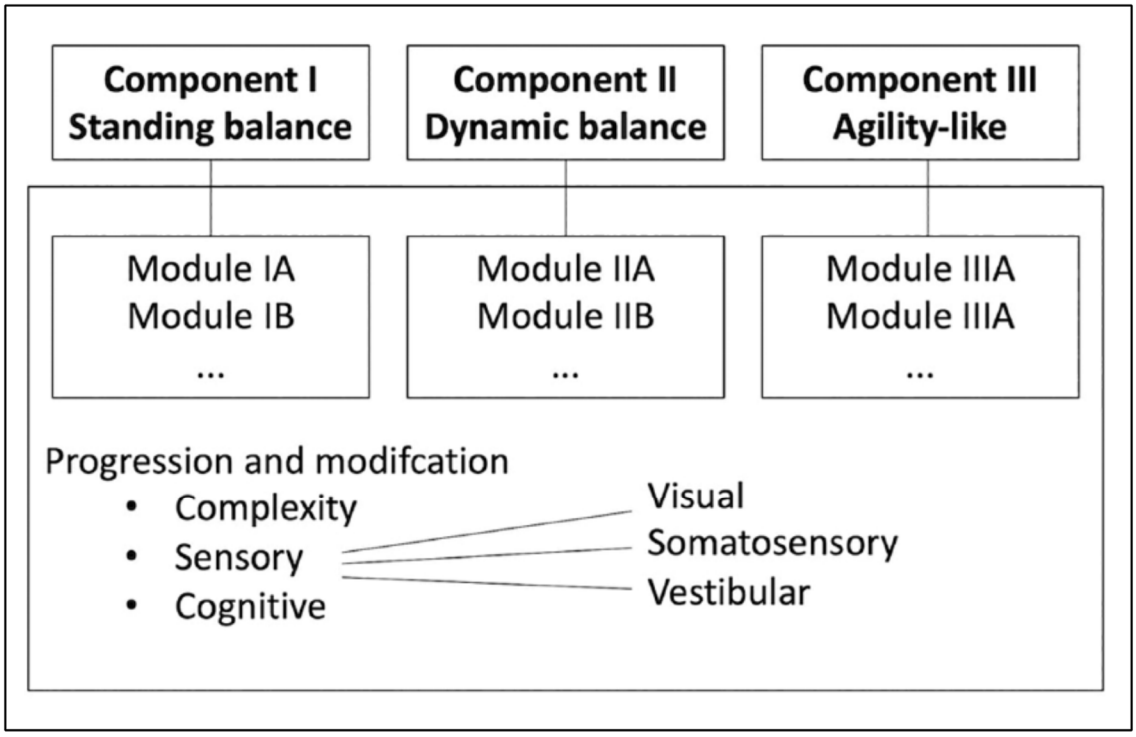
The problem: Current recommendations advise pwMS to perform a multitude of different exercise training activities, as each of these has its separate evidence. However, pwMS struggle even more than the general population to be physically active. Additionally, MS often leads to co-occurring mobility and cognitive dysfunctions, for which simultaneous, time-efficient, and engaging training approaches are still limited in clinical practice and healthcare.

The solution: The MAT framework has been developed to integratively improve cardiovascular, neuromuscular, and cognitive function by combining aspects of perception and orientation, change of direction, as well as stop-and-go patterns (i.e., agility), in a group-training format. For pwMS, the MAT framework is conceptualized to include three Components: standing balance, dynamic balance (including functional leg strength), and agility-based exercises. Within these Components sensory, cognitive, and cardiovascular challenges can be adapted to individual needs.

Recommendations: We recommend investigating multimodal exercise interventions that go beyond easily standardized, unimodal types of exercise (e.g., aerobic or resistance exercise), which could allow for time-efficient training, targeting multiple frequent symptoms of persons with mild disability at once. MAT should be compared to unimodal approaches, regarding sensor-based gait outcomes, fatigue-related outcomes, cognition, as well as neuroprotective, and (supportive) disease-modifying effects.

Figure 5

Structure of the MAT Framework for pwMS



Note. Figure from "Multimodal Agility-Based Exercise Training for Persons with Multiple Sclerosis: A New Framework", by F. Wolf, M. Eschweiler, et al., 2022, *Neurorehabilitation and Neural Repair*, *36*(12), p. 780 (https://doi.org/10.1177/15459683221131789) Copyright 2022 by the Authors.

Publication 3

Wolf, F.*, Nielsen, J.*, Saliger, J., Hennecken, E., Eschweiler, M., Folkerts, A.-K., Karbe, H., & Zimmer, P. (2022). Randomised controlled pilot and feasibility study of multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve multiple sclerosis-related fatigue and fatigability during inpatient rehabilitation (ReFEx): study protocol. *BMJ Open*, *12*(9). https://doi.org/10.1136/bmjopen-2022-062160

*shared first authorship

Introduction: Subjective fatigue and objectively assessed fatigability are common symptoms in pwMS. Recent work has suggested a positive effect of balance and motor control training (BMCT) in reducing fatigue. It is unclear whether this effect can also be attained during inpatient rehabilitation. MAT has been developed as a framework that incorporates BMCT with added agility components but has not been applied to pwMS. Therefore, this study will evaluate the feasibility of a RCT comparing MAT against SET for the improvement of MS-related fatigue and fatigability in a German neurological rehabilitation center.

Methods and analysis: A total of 24 pwMS (EDSS ≤5.0, FSMC ≥53) will be randomly assigned to either SET or land and water-based MAT for 4–6 weeks during inpatient rehabilitation. Assessments of subjective fatigue, motor and cognitive fatigability, cognitive and cardiorespiratory performance, and balance confidence will be performed at admission and discharge. Subjective fatigue will also be assessed at 1, 4 and 12 weeks after discharge. Feasibility outcomes will include patients' acceptance of study procedures and interventions, recruitment rate, retention rate, time needed to complete baseline assessments, intervention adherence and fidelity. All quantitative outcomes will be reported descriptively. A total of 12 pwMS (six per group) will be interviewed to gain insights into participants' experiences during study participation.

Ethics and dissemination: Ethical approval has been obtained from the Ethics Committee of the University of Bonn (reference number: 543/20). Dissemination of findings is planned via peer-reviewed journals, conferences, and media releases.

Publication 4

Wolf, F., Nielsen, J., Saliger, J., Hennecken, E., Kröber, P., Eschweiler, M., Folkerts, A.-K., Karbe, H., & Zimmer, P. (2023). Multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve multiple sclerosis-related fatigue and fatigability during inpatient rehabilitation: a randomized controlled pilot and feasibility study [ReFEx]. *BMC Neurology*, *23*(1), 388. https://doi.org/10.1186/s12883-023-03436-8

Background: MAT is a group-based exercise training framework for pwMS with a potential to impact fatigue and fatigability. In a mixed-methods design, this study evaluated the feasibility of implementing MAT in an inpatient rehabilitation setting and the feasibility of a RCT study protocol with 'traditional' SET as an active control condition. Secondarily, preliminary outcome data was acquired.

Methods: PwMS with low to moderate disability and self-reported fatigue were randomly allocated to either MAT or SET when starting inpatient rehabilitation (4–6 weeks). The MAT-participants exercised in a group following a MAT-manual (sessions were gym- (5x/week) and pool-based (3x/week)). SET-participants exercised individually 5x/week on a cycle ergometer, and 3x/week on strength training machines. Feasibility assessments focused on processes, resources, management, time, and scientific domains. Assessed clinical outcomes at admission and discharge included perceived fatigue, motor and cognitive fatigability, cognitive performance, motor function, and balance confidence. Perceived fatigue was reassessed 1, 4, and 12 weeks after discharge. Feasibility was determined regarding predetermined progression criteria.

Results: Twenty-two participants were randomized. Both groups performed the minimum number of sessions (>18), and retention was adequate (73–91%). SET-participants performed more sessions than MAT-participants (30.8 vs. 22.7) and stayed longer in the facility (34.2 vs. 31.6 days). Non-eligibility of admitted pwMS was high (74% non-eligible), mainly due to high EDSS and inability to attend pool-based sessions. Consequently, recruitment (1.8/month) was
slower than the predetermined progression criterium. Baseline assessments took longer than required (only 50% completed within 3 days). Short-term fatigue reduction

was similar for both groups. Motor fatigability also improved in both groups, whereas cognitive fatigability deteriorated. In MAT, average improvement in walking endurance (43.9m) exceeded minimal important change values for individuals (>26.9m).

Conclusions: Progressing to a definitive RCT necessitates adaptation of eligibility criteria. In the present design it will also be difficult to attain similar dosing of interventions. A multicenter RCT focused only on gym-based MAT might be another option to assess the effect of MAT. The primary outcome measure should be able to measure change in perceived fatigue more robustly.

Table 6

Predefined Quantitative Progression Categories and Results

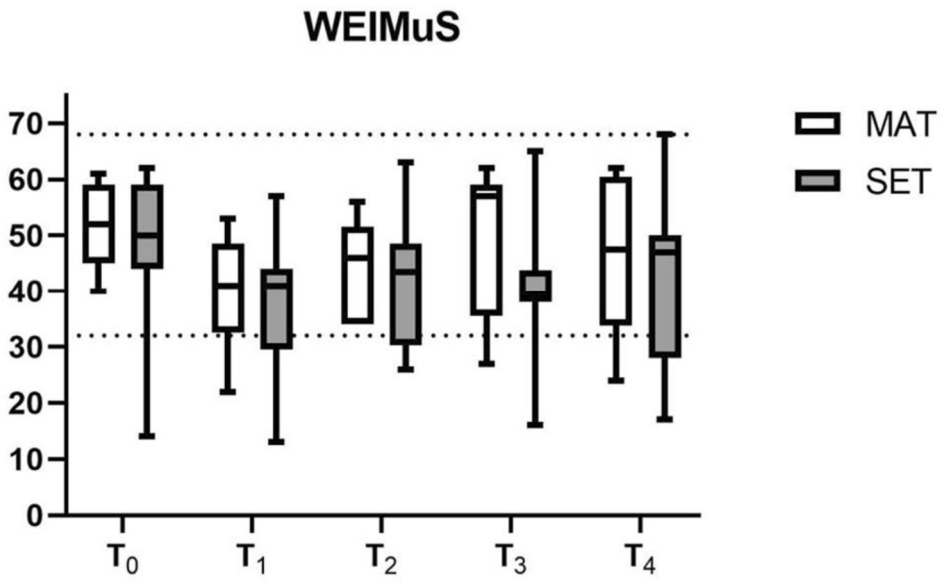
Requirement	Results
quantitative	
1. Adherence	
Average of at least 18 therapy sessions completed during the stay per group	+ MAT: 22.7 (12–33) + SET: 30.8 (18–38)
2. Recruitment	
4 participants/month	– 1.8/month
< 25% non-eligible pwMS	– 74% non-eligible
< 10% eligible but unwilling to participate	– 12%
3. Retention	
T_1 > 90% per group	+ 91% (both groups)
T_2 > 80% per group	+ 82% (MAT) – 73% (SET)
4. Time	
> 80% able to complete all baseline assessments within the first 3 days of therapy	– 50%

Note. Adherence data is presented as mean (minimum-maximum). Table from "Multimodal Agility-Based Exercise Training (MAT) Versus Strength and Endurance Training (SET) to Improve Multiple Sclerosis-Related Fatigue and Fatigability During Inpatient Rehabilitation: A Randomized Controlled Pilot and Feasibility Study [ReFEx]", by F. Wolf, J. Nielsen, et al., 2023, *BMC Neurology*, *23*(1), p.388 (https://doi.org/10.1186/s12883-023-03436-8) Copyright 2023 by the Authors. + = requirement fulfilled; - = requirement not fulfilled; MAT = multimodal agility-based

exercise training; pwMS = persons with multiple sclerosis; SET = strength and endurance training; T_1 = discharge; T_2 = 1 week post-discharge.

Figure 6

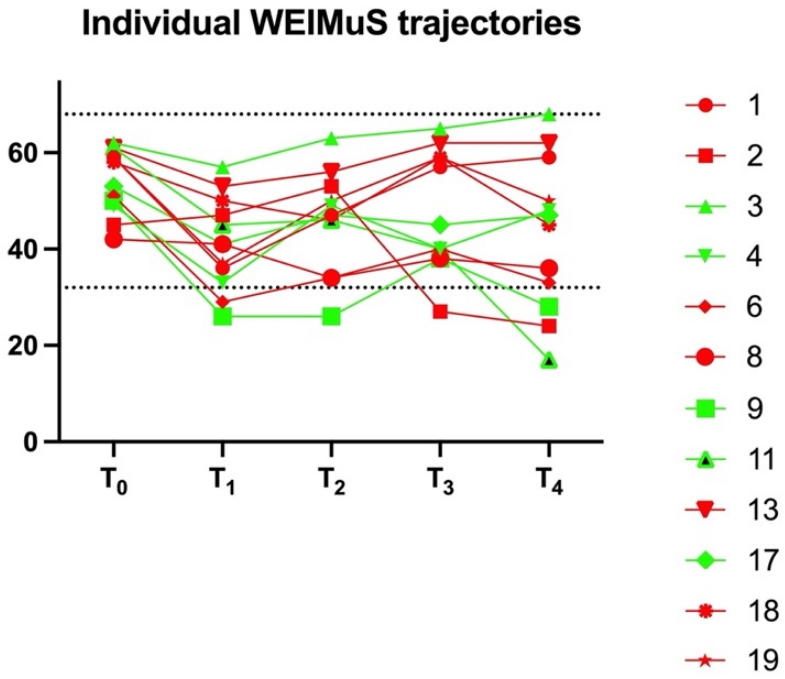
WEIMuS Scores for Both Groups Across all Measurement Timepoints



Note. Scores refer to the total score on the WEIMuS. Lower scores indicate less fatigue. Box plot: line = median, whiskers = minimum and maximum; upper dotted line = maximum WEIMuS total score (=68); lower dotted line = cut-off for fatigue (=32); Figure from "Multimodal Agility-Based Exercise Training (MAT) Versus Strength and Endurance Training (SET) to Improve Multiple Sclerosis-Related Fatigue and Fatigability During Inpatient Rehabilitation: A Randomized Controlled Pilot and Feasibility Study [ReFEx]", by F. Wolf, J. Nielsen, et al., 2023, *BMC Neurology*, *23*(1), p.388 (https://doi.org/10.1186/s12883-023-03436-8) Copyright 2023 by the Authors. MAT = multimodal agility-based exercise training; SET = strength and endurance training; T_0 = admission; T_1 = discharge; T_2 = 1 week post-discharge; T_3 = 4 weeks post-discharge; T_4 = 12 weeks post-discharge; WEIMuS = Würzburg Fatigue Inventory for Multiple Sclerosis.

Figure 7

Individual WEIMuS Score Trajectories for Participants with a Full Data Set



Note. Numbers on the right denote the participant ID. A decrease in score indicates less fatigue. Red = multimodal agility-based exercise training; green = strength and endurance training; upper dotted line = maximum WEIMuS total score (=68); lower dotted line = cut-off for fatigue (=32). Figure from "Multimodal Agility-Based Exercise Training (MAT) Versus Strength and Endurance Training (SET) to Improve Multiple Sclerosis-Related Fatigue and Fatigability During Inpatient Rehabilitation: A Randomized Controlled Pilot and Feasibility Study [ReFEx]", by F. Wolf, J. Nielsen, et al., 2023, *BMC Neurology*, 23(1), p.388 (https://doi.org/10.1186/s12883-023-03436-8) Copyright 2023 by the Authors. T_0 = admission; T_1 = discharge; T_2 = 1 week post-discharge; T_3 = 4 weeks post-discharge; T_4 = 12 weeks post-discharge.

Publication 5

Wolf, F., Folkerts, A. K., Zimmer, P., & Nielsen, J. (2024). Experiences of fatigued persons with multiple sclerosis with multimodal agility-based exercise training and the ReFEx study protocol: a qualitative extension of a feasibility study. *BMJ Open*, *14*(2), e076333. https://doi.org/10.1136/bmjopen-2023-076333

Objectives: (i) to explore experiences of fatigued pwMS with a new MAT framework and (ii) to investigate the demands of the ReFEx study protocol, which compares high-frequency MAT and 'traditional' SET to identify possible adaptations for a powered RCT.

Design: A qualitative interview study nested within a feasibility RCT, comparing MAT and SET.

Setting: Neurological inpatient rehabilitation center in Germany.

Participants: Twenty-two pwMS were recruited for the feasibility study. Six were selected from MAT and SET, respectively, for semi-structured face-to-face interviews prior to discharge, following a purposive sampling strategy. Participants had low physical disability but were at least moderately fatigued.

Interventions: During inpatient rehabilitation (4-6 weeks) MAT-participants attended group- and manual-based MAT sessions in the gym (5x/week, 30 min) and the pool (3x/week, 30 min). SET-participants exercised individually on a cycle ergometer (5x/week, 22 min) and on strength training machines (3x/week, 30 min).

Results: Three key categories emerged from the interviews. (i) *Facilitators* regarding MAT were variety and playfulness, group setting, and challenging exercises. *Barriers* regarding MAT were feeling overburdened, feeling pressured in the group setting, and the wish to perform 'traditional' strength training (not part of MAT). (ii) MAT *benefits* were of physical and psychological nature, with improved balance stated the most. (iii) *Demands* described the perceived exertion during MAT and SET, reflecting that there is no accumulation of fatigue during the intervention.

Conclusions: MAT is appreciated by pwMS and includes facilitators less attainable with ‘traditional’ SET. Evaluation of MAT in a powered RCT is indicated, if rest breaks post-session, and screening for negative self-evaluation and social comparison are considered. Future (qualitative) research should investigate the important factors of inpatient rehabilitation contributing to fatigue reduction in pwMS.

5 Discussion

5.1 Discussion of Results

RQ1 Can previously described associations between aerobic capacity and fatigue be reproduced on a cross-sectional and interventional level?

In Publication 1, the secondary analysis of pooled data from two similar RCTs conducted at the Rehabilitation Center Valens, Switzerland, revealed no association between aerobic capacity and fatigue for pwMS entering the trial, and thus could not reproduce the considerably stronger association reported in the cross-sectional meta-analysis of Rooney et al. (2019). PwMS also did not report a statistically significant change in fatigue from start to end of the inpatient rehabilitation period and the two endurance training programs did not differ in their effects, despite differences in intensity. These results did not change when analyzing only participants which should benefit the most, i.e., those who were severely fatigued at baseline, or those who substantially improved their cardiorespiratory fitness. Looking at Figure 4(B), a stronger effect of HIIT compared to MCT might be detectable in a fully powered trial (also supported by the effect sizes reported in the paper), but the absolute changes in FSMC score stayed below a clinically relevant change of 10 points (this value was communicated by the FSMC developer, Dr. Penner, to be clinically relevant (D'Hooghe et al., 2018)). Thus, the analysis “could not establish a translational effect of VO_{2peak} improvement on fatigue” (Wolf, Rademacher, et al., 2022, p. 4).

When integrating these results into the existing literature, a first option could be that functional status might moderate the association between fatigue and aerobic capacity. That is, correlation between the two measures might be stronger in pwMS with higher disability (i.e., with a higher EDSS). The two studies that reported the strongest correlations (r = −0.58 (Koseoglu et al., 2006) and r = −0.70 (Pilutti et al., 2015)) in the meta-analysis by Rooney et al. (2019) used arm or recumbent ergometry in patients with higher mobility limitations (who might be unable to perform leg cycle ergometry). This might explain why Rooney et al. (2019) also quantified significant heterogeneity among the five studies included in the meta-analysis, as the other samples had lower disability values and applied leg cycle ergometry - similar to the present design. Post-publication of Publication 1, the network meta-analysis by Torres-Costoso et al. (2022) became available (Table 5). These authors performed

subgroup analyses regarding the effect of aerobic exercise on fatigue in mild, moderate, and severe disability subgroups. Even though effect sizes were highest in the severe subgroup, data were lacking for aerobic training interventions in patients with higher disability, and all reported effect sizes were non-significant for the subgroup analyses. The authors suggested that existing studies on aerobic exercise might “be penalized for not being long enough to result in improvements in cardiovascular function and reduced fatigue“ (Torres-Costoso et al., 2022, p. 14).

Langeskov-Christensen et al. (2022) compared 6 months of twice weekly supervised progressive aerobic exercise against a waitlist control in 86 pwMS with mild disability and reported a significant and clinically relevant decrease in fatigue impact (measured using the MFIS), but not in fatigue severity (measured using the FSS). The authors similarly quantified a significant moderate correlation of aerobic capacity and MFIS scores at baseline, contrary to the present results. Interestingly, this was not verified with the FSS. Positive results of the aerobic training intervention might be explained by the considerably longer training duration compared to the present inpatient rehabilitation setting, while the differing results on correlation at baseline might be explained by different questionnaires in use, or better validity of the cardiopulmonary exercise test in the slightly less disabled sample of Langeskov-Christensen et al. (2022).

In another recent high-quality study by the same group, including 84 pwMS, no difference in effect between high-intensity aerobic exercise, progressed within and between four cycles of 12 weeks (i.e., one year of training) and a health education control group was observed (Riemenschneider et al., 2023). The comprehensive exercise program included two weekly sessions, and a mixture of continuous and interval training sessions. All sessions were supervised. The differing results of the two studies with similar training content executed by the same group might suggest that placebo effects from a health education control group are large enough to match the effects by the aerobic exercise, or a lack of granularity and placebo responsiveness of the applied fatigue measures (Block et al., 2022; Nourbakhsh et al., 2021). Missing effects are also supported by evidence from the mentioned meta-analysis (Moss-Morris et al., 2021). In pwMS, a change in secondary fatigue (i.e., less deconditioned) might not have a meaningful impact “on a subject’s overall fatigue experience, if primary fatigue [e.g., inflammation-based disruption of neural connectivity] remains unchanged” (Wolf, Rademacher, et al., 2022, p. 4).

Together, these findings contradict the large effect size reported for aerobic training in the meta-analysis of Taul-Madsen et al. (2021). Furthermore, despite these results, aerobic training continues to be highlighted as a primary exercise strategy, for example by Marchesi et al. (2022): “and performing sports, particularly aquatic exercise and aerobic training, is a good suggestion for fatigued MS patients” (p. 686). This seems to be questionable regarding the evidence for other exercise modalities being (more) promising.

A similar connection between fatigue and physical fitness (including aerobic capacity as one component) is hypothesized to exist in stroke survivors (Larsson et al., 2023). Interestingly, a recent meta-analysis found only two studies quantifying the association between post-stroke fatigue and VO_{2peak}, which were combined with studies assessing other aspects of physical fitness (e.g., gait speed, lower extremity strength) in the meta-analysis (Larsson et al., 2023). Both studies did not find a significant relationship between fatigue and VO_{2peak} (Oyake et al., 2021; Tang et al., 2010). However, Oyake et al. (2021) did quantify a significant association with a submaximal oxygen uptake measure. Taken together, results from the stroke literature do not provide compelling evidence transferable to pwMS.

Nevertheless, there are several aspects that can be investigated, which might still find associations in specific areas of the aerobic capacity – fatigue relationship in pwMS. Specifying the components of the relationship and potential moderators seems to be critical for future research. The association between aerobic capacity and fatigue might substantially depend on whether fatigue is being studied as a trait characteristic or a state variable, i.e., is aerobic training conceptualized to decrease retrospective fatigue ratings for everyday life or to decrease fatigue ratings while performing certain physical activities? A study assessing the associations with both aspects would be beneficial. Similarly, different aspects of aerobic capacity can be assessed. As will be further examined in the discussion of methods, measures of VO_{2peak} might be suboptimal in pwMS (Schlagheck et al., 2023). Studies using submaximal measures of aerobic capacity (Valet et al., 2020) might be more appropriate to find associations with fatigue. Addressing flaws in the assessment of fatigue as well as aerobic capacity might lead to more robust associations between both constructs. Studies should apply one of the recently developed fatigue questionnaires with better psychometric properties to see whether results differ compared to the usually applied questionnaires with limited quality (Close et al., 2023). Lastly, future studies should design direct

comparisons of different types of exercise, which have different targets regarding fatigue. One example for this is the ReFEx protocol (Wolf, Nielsen, et al., 2022).

RQ2 Is it feasible to conduct a randomized controlled trial including a newly developed multimodal agility-based exercise training framework to improve fatigue and fatigability in an inpatient rehabilitation setting?

After Publication 1, a MAT framework for pwMS was developed with all rationales being described in Publication 2. This was followed by Publication 3, outlining the ReFEx study protocol for comparing the new framework with 'traditional' SET in an inpatient rehabilitation setting. As Publications 2 and 3 do not contain results, discussion of results proceeds with Publication 4, which emphasized feasibility measures of the ReFEx protocol. The following part will only discuss feasibility aspects, which were set as progression requirements, as these were the main markers to answer the research question. Details on other aspects of feasibility, including fidelity, data management, perceived exertion, and adverse events, are reported in Publication 4.

Results were summarized in Publication 4 as follows: "one category was fulfilled (adherence), one was mixed, but approached a positive value (retention), and two were negative (recruitment, time)" (Wolf et al., 2023, p. 3) (Table 6). Therefore, it is not feasible to conduct a RCT with the present study protocol.

The most important negative category was recruitment, as only about 1.8 participants were randomized each month (four were intended). "A preliminary sample size calculation for a clinically relevant difference between the two groups regarding the Würzburg Fatigue Inventory for Multiple Sclerosis (WEIMuS) retrieved a sample size of n = 66" (Wolf et al., 2023, p. 9), which would take almost 4 years to recruit with the present study protocol, making it unfeasible to continue in the present form. The primary reason for the low recruitment rate was the very high rate of non-eligibility for trial participation (74%), which was attributable to high EDSS scores and the inability to attend pool-based sessions among pwMS admitted to the NRC.

The second negative category (time) showed that only one in two participants completed all baseline assessments within the first 3 days, with an average of 4.1 days needed. Reasons for this were manifold, including (I) delays in the screening process (e.g., clarification of participants' actual ability to attend aquatic therapy, delays in physician's assessment of EDSS) affecting when baseline assessments could be initiated, (II) scheduling issues (issues with the scheduling process itself, or limited

time slots where assessments could be carried out), (III) participants not showing up for the appointment due to personal reasons or conflicts with other appointments.

The category of retention showed that more than 90% in both groups completed the assessments pre-discharge, as intended. One-week post-discharge (i.e., at home), the MAT-group fulfilled the criterion of at least 80% completing the online questionnaires, while the SET-group reached 73%. This reflects three of 11 participants not returning the questionnaires post-discharge in the SET-group, which includes one participant dropping out of the study due to acute Lyme disease. Therefore, despite the mixed result, it can be expected that once participants are enrolled in the study, there is an adequate probability for them to complete the post-intervention and post-discharge assessments.

Lastly, the results on adherence "indicated that a high frequency of sessions was possible on an organizational level" (Wolf et al., 2023, p. 8) and regarding the fatigued patient collective, as both groups performed more than the intended 18 sessions during the intervention period (90% adherence overall). An exception was the pool session (76% adherence), which was attributed to scheduling issues (the session was scheduled after the lunch break).

Only few other studies have reported adherence rates of exercise interventions conducted in inpatient rehabilitation settings. Some of the existing ones have reported even higher adherence rates. For example, Zimmer et al. (2018) reported 100% adherence in an endurance training study (RCT1 pooled for Publication 1), but this trial also included less study-related sessions per week (3-5x/week for 3 weeks vs. 8x/week for >4 weeks in the present study). Similarly, Smedal et al. (2011) performed a study in a Norwegian as well as a Spanish inpatient rehabilitation center and reported 99.3% adherence to 17 physiotherapy sessions conducted during a period of 4 weeks – again showing higher adherence, but also only about four sessions/week. In a study on persons with moderate to severe MS, 100% adherence was also attained for 4 weeks of active-passive cycling with five sessions/week (Barclay et al., 2019). The scarcity of adherence assessments in this setting potentially shows weaknesses in overall feasibility assessment and, consequentially, compromised interpretability of training results. Moreover, compromised interpretability of training results is not only a problem confined to the setting of inpatient rehabilitation, but a general problem of exercise studies conducted in pwMS (Dennett et al., 2020; Motl et al., 2023; Schlagheck et al., 2021).

Regarding retention, post-intervention, Smedal et al. (2011) and Zimmer et al. (2018) reported 85% and 95% retention, respectively. For other exercise intervention studies conducted in inpatient rehabilitation settings, similar values of 85% (Claerbout et al., 2012) or even 97% (Dettmers et al., 2009) can be calculated from the data provided. A systematic review conducted on exercise training RCTs - irrespective of setting - reported an average of just under 85% retention for the exercise and control arms (Pilutti et al., 2014), emphasizing a high level of retention for the present study and for studies in inpatient settings in general.

The author is not aware of any other studies reporting the time (i.e., days) it took to complete baseline assessments. Three days were the minimum expected number for the physical and cognitive testing, and the research team was aware that this number was challenging. From a trial design perspective, to capture a true baseline score, participants should only start training after finishing all baseline assessments. Therefore, the longer it takes to complete baseline assessments, the less training time will be available, and this is especially relevant in rehabilitation settings with a fixed rehabilitation duration (e.g., 4 weeks).

There are examples of other inpatient rehabilitation trials conducted in similar settings, recording similarly low eligibility. In the study by Zimmer et al. (2018), 106 persons fulfilled the MS phenotype (relapsing-remitting, or secondary-progressive MS, identical to the present study) and EDSS criteria (1.0 – 6.5). Despite the wider EDSS range, only 60 persons were eligible to participate in the trial, resulting in a non-eligibility rate of 43%. Notably, the eligibility rate of all pwMS admitted to the clinic was not reported, potentially explaining why the present rate of non-eligibility was even higher. Additionally, no aquatic training was performed, excluding an eligibility criterion, which increased non-eligibility in the present study. In a trial on walking exercise conducted in a German rehabilitation facility, Dettmers et al. (2009) described a rate of 70% of admitted persons being excluded from study participation, equaling the present rate of 74%, but focusing on patients with even lower functional disability (i.e., EDSS <4.5). Yet, the paper did not make a precise distinction between the eligibility and recruitment rate, making interpretation difficult. In a recent study on combined energy management education and endurance training, also conducted in the RCV, 182 admitted pwMS fulfilled the EDSS criterion (≤6.5) (Patt et al., 2023). Of those, only 18% were non-eligible to participate in the trial. However, the same

constrains apply, as the eligibility rate of all pwMS admitted to the clinic was not reported, but only for those, who fulfilled the EDSS criterion. In this study, a higher refusal rate (24%) than in the present study (12%) was identified.

With these results, the primary target of protocol adaptions should be the enhancement of the recruitment rate. To recruit the targeted four participants per month (resulting in a recruitment period of about 17 months to reach the calculated sample size) - with the current refusal rate (12%) - a maximum of 35% of admitted pwMS should be evaluated as non-eligible. This research has shown that the main mechanism for decreasing non-eligibility, would be the criteria of (I) EDSS and (II) the ability to attend aquatic therapy. Adaptation of the EDSS criterion, however, is constrained. From the experience gained during the intervention and the feedback from participant interviews (see RQ3, below), MAT requires a rather homogenous group from a motor performance perspective. Therefore, increasing the EDSS limit does not seem to be viable. The other option would be to increase the pool of persons with an adequate EDSS. This might be accomplished by expanding to a multicenter trial, which would increase external validity of the findings, but also influences resources needed. If the trial would be restricted to evaluate gym-based MAT only, that is, abandoning the ‘aquatic therapy’ criterion, non-eligibility would have decreased by only five persons (6%) in the current sample, as many persons with high EDSS are also not able to attend group-therapy in the pool. Regarding other criteria that could be changed, the criterion of MS phenotype could be expanded to include primary-progressive MS forms as well. However, in the current sample, this would only lead to a negligible decrease of the non-eligibility rate to about 65% (when changing the criteria of aquatic therapy and MS phenotype together).

Furthermore, cutting the aquatic part has other consequences to be considered. The main reason to introduce pool-based MAT to the study design was to increase the amount of standardized therapy content for the MAT-group. The same is true for introducing strength training in the SET-group. This is based on the issue that, if these sessions would not have been part of the study, the available time would have been filled with ‘unstandardized’ therapy sessions, as the amount of therapy received by patients during rehabilitation is regulated, for example, by the German pension insurance company. Increasing the amount of ‘unstandardized’ therapy would make the two study groups less comparable and would further dilute the effects of the study interventions. Thus, for the current mono-center setting, there seems to be no viable

option to attain the desired recruitment rate, leaving a multicenter trial as the only option.

Overall, the results on adherence have confirmed the advantages of inpatient rehabilitation settings, including the possibility of high frequency exercise and high retention rates, as patients are on-site, out of their everyday life. However, pwMS are also embedded in a multidisciplinary setting, with study-unrelated appointments possibly interfering with study-related sessions. Therefore, MAT should also be evaluated in outpatient settings with a longer intervention duration.

RQ3 How do pwMS experience the multimodal agility-based exercise training and what are the demands of the study protocol from a patient perspective?

Publication 5 followed the quantitative feasibility evaluation in Publication 4 with a qualitative analysis of pwMS' experiences. The qualitative analysis was designed to acquire information on factors influencing future adherence and uptake of MAT as well as feasibility of the ReFEx protocol from the participant's perspective. Face-to-face interviews with a purposive sample of 12 ReFEx participants were performed. Questions in the interview guide were based on relevant topics from the qualitative MS literature (Learmonth & Motl, 2016) and guidance on qualitative research in the context of feasibility studies (O'Cathain et al., 2015; Skivington et al., 2021). Results of the qualitative evaluation were summarized in Publication 5 as follows:

> facilitators regarding MAT were variety and playfulness, the group setting and the feeling of being challenged by the exercises, whereas pre-existing expectations on the benefit of 'traditional' strength training, feeling overburdened and feeling pressured in the group were barriers. . . . As expected, some participants from MAT and SET acutely experienced fatigue after the sessions, while occasionally being unable to recover for the next appointment. However, this did not result in being unable to attend the second study-related session of the day or sessions on the following day. None stated experiencing an accumulation of fatigue, instead, improved fatigue was reported prior to discharge (ie, the time of the interview). (Wolf et al., 2024, p. 8)

These results can be interpreted as pwMS appreciating several aspects of MAT, which are not part of 'traditional' training approaches (i.e., SET) such as the companionship and motivation gained by training in a group, the variety of the training content, and the playfulness. All these factors facilitate exercise adherence, a critical aspect for the positive impact of exercise (Motl et al., 2023). Furthermore, considering minor

adjustments such as rest breaks after exercise sessions, the protocol was feasible to conduct from the participant perspective.

As mentioned in the discussion of RQ2, a high degree of adherence and retention can be expected in inpatient rehabilitation settings. However, if MAT would be applied in an outpatient setting, the mentioned facilitators of MAT might have an even more profound impact, fostering adherence in less supervised conditions. Other researchers evaluating a similar balance and core stability intervention suggested the combination of supervised and unsupervised (home-based) training to achieve a sustainable routine, as the unsupervised part had considerably lower adherence (Carling et al., 2017). The same group also highlighted the importance of a mixed-methods approach for the evaluation of new interventions (Carling et al., 2018).

Besides the characteristic of supervised exercise, several authors suggested group exercise to be a main driver of exercise adherence, also reflected in qualitative evaluations (Aubrey & Demain, 2012; Carling et al., 2018; Learmonth & Motl, 2016) and the present results. Interestingly, positive attitudes towards training in a group emerged despite of the current group setting not being as permanent compared to other settings, as there was a continuous flow of participants entering and leaving the group when they were admitted or discharged from the clinic. On the other hand, being part of a group and having regular opportunities to socialize might be even more important in an inpatient setting, as pwMS are away from their usual social environment for several weeks.

Being challenged by the exercises was a theme that similarly emerged in the qualitative evaluation by Carling et al. (2018) despite of their sample having higher mobility disability. The authors also described that performing challenging exercises was connected to experiencing a boost in self-confidence, mirroring experiences from the MAT-participants.

Regarding the barriers for MAT mentioned in the citation above, other research has shown that pwMS tend to avoid exercising amongst ‘healthy’ people (Learmonth et al., 2012). Notwithstanding that the current participants exercised together with other pwMS (or persons with other neurologic illnesses), the group setting still posed a challenge for some regarding negative effects of social comparison. Upward and downward social comparison was also described by Russell et al. (2022) who examined experiences of pwMS participating in a social cognitive behavior change physical activity intervention. The authors described how social comparison can have

positive and negative consequences, which was also observable in the current group. To hone positive aspects of the group environment - such as improved learning and encouragement (Horton et al., 2015) – a similar level of motor performance of participating pwMS seems to be important, as is a group leader/therapist carefully selecting exercise content. That some participants felt overburdened at times, might likewise be connected to upward social comparison coupled with low self-esteem.

Prior beliefs about the benefits of ‘traditional’ strength training emerged as another barrier for the new MAT, a factor less relevant in other qualitative research. Strength training is a common form of exercise and part of MS exercise guidelines (Kalb et al., 2020). Accordingly, many pwMS have experiences with this form of exercise. Studies evaluating new exercise approaches may need to invest more energy in explaining its specific benefits to participants during exercise sessions, but also in the study information sheet – especially, if a traditional exercise approach is evaluated against a new form of exercise.

In the present qualitative investigation participants reported that they were able to recover for the second study-related session of the day or sessions on the next day. This contrasts statements from more disabled participants in the study by Carling et al. (2018), who were sometimes not able to recover between separate days, demonstrating differences between these MS samples. Nevertheless, the present participants did advocate for consistent rest breaks of 30 min to 60 min after the exercise sessions to recover for the subsequent study-unrelated appointments. Rest breaks to alleviate fatigue were also a facilitator for exercise participation in the studies reviewed by Learmonth and Motl (2016). Following the considerations of Ware et al. (2022), the expected fatigue after exercise participation is an important predictor for future exercise engagement and might be based on the interpretation of bodily signals (i.e., interoception). Indeed, in the present study, pwMS frequently commented on bodily sensations after exercise cessation. Accordingly, during inpatient rehabilitation, pwMS might experience reduced worry regarding the negative effects of exercise on their energy levels as they do not have to work, care, or adhere to household duties. In that way, the inpatient environment might enable them to experience the positive effects of exercise. Several participants commented that just being in the rehabilitation facility and being freed from their usual obligations, had a profound impact on their fatigue. This was summarized under the term ‘vacation from daily grind’ in the qualitative analysis. Interestingly, a recent qualitative study (Ghaidar et al., 2022)

reported that factors for the decision of pwMS to attend inpatient rehabilitation in Germany were: “the escape from everyday life, finding time to relax, and to fully concentrate on one’s health” (Wolf et al., 2024, p. 9). This finding matches very well with the experiences of the current participants.

Overall, qualitative investigations can be seen as a valuable methodology in the field of MS and fatigue, especially regarding the mentioned issues of existing fatigue questionnaires. Future studies should embark on similar mixed-methods study designs. Additionally, patient representatives should be included in the construction of the interview guide and the analysis process to increase patient involvement in the research.

5.2 Discussion of Methods

The following chapter will discuss strengths and weaknesses of the performed studies regarding the study Populations, Interventions, Comparators, Outcomes, Timing, and Settings (i.e., based on the PICOTS framework). This approach was partially influenced by a recent publication of the Moving Exercise Research Forward initiative on study designs in MS exercise studies (Dalgas et al., 2023).

Study Populations

The current research focused on pwMS reporting fatigue, which is an advantage compared to many previous studies, reporting results on patient populations, that were not prescreened for the presence of fatigue (Moss-Morris et al., 2021). Furthermore, pooling samples from two RCTs for Publication 1 enabled a large sample size and sub-group analysis. Notably, using sub-group analysis, the hypothesis that fatigued pwMS benefit the most from endurance exercise was not supported. Distinguishing fatigued from non-fatigued pwMS was attained by using the same questionnaire (FSMC) in both study settings (i.e., RCV and NRC), which had been specifically suggested for this purpose (Sander et al., 2017).

Another strength of the acquired samples is the reduced 'risk of selection bias' (Dalgas et al., 2023), as it might be more probable for 'non-exercisers' to take part in an exercise study in the setting of inpatient rehabilitation, as they are not restrained by their usual environment (e.g., time problems, social obligations, etc.), compared to outpatient settings. Therefore, one can be confident that results apply to persons with average motivation for exercise.

Weaknesses of the study populations mainly pertain to the EDSS. For the studies at the RCV, functional disability might have been too high for some persons to be adequately assessed for aerobic capacity using a cycle ergometer (see Outcomes section below). For the ReFEx study, EDSS criteria were lower but hard to recruit, as described. It can be argued that the target population of MAT might be even lower than the current limit of EDSS 5.0. From a motor performance perspective, the gap between EDSS 1.0 and 5.0, for example, might be too large in a group-training setting. Another way to construct inclusion criteria might be to screen for the targeted fatigue pathway. In theory, if an intervention like MAT focuses on "improvement of sensory integration with a subsequent reduction of the cognitive load associated with motor

processing" (Callesen et al., 2020, p. 2), a test of sensory integration might be used to screen for persons with decreased sensory integration and fatigue.

Lastly, none of the reported results were based on *a priori* sample size calculations, as Publication 1 was a secondary data analysis and the ReFEx study was a feasibility study.

Interventions

The MAT intervention was fatigue-targeted with a profound theoretical background. Furthermore, fatigue is the primary outcome of the ReFEx protocol. Both were points of critique in previous exercise studies (Moss-Morris et al., 2021). Considering these aspects helps to study the 'active ingredients' of a rehabilitation treatment and to understand mechanisms of action (Van Stan et al., 2021). Fatigue as the primary outcome also enables an appropriate sample size calculation. The MAT framework itself was thoroughly described and defined in a 'point-of-view' paper (i.e., Publication 2), offering far more information regarding the exercise content than usual for exercise studies. By publishing a feasibility protocol paper and adhering to the Consensus on Exercise Reporting Template for Therapeutic Exercise Interventions (Page et al., 2017), detailed descriptions of intervention components are available to other researchers.

As described in the previous section, the influence of concurrent treatments during inpatient rehabilitation was reflected in the study design and monitored during the study.

Furthermore, the principles of exercise training (Dalgas et al., 2023; Schlagheck et al., 2021) were thoroughly considered when constructing the exercise programs: the principle of *specificity* is essentially under investigation in the ReFEx protocol, as it asks whether MAT or SET is more specific to alleviate fatigue in fatigued pwMS. All MAT modules included modifications and *progressions* in exercise complexity. The strength training also included predetermined *progressions* in training load. The endurance training was *progressed* based on individual's perceived exertion (but not predetermined). The principle of *initial values* was considered by only including persons with fatigue. However, the more proximal training targets were less considered, e.g., persons in the MAT were not screened for sensory integration deficits, as described above. Hence, another adaptation for the ReFEx protocol could be a test of high-level mobility functions, such as the High Level Mobility Assessment

Tool (Smith et al., 2020; Williams et al., 2012) to acquire *initial values* of high-level mobility/agility. Finally, the achievement of sufficient *overload* was mostly subjective (apart from the strength training). Nevertheless, 'session-rating of perceived exertion' was used, which is a valid method to measure training load and frequently applied even in athletic populations (Haddad et al., 2017).

Comparators

Control groups are of substantial importance in exercise training studies (Hecksteden et al., 2018). In inpatient rehabilitation settings, only active control conditions are feasible from an ethical point of view. Therefore, the studies at the RCV and the NRC included active comparators. However, actually, these designs must be described as 'intervention + usual care' versus 'active comparator + usual care', with usual care incorporating all the processes of a patient-tailored multidisciplinary rehabilitation program. In both study settings, the problem of high variability in what constitutes usual care for individual patients has not been solved and continues to be an intrinsic challenge of the rehabilitation environment (Arienti et al., 2022; Dalgas et al., 2023).

Outcomes

Fatigue is the primary outcome in the ReFEx protocol. However, it was only a secondary outcome in the RCTs analyzed for Publication 1. Both RCTs applied the FSMC, which might have unsatisfactory responsiveness in the inpatient rehabilitation setting due to problems with its timeframe. As described in a conference paper (Wolf & Nielsen, 2022), the unspecified reference timeframe of the FSMC might lead to fewer 'fatigue-responders' compared to the WEIMuS (reference timeframe: last week), for example. Accordingly, Publication 1 showed that in the overall sample as well as in the subgroup analyses, all changes in the FSMC were non-significant. Therefore, and in light of the issues of fatigue assessment described in section 2.3.1, choosing and developing better ways to assess change in fatigue will be critical for future studies.

Likewise, no gold standard exists to quantify walking fatigability (Van Geel, Moumdjian, et al., 2020). Assessment of the Distance Walked Index (Van Geel, Veldkamp, et al., 2020) is one option and was easily implementable in the inpatient rehabilitation setting. Instrumented walking fatigability assessment has been

advocated recently as another option and might be selected for a future RCT (Broscheid et al., 2022; Santinelli et al., 2024; Van Geel, Moumdjian, et al., 2020).

Regarding the aerobic capacity – fatigue relationship, assessment of VO_{2peak} in pwMS has been challenging (Schlagheck et al., 2023). Specifically, the measured VO_{2peak} should only be regarded as valid, when established criteria are met (e.g., heart rate within 90% of calculated HRmax, plateau in oxygen consumption while the workload is still increasing) (Heine et al., 2014). PwMS may be prevented from meeting these criteria for a variety of reasons (e.g., spasticity, reduced muscle strength). These limiting factors might prevent the assessment of the ‘true‘ aerobic capacity in these persons, especially via leg cycle ergometry. Measurement variability also complicates the analysis of relevant changes in aerobic capacity when derived from a cardiopulmonary exercise test in pwMS. Heine et al. (2014) showed that variability of results increases as measurement procedures become less standardized. This might also be the case for patients with higher EDSS. Consequently, the results of Publication 1 have to be examined in light of the relatively high proportion of participants with higher disability in this sample.

Timing

This aspect concerns the timing of assessment time points. Problems with the FSMC reference timeframe were already mentioned. It can be added that few studies have considered the reference timeframes of the fatigue questionnaire in use regarding the post-intervention assessment. Usually, an intervention study compares symptom severity pre-intervention versus post-intervention, which usually is the time point of the highest effect, followed by a decrease during a follow up period. Fatigue questionnaires are based on internal averaging of fatigue experienced during 1 to 4 weeks (Sander et al., 2017). If the participants receive a questionnaire right at the end of an intervention – or, post-discharge, as in the inpatient rehabilitation examples provided here - the participants will essentially rate their fatigue during the process of the intervention and not post-intervention. This might be solved by using questionnaires with shorter reference timeframes (such as the WEIMuS), and by using more appropriate assessment time points after the intervention, as was the case for the ReFEx protocol, where the primary time point of interest was 1 week after discharge.

Setting

Strengths of the inpatient rehabilitation setting include the high frequency of exercise sessions that can be scheduled, the high degree of supervised exercise, and with that, the possibility of performing more complex forms of exercise training (e.g., MAT). Supervised exercise has been shown to have superior effects compared to unsupervised exercise (Dalgas et al., 2023; Snook & Motl, 2009).

Nevertheless, the setting also includes specific challenges. Regarding the patient sample, the ReFEx feasibility study showed that disability among pwMS admitted to inpatient rehabilitation is rather high, and high-functioning pwMS might not express the need to attend inpatient rehabilitation (which are a target group for MAT). Frequently, the evaluation of working capacity is a focus of the inpatient stay, and pwMS might arrive at the clinic with pivotal life decisions to be made. This might challenge the readiness to take part in an exercise training study.

Lastly, a multitude of professions are involved in the rehabilitation clinic (physician, neuropsychologists, etc.). All professions are working in clinical routines, and study-related tasks usually means extra work. Therefore, it is always important to check whether the necessary study-related resources can be provided, and to keep in mind that procedures from an academic setting might not be attainable in a clinical environment.

6 Conclusions and Future Directions

This thesis conveys several ‘negative’ results. The secondary analysis of two pooled RCTs did not confirm the aerobic capacity - fatigue relationship on a correlational and experimental level, even when analyzing subgroups that should benefit the most according to proposed hypotheses (RQ1). Furthermore, the feasibility analysis of a study protocol investigating a new exercise framework targeting fatigue was deemed unfeasible in the present form and the inpatient rehabilitation setting (RQ2), even though pwMS appreciated the new MAT framework (RQ3).

Regarding RQ1 and the aerobic capacity – fatigue relationship, future studies should specify whether perceived fatigue is being studied as a trait characteristic or a state variable, i.e., is aerobic training conceptualized to decrease retrospective fatigue ratings for everyday life or to decrease fatigue ratings while performing certain physical activities? Assessment of both, aerobic capacity, and fatigue should be improved by using submaximal measures of aerobic capacity, and fatigue questionnaires with better psychometric properties. Furthermore, reference timeframes of fatigue questionnaires should be considered, and assessment time points should reflect the reference timeframes.

The importance of evaluating feasibility aspects in MS exercise studies has been increasingly highlighted (Learmonth et al., 2019; Learmonth & Motl, 2018; Motl et al., 2022). The current feasibility results regarding RQ2 suggest that future studies might engage in efforts to expand the ReFEx protocol to a multi-center trial or transfer to a different setting. Furthermore, Publication 2 provided directions for research regarding MAT in pwMS apart from the symptom of fatigue. For example, future studies might determine the efficacy of MAT to provide multi-systemic benefits, going from proximal (motor outcomes) to more distal targets (cognitive outcomes, imaging/biomarkers), and compare it with unimodal/traditional approaches.

From a clinical standpoint, results regarding RQ3 suggest that fatigued pwMS can be involved in high-frequency exercise, and that the MAT framework includes several aspects appreciated by pwMS, therefore encouraging the uptake of MAT in clinical practice.

Methodologically, future studies evaluating an exercise intervention to treat fatigue should consider the following points:

- Include pwMS prescreened for fatigue

- Choose a fatigue pathomechanism that has been described in the literature
- Provide a rational how this mechanism can be targeted with the type of exercise under investigation
- Chose a fatigue questionnaire suitable for the study design with high psychometric qualities
- Chose a secondary biomarker outcome that connects to the fatigue pathomechanism/mechanism of action

Some RCTs have been published after the most recent fatigue meta-analyses. Unfortunately, few were designed with the primary objective to target fatigue. One notable study, which considered the points mentioned above, was performed by Englund et al. (2022), and evaluated the effects of 12 weeks of high-intensity resistance training on self-reported fatigue in 71 fatigued pwMS. Analogous to the ReFEx protocol, the authors chose a FSMC score above 53 as a cut-off value for inclusion. In the manner of a dose-finding study (Dalgas et al., 2023) participants were randomized to either twice or once weekly resistance training, while the authors elegantly compared these against a non-randomized FSMC score-matched group (*n* = 69) as a non-active control. As a mechanism of action, resistance training was hypothesized to aid in the release of anti-inflammatory mediators, which were also assessed as secondary outcomes. They reported a clinically relevant and significant decrease in FSMC scores in the combined resistance training groups, while the control group retained their scores. There was no difference between the once or twice weekly training groups. These results are very encouraging and were achieved despite the discussed problems of the FSMC. Of note, participants had an EDSS ≤2.5. The authors advocated the comparison of high-intensity resistance training with other types of exercise.

Moreover, a comprehensive, high-quality study was published on the effects of exercise on cognition in pwMS (Feinstein et al., 2023). Despite a negative outcome, in many regards this trial could act as a role model for fatigue trials, as many issues in the study of cognitive function are similar to fatigue (e.g., previous studies not prescreening for the presence of the symptom, divergence between objective cognitive performance and subjective cognitive impairments (Rademacher et al.,

2020)). Unfortunately, a similar, focused, multi-center effort does not seem to currently exist regarding fatigue.

Results in other areas of MS research will likely impact how exercise studies for fatigue will be designed in the future. Several authors have highlighted the fact that fatigue probably arises from different sources which can also differ between pwMS. Manjaly et al. (2019) provided this vision:

> In order to select treatments in a rational and predictive manner, novel clinical tests are needed. Importantly, these need to go beyond detecting fatigue; instead, they should inform the choice of patient-specific treatment - by enabling differential diagnosis of alternative mechanisms and/or predicting individual therapeutic response. (p.7)

Similarly, Krieger and Sumowski (2020) wrote that “Clinical trials for fatigue agents will need to be designed to include and address specific biologically distinct fatigue phenotypes, lest the impact of a therapeutic agent be washed out by overly broad inclusion criteria“ (p.621). Therefore, future exercise-based fatigue treatment will probably determine the most likely contributors to fatigue in an individual person and evaluate whether a specific form of exercise could be helpful, i.e., following a treatment algorithm (some fatigue algorithms have already been proposed (Cohen et al., 2020; Veauthier et al., 2016)). Consistently, Harrison et al. (2021) noted that there likely is not one most beneficial type of exercise. This emphasizes the importance for studies to target a certain fatigue pathway, at best, recruiting a sample with a homogenous fatigue phenotype (Sparasci et al., 2022).

Another interesting route might come from research showing that exercise might have more effects on ‘energy’ than on fatigue (Filippi et al., 2022; Wender et al., 2022). This approach has not received attention in pwMS, showing the vast range of possibilities to improve research regarding fatigue.

7 References

Abasıyanık, Z., Kahraman, T., Veldkamp, R., Ertekin, Ö., Kalron, A., & Feys, P. (2022). Changes in Gait Characteristics During and Immediately After the 6-Minute Walk Test in Persons With Multiple Sclerosis: A Systematic Review. *Physical Therapy*, *102*(7). https://doi.org/10.1093/ptj/pzac036

Andreu-Caravaca, L., Ramos-Campo, D. J., Chung, L. H., & Rubio-Arias, J. (2021). Dosage and Effectiveness of Aerobic Training on Cardiorespiratory Fitness, Functional Capacity, Balance, and Fatigue in People With Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Archives of Physical Medicine and Rehabilitation*, *102*(9), 1826-1839. https://doi.org/10.1016/j.apmr.2021.01.078

Arienti, C., Buraschi, R., Pollet, J., Lazzarini, S. G., Cordani, C., Negrini, S., & Gobbo, M. (2022). A systematic review opens the black box of "usual care" in stroke rehabilitation control groups and finds a black hole. *European Journal of Physical and Rehabilitation Medicine*, *58*(4), 520-529. https://doi.org/10.23736/s1973-9087.22.07413-5

Aubrey, G., & Demain, S. (2012). Perceptions of group exercise in the management of multiple sclerosis. *Int J Ther Rehabil*, *19*, 557-565. https://doi.org/10.12968/ijtr.2012.19.10.557

Barclay, A., Paul, L., MacFarlane, N., & McFadyen, A. K. (2019). The effect of cycling using active-passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe Multiple Sclerosis (MS); a feasibility study. *Multiple Sclerosis and Related Disorders*, *34*, 128-134. https://doi.org/10.1016/j.msard.2019.06.019

Barin, L., Salmen, A., Disanto, G., Babacic, H., Calabrese, P., Chan, A., Kamm, C. P., Kesselring, J., Kuhle, J., Gobbi, C., Pot, C., Puhan, M. A., von Wyl, V., & Swiss Multiple Sclerosis, R. (2018). The disease burden of Multiple Sclerosis from the individual and population perspective: Which symptoms matter most? *Multiple Sclerosis and Related Disorders*, *25*, 112-121. https://doi.org/10.1016/j.msard.2018.07.013

Beets, M. W., von Klinggraeff, L., Weaver, R. G., Armstrong, B., & Burkart, S. (2021). Small studies, big decisions: the role of pilot/feasibility studies in incremental science and premature scale-up of behavioral interventions. *Pilot Feasibility Stud*, *7*(1), 173. https://doi.org/10.1186/s40814-021-00909-w

Behrens, M., Broscheid, K.-C., & Schega, L. (2021). Taxonomie und Determinanten motorischer Performance Fatigability bei Multipler Sklerose [Taxonomy and determinants of motor performance fatigability in multiple sclerosis]. *Neurologie und Rehabilitation*, *27*, 3-12. https://doi.org/10.14624/NR2101001

Behrens, M., Gube, M., Chaabene, H., Prieske, O., Zenon, A., Broscheid, K. C., Schega, L., Husmann, F., & Weippert, M. (2023). Fatigue and Human Performance: An Updated Framework. *Sports Medicine*, *53*(1), 7-31. https://doi.org/10.1007/s40279-022-01748-2

Bertoli, M., & Tecchio, F. (2020). Fatigue in multiple sclerosis: Does the functional or structural damage prevail? *Multiple Sclerosis Journal*, *26*(14), 1809-1815. https://doi.org/10.1177/1352458520912175

Bjornevik, K., Cortese, M., Healy, B. C., Kuhle, J., Mina, M. J., Leng, Y., Elledge, S. J., Niebuhr, D. W., Scher, A. I., Munger, K. L., & Ascherio, A. (2022). Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated

with multiple sclerosis. *Science*, *375*(6578), 296-301. https://doi.org/10.1126/science.abj8222
Bjornevik, K., Münz, C., Cohen, J. I., & Ascherio, A. (2023). Epstein–Barr virus as a leading cause of multiple sclerosis: mechanisms and implications. *Nature Reviews Neurology*, *19*(3), 160-171. https://doi.org/10.1038/s41582-023-00775-5
Block, V. J., Bove, R., & Nourbakhsh, B. (2022). The Role of Remote Monitoring in Evaluating Fatigue in Multiple Sclerosis: A Review. *Frontiers in Neurology*, *13*, 878313. https://doi.org/10.3389/fneur.2022.878313
Broscheid, K. C., Behrens, M., Bilgin-Egner, P., Peters, A., Dettmers, C., Jöbges, M., & Schega, L. (2022). Instrumented Assessment of Motor Performance Fatigability During the 6-Min Walk Test in Mildly Affected People With Multiple Sclerosis. *Frontiers in Neurology*, *13*. https://doi.org/10.3389/fneur.2022.802516
Broscheid, K. C., Dettmers, C., Behrens, M., Wolff, W., Peters, A., Schega, L., Vieten, M., & Jöbges, M. (2023). Motor Performance Fatigability in MS. In I.-K. Penner (Ed.), *Fatigue in Multiple Sclerosis: Background, Clinic, Diagnostic, Therapy* (pp. 59-72). Springer International Publishing. https://doi.org/10.1007/978-3-031-13498-2_5
Callesen, J., Cattaneo, D., Brincks, J., Kjeldgaard Jørgensen, M. L., & Dalgas, U. (2020). How do resistance training and balance and motor control training affect gait performance and fatigue impact in people with multiple sclerosis? A randomized controlled multi-center study. *Multiple Sclerosis*, *26*(11), 1420-1432. https://doi.org/10.1177/1352458519865740
Carling, A., Forsberg, A., Gunnarsson, M., & Nilsagård, Y. (2017). CoDuSe group exercise programme improves balance and reduces falls in people with multiple sclerosis: A multi-centre, randomized, controlled pilot study. *Multiple Sclerosis*, *23*(10), 1394-1404. https://doi.org/10.1177/1352458516677591
Carling, A., Nilsagård, Y., & Forsberg, A. (2018). Balance exercise facilitates everyday life for people with multiple sclerosis: A qualitative study. *Physiotherapy Research International*, *23*(4), e1728. https://doi.org/10.1002/pri.1728
Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Reports*, *100*(2), 126-131.
Chaudhuri, A., & Behan, P. O. (2004). Fatigue in neurological disorders. *The Lancet*, *363*(9413), 978-988. https://doi.org/https://doi.org/10.1016/S0140-6736(04)15794-2
Chen, Y., Xu, S., Shen, J., Yang, H., Xu, W., Shao, M., & Pan, F. (2021). Effect of Exercise on Fatigue in Multiple Sclerosis Patients: A Network Meta-analysis. *International Journal of Sports Medicine*, *42*(14), 1250-1259. https://doi.org/10.1055/a-1524-1935
Claerbout, M., Gebara, B., Ilsbroukx, S., Verschueren, S., Peers, K., Van Asch, P., & Feys, P. (2012). Effects of 3 weeks' whole body vibration training on muscle strength and functional mobility in hospitalized persons with multiple sclerosis. *Multiple Sclerosis*, *18*(4), 498-505. https://doi.org/10.1177/1352458511423267
Claros-Salinas, D., Bratzke, D., Greitemann, G., Nickisch, N., Ochs, L., & Schröter, H. (2010). Fatigue-related diurnal variations of cognitive performance in multiple sclerosis and stroke patients. *Journal of the Neurological Sciences*, *295*(1-2), 75-81. https://doi.org/10.1016/j.jns.2010.04.018

Close, J., Vandercappellen, J., King, M., & Hobart, J. (2023). Measuring Fatigue in Multiple Sclerosis: There may be Trouble Ahead. *Neurol Ther*, *12*(5), 1649-1668. https://doi.org/10.1007/s40120-023-00501-9

Cohen, E. T., Karpatkin, H. I., DiCarrado, S., & Zervas, M. (2020). A clinical reasoning framework for fatigue for neurologic physical therapy. *Physical Therapy Reviews*, *25*(4), 271-282. https://doi.org/10.1080/10833196.2020.1834329

Cohen, E. T., Matsuda, P. N., Fritz, N. E., Allen, D. D., Yorke, A. M., Widener, G. L., Jewell, S. T., & Potter, K. (2023). Self-Report Measures of Fatigue for People With Multiple Sclerosis: A Systematic Review. *Journal of Neurologic Physical Therapy*. https://doi.org/10.1097/npt.0000000000000452

Czajkowski, S., Powell, L., Adler, N., Naar-King, S., Reynolds, K., Hunter, C., Laraia, B., Olster, D., Perna, F., Peterson, J., Boyington, J., & Charlson, M. (2015). From Ideas to Efficacy: The ORBIT Model for Developing Behavioral Treatments for Chronic Diseases. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association*, *34*. https://doi.org/10.1037/hea0000161

D'Hooghe, M., Van Gassen, G., Kos, D., Bouquiaux, O., Cambron, M., Decoo, D., Lysandropoulos, A., Van Wijmeersch, B., Willekens, B., Penner, I. K., & Nagels, G. (2018). Improving fatigue in multiple sclerosis by smartphone-supported energy management: The MS TeleCoach feasibility study. *Multiple Sclerosis and Related Disorders*, *22*, 90-96. https://doi.org/10.1016/j.msard.2018.03.020

Dalgas, U., Hvid, L. G., Kwakkel, G., Motl, R. W., de Groot, V., Feys, P., Op't Eijnde, B., Coote, S., Beckerman, H., Pfeifer, K., Streber, R., Peters, S., Riemann-Lorenz, K., Rosenkranz, S. C., Centonze, D., Van Asch, P., Bansi, J., Sandroff, B. M., Pilutti, L. A., . . . Heesen, C. (2020). Moving exercise research in multiple sclerosis forward (the MoXFo initiative): Developing consensus statements for research. *Multiple Sclerosis*, *26*(11), 1303-1308. https://doi.org/10.1177/1352458520910360

Dalgas, U., Langeskov-Christensen, M., Stenager, E., Riemenschneider, M., & Hvid, L. G. (2019). Exercise as Medicine in Multiple Sclerosis—Time for a Paradigm Shift: Preventive, Symptomatic, and Disease-Modifying Aspects and Perspectives. *Current Neurology and Neuroscience Reports*, *19*(11), 88. https://doi.org/10.1007/s11910-019-1002-3

Dalgas, U., Riemenschneider, M., Gold, S. M., Kalron, A., Beckerman, H., de Groot, V., Dennett, R., Edwards, T., Pilutti, L. A., & Freeman, J. (2023). The MoXFo initiative - study design: Considerations related to study design and methodology in exercise research for people with multiple sclerosis. *Multiple Sclerosis*, *29*(13), 1561-1568. https://doi.org/10.1177/13524585231204456

Dantzer, R., Heijnen, C. J., Kavelaars, A., Laye, S., & Capuron, L. (2014). The neuroimmune basis of fatigue. *Trends in Neurosciences*, *37*(1), 39-46. https://doi.org/10.1016/j.tins.2013.10.003

das Nair, R., de Groot, V., & Freeman, J. (2019). Beyond current research practice: Methodological considerations in MS rehabilitation research (is designing the perfect rehabilitation trial the Holy Grail or a Gordian knot?). *Multiple Sclerosis*, *25*(10), 1337-1347. https://doi.org/10.1177/1352458519858271

Dennett, R., Madsen, L. T., Connolly, L., Hosking, J., Dalgas, U., & Freeman, J. (2020). Adherence and drop-out in randomized controlled trials of exercise interventions in people with multiple sclerosis: A systematic review and meta-

analyses. *Multiple Sclerosis and Related Disorders*, *43*, 102169. https://doi.org/10.1016/j.msard.2020.102169
Dettmers, C., Marchione, S., Weimer-Jaekel, A., Godde, B., & Joebges, M. (2021). Cognitive Fatigability, not Fatigue predicts employment status in patients with MS three months after rehabilitation. *Multiple Sclerosis and Related Disorders*, *56*, 103215. https://doi.org/10.1016/j.msard.2021.103215
Dettmers, C., Sulzmann, M., Ruchay-Plössl, A., Gütler, R., & Vieten, M. (2009). Endurance exercise improves walking distance in MS patients with fatigue. *Acta Neurologica Scandinavica*, *120*(4), 251-257. https://doi.org/10.1111/j.1600-0404.2008.01152.x
Donath, L., van Dieen, J., & Faude, O. (2016). Exercise-Based Fall Prevention in the Elderly: What About Agility? *Sports Medicine*, *46*(2), 143-149. https://doi.org/10.1007/s40279-015-0389-5
Drebinger, D., Rasche, L., Kroneberg, D., Althoff, P., Bellmann-Strobl, J., Weygandt, M., Paul, F., Brandt, A. U., & Schmitz-Hübsch, T. (2020). Association Between Fatigue and Motor Exertion in Patients With Multiple Sclerosis-a Prospective Study. *Frontiers in Neurology*, *11*, 208. https://doi.org/10.3389/fneur.2020.00208
Eldridge, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L., & Lancaster, G. A. (2016). CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*, *355*, i5239. https://doi.org/10.1136/bmj.i5239
Englund, S., Piehl, F., & Kierkegaard, M. (2022). High-intensity resistance training in people with multiple sclerosis experiencing fatigue: A randomised controlled trial. *Multiple Sclerosis and Related Disorders*, *68*, 104106. https://doi.org/10.1016/j.msard.2022.104106
Enoka, R. M., Almuklass, A. M., Alenazy, M., Alvarez, E., & Duchateau, J. (2021). Distinguishing between Fatigue and Fatigability in Multiple Sclerosis. *Neurorehabilitation and Neural Repair*, *35*(11), 960-973. https://doi.org/10.1177/15459683211046257
Enoka, R. M., & Duchateau, J. (2016). Translating Fatigue to Human Performance. *Medicine and Science in Sports and Exercise*, *48*(11), 2228-2238. https://doi.org/10.1249/mss.0000000000000929
Feinstein, A., Amato, M. P., Brichetto, G., Chataway, J., Chiaravalloti, N. D., Cutter, G., Dalgas, U., DeLuca, J., Farrell, R., Feys, P., Filippi, M., Freeman, J., Inglese, M., Meza, C., Motl, R. W., Rocca, M. A., Sandroff, B. M., & Salter, A. (2023). Cognitive rehabilitation and aerobic exercise for cognitive impairment in people with progressive multiple sclerosis (CogEx): a randomised, blinded, sham-controlled trial. *Lancet Neurology*, *22*(10), 912-924. https://doi.org/10.1016/s1474-4422(23)00280-6
Filippi, M., Krähenmann, R., & Fissler, P. (2022). The Link Between Energy-Related Sensations and Metabolism: Implications for Treating Fatigue. *Frontiers in Psychology*, *13*, 920556. https://doi.org/10.3389/fpsyg.2022.920556
Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., & Schlech, W. F. (1994). Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clinical Infectious Diseases*, *18 Suppl 1*, S79-83. https://doi.org/10.1093/clinids/18.supplement_1.s79
Geddes, E. L., Costello, E., Raivel, K., & Wilson, R. (2009). The effects of a twelve-week home walking program on cardiovascular parameters and fatigue

perception of individuals with multiple sclerosis: a pilot study. *Cardiopulmonary Physical Therapy Journal*, *20*(1), 5-12.
Ghaidar, D., Sippel, A., Riemann-Lorenz, K., Kofahl, C., Morrison, R., Kleiter, I., Schmidt, S., Dettmers, C., Schulz, H., & Heesen, C. (2022). Experiences of persons with multiple sclerosis with rehabilitation—a qualitative interview study. *BMC Health Services Research*, *22*(1), 770. https://doi.org/10.1186/s12913-022-08150-8
Gonzalez Campo, C., Salamone, P. C., Rodríguez-Arriagada, N., Richter, F., Herrera, E., Bruno, D., Pagani Cassara, F., Sinay, V., García, A. M., Ibáñez, A., & Sedeño, L. (2019). Fatigue in multiple sclerosis is associated with multimodal interoceptive abnormalities. *Multiple Sclerosis Journal*, *26*(14), 1845-1853. https://doi.org/10.1177/1352458519888881
Haddad, M., Stylianides, G., Djaoui, L., Dellal, A., & Chamari, K. (2017). Session-RPE Method for Training Load Monitoring: Validity, Ecological Usefulness, and Influencing Factors. *Frontiers in Neuroscience*, *11*, 612. https://doi.org/10.3389/fnins.2017.00612
Hanken, K., Eling, P., & Hildebrandt, H. (2014). The representation of inflammatory signals in the brain - a model for subjective fatigue in multiple sclerosis. *Frontiers in Neurology*, *5*, 264. https://doi.org/10.3389/fneur.2014.00264
Harrison, A. M., das Nair, R., & Moss-Morris, R. (2017). Operationalising cognitive fatigability in multiple sclerosis: A Gordian knot that can be cut? *Multiple Sclerosis*, *23*(13), 1682-1696. https://doi.org/10.1177/1352458516681862
Harrison, A. M., Safari, R., Mercer, T., Picariello, F., van der Linden, M. L., White, C., Moss-Morris, R., & Norton, S. (2021). Which exercise and behavioural interventions show most promise for treating fatigue in multiple sclerosis? A network meta-analysis. *Multiple Sclerosis*, *27*(11), 1657-1678. https://doi.org/10.1177/1352458521996002
Hebert, J. R., & Corboy, J. R. (2013). The association between multiple sclerosis-related fatigue and balance as a function of central sensory integration. *Gait and Posture*, *38*(1), 37-42. https://doi.org/10.1016/j.gaitpost.2012.10.015
Hebert, J. R., Corboy, J. R., Manago, M. M., & Schenkman, M. (2011). Effects of vestibular rehabilitation on multiple sclerosis-related fatigue and upright postural control: a randomized controlled trial. *Physical Therapy*, *91*(8), 1166-1183. https://doi.org/10.2522/ptj.20100399
Hebert, J. R., Corboy, J. R., Vollmer, T., Forster, J. E., & Schenkman, M. (2018). Efficacy of Balance and Eye-Movement Exercises for Persons With Multiple Sclerosis (BEEMS). *Neurology*, *90*(9), e797-e807. https://doi.org/10.1212/WNL.0000000000005013
Hecksteden, A., Faude, O., Meyer, T., & Donath, L. (2018). How to Construct, Conduct and Analyze an Exercise Training Study? *Frontiers in Physiology*, *9*, 1007. https://doi.org/10.3389/fphys.2018.01007
Heine, M., Hoogervorst, E. L., Hacking, H. G., Verschuren, O., & Kwakkel, G. (2014). Validity of maximal exercise testing in people with multiple sclerosis and low to moderate levels of disability. *Physical Therapy*, *94*(8), 1168-1175. https://doi.org/10.2522/ptj.20130418
Heine, M., van de Port, I., Rietberg, M. B., van Wegen, E. E., & Kwakkel, G. (2015). Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database of Systematic Reviews*, *2015*(9), Cd009956. https://doi.org/10.1002/14651858.CD009956.pub2

Heine, M., Verschuren, O., Hoogervorst, E. L., van Munster, E., Hacking, H. G., Visser-Meily, A., Twisk, J. W., Beckerman, H., de Groot, V., & Kwakkel, G. (2017). Does aerobic training alleviate fatigue and improve societal participation in patients with multiple sclerosis? A randomized controlled trial. *Multiple Sclerosis*, *23*(11), 1517-1526. https://doi.org/10.1177/1352458517696596

Horton, S., MacDonald, D. J., Erickson, K., & Dionigi, R. A. (2015). A qualitative investigation of exercising with MS and the impact on the spousal relationship. *European Review of Aging and Physical Activity*, *12*(1), 3. https://doi.org/10.1186/s11556-015-0148-5

Hubbard, A. L., Golla, H., & Lausberg, H. (2021). What's in a name? That which we call Multiple Sclerosis Fatigue. *Multiple Sclerosis*, *27*(7), 983-988. https://doi.org/10.1177/1352458520941481

Ibrahim, A. A., Flachenecker, F., Gaßner, H., Rothhammer, V., Klucken, J., Eskofier, B. M., & Kluge, F. (2022). Short inertial sensor-based gait tests reflect perceived state fatigue in multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *58*, 103519. https://doi.org/10.1016/j.msard.2022.103519

Ibrahim, A. A., Küderle, A., Gaßner, H., Klucken, J., Eskofier, B. M., & Kluge, F. (2020). Inertial sensor-based gait parameters reflect patient-reported fatigue in multiple sclerosis. *Journal of Neuroengineering and Rehabilitation*, *17*(1), 165-165. https://doi.org/10.1186/s12984-020-00798-9

Kalb, R., Brown, T. R., Coote, S., Costello, K., Dalgas, U., Garmon, E., Giesser, B., Halper, J., Karpatkin, H., Keller, J., Ng, A. V., Pilutti, L. A., Rohrig, A., Van Asch, P., Zackowski, K., & Motl, R. W. (2020). Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. *Multiple Sclerosis*, *26*(12), 1459-1469. https://doi.org/10.1177/1352458520915629

Klaren, R. E., Sandroff, B. M., Fernhall, B., & Motl, R. W. (2016). Comprehensive Profile of Cardiopulmonary Exercise Testing in Ambulatory Persons with Multiple Sclerosis. *Sports Medicine*, *46*(9), 1365-1379. https://doi.org/10.1007/s40279-016-0472-6

Kluger, B. M., Krupp, L. B., & Enoka, R. M. (2013). Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology*, *80*(4), 409-416. https://doi.org/10.1212/WNL.0b013e31827f07be

Kobelt, G., Langdon, D., & Jönsson, L. (2019). The effect of self-assessed fatigue and subjective cognitive impairment on work capacity: The case of multiple sclerosis. *Multiple Sclerosis*, *25*(5), 740-749. https://doi.org/10.1177/1352458518769837

Kos, D., Kerckhofs, E., Nagels, G., D'hooghe, M. B., & Ilsbroukx, S. (2008). Origin of Fatigue in Multiple Sclerosis: Review of the Literature. *Neurorehabilitation and Neural Repair*, *22*(1), 91-100. https://doi.org/10.1177/1545968306298934

Koseoglu, B. F., Gokkaya, N. K. O., Ergun, U., Inan, L., & Yesiltepe, E. (2006). Cardiopulmonary and metabolic functions, aerobic capacity, fatigue and quality of life in patients with multiple sclerosis. *Acta Neurologica Scandinavica*, *114*(4), 261-267. https://doi.org/https://doi.org/10.1111/j.1600-0404.2006.00598.x

Krieger, S. C., & Sumowski, J. F. (2020). Toward biologically meaningful categories of MS-related fatigue. *Multiple Sclerosis Journal*, *26*(6), 620-621. https://doi.org/10.1177/1352458520901705

Krupp, L. B. (2004). *Fatigue in Multiple Sclerosis: A Guide to Diagnosis and Management*. Springer Publishing Company. https://books.google.de/books?id=tDdPivTvikAC

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*, *46*(10), 1121-1123. https://doi.org/10.1001/archneur.1989.00520460115022

Kuppuswamy, A. (2022). The Neurobiology of Pathological Fatigue: New Models, New Questions. *Neuroscientist*, *28*(3), 238-253. https://doi.org/10.1177/1073858420985447

Kuppuswamy, A. (2023). Role of selective attention in fatigue in neurological disorders. *European Journal of Neurology*, *30*(5), 1453-1458. https://doi.org/10.1111/ene.15739

Langeskov-Christensen, M., Bisson, E. J., Finlayson, M. L., & Dalgas, U. (2017). Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: A scoping review. *Journal of the Neurological Sciences*, *373*, 307-320. https://doi.org/10.1016/j.jns.2017.01.002

Langeskov-Christensen, M., Hvid, L. G., Jensen, H. B., Nielsen, H. H., Petersen, T., Stenager, E., & Dalgas, U. (2022). Efficacy of high-intensity aerobic exercise on common multiple sclerosis symptoms. *Acta Neurologica Scandinavica*, *145*(2), 229-238. https://doi.org/10.1111/ane.13540

Larsson, P., Bidonde, J., Olsen, U., Gay, C. L., Lerdal, A., Ursin, M., Mead, G. E., & Edvardsen, E. (2023). Association of post-stroke fatigue with physical activity and physical fitness: A systematic review and meta-analysis. *International Journal of Stroke*, *18*(9), 1063-1070. https://doi.org/10.1177/17474930231152132

Learmonth, Y., Marshall-McKenna, R., Paul, L., Mattison, P., & Miller, L. (2012). A qualitative exploration of the impact of a 12-week group exercise class for those moderately affected with multiple sclerosis. *Disability and Rehabilitation*, *35*. https://doi.org/10.3109/09638288.2012.688922

Learmonth, Y. C., Kinnett-Hopkins, D., & Motl, R. W. (2019). Capitalising on the opinions of persons with multiple sclerosis to inform the main trial – participant opinions from participation in a feasibility study, a qualitative extension study. *Disability and Rehabilitation*, *41*(25), 3071-3078. https://doi.org/10.1080/09638288.2018.1490823

Learmonth, Y. C., & Motl, R. W. (2016). Physical activity and exercise training in multiple sclerosis: a review and content analysis of qualitative research identifying perceived determinants and consequences. *Disability and Rehabilitation*, *38*(13), 1227-1242. https://doi.org/10.3109/09638288.2015.1077397

Learmonth, Y. C., & Motl, R. W. (2018). Important considerations for feasibility studies in physical activity research involving persons with multiple sclerosis: a scoping systematic review and case study. *Pilot Feasibility Stud*, *4*, 1. https://doi.org/10.1186/s40814-017-0145-8

Leon, A. C., Davis, L. L., & Kraemer, H. C. (2011). The role and interpretation of pilot studies in clinical research. *Journal of psychiatric research*, *45*(5), 626-629. https://doi.org/10.1016/j.jpsychires.2010.10.008

Manjaly, Z. M., Harrison, N. A., Critchley, H. D., Do, C. T., Stefanics, G., Wenderoth, N., Lutterotti, A., Muller, A., & Stephan, K. E. (2019). Pathophysiological and

cognitive mechanisms of fatigue in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, *90*(6), 642-651. https://doi.org/10.1136/jnnp-2018-320050

Marchesi, O., Vizzino, C., Filippi, M., & Rocca, M. A. (2022). Current perspectives on the diagnosis and management of fatigue in multiple sclerosis. *Expert Review of Neurotherapeutics*, *22*(8), 681-693. https://doi.org/10.1080/14737175.2022.2106854

Mills, R. J., & Young, C. A. (2008). A medical definition of fatigue in multiple sclerosis. *QJM*, *101*(1), 49-60. https://doi.org/10.1093/qjmed/hcm122

Mills, R. J., Young, C. A., Pallant, J. F., & Tennant, A. (2010). Development of a patient reported outcome scale for fatigue in multiple sclerosis: The Neurological Fatigue Index (NFI-MS). *Health Qual Life Outcomes*, *8*, 22. https://doi.org/10.1186/1477-7525-8-22

Moss-Morris, R., Harrison, A. M., Safari, R., Norton, S., van der Linden, M. L., Picariello, F., Thomas, S., White, C., & Mercer, T. (2021). Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis. *Behaviour Research and Therapy*, *137*, 103464. https://doi.org/10.1016/j.brat.2019.103464

Mostert, S., & Kesselring, J. (2002). Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. *Multiple Sclerosis*, *8*(2), 161-168. https://doi.org/10.1191/1352458502ms779oa

Motl, R. W., Casey, B., Learmonth, Y. C., Latimer-Cheung, A., Kinnett-Hopkins, D. L., Marck, C. H., Carl, J., Pfeifer, K., Riemann-Lorenz, K., Heesen, C., & Coote, S. (2023). The MoXFo initiative - adherence: Exercise adherence, compliance and sustainability among people with multiple sclerosis: An overview and roadmap for research. *Multiple Sclerosis*, *29*(13), 1595-1603. https://doi.org/10.1177/13524585231204446

Motl, R. W., Fernhall, B., McCully, K. K., Ng, A., Plow, M., Pilutti, L. A., Sandroff, B. M., & Zackowski, K. M. (2022). Lessons learned from clinical trials of exercise and physical activity in people with MS - guidance for improving the quality of future research. *Multiple Sclerosis and Related Disorders*, *68*, 104088. https://doi.org/10.1016/j.msard.2022.104088

Motl, R. W., Sandroff, B. M., Kwakkel, G., Dalgas, U., Feinstein, A., Heesen, C., Feys, P., & Thompson, A. J. (2017). Exercise in patients with multiple sclerosis. *The Lancet Neurology*, *16*(10), 848-856. https://doi.org/10.1016/s1474-4422(17)30281-8

Multiple Sclerosis Council. (1998). *Fatigue and Multiple Sclerosis: Evidence-based Management Strategies for Fatigue in Multiple Sclerosis*. Paralyzed Veterans of America. https://books.google.de/books?id=zo_7MAAACAAJ

Multiple Sclerosis International Federation. (2020). *Atlas of MS - 3rd Edition*. Retrieved 10. July from atlasofms.org

Neumann, M., Sterr, A., Claros-Salinas, D., Gütler, R., Ulrich, R., & Dettmers, C. (2014). Modulation of alertness by sustained cognitive demand in MS as surrogate measure of fatigue and fatigability. *Journal of the Neurological Sciences*, *340*(1-2), 178-182. https://doi.org/10.1016/j.jns.2014.03.024

Nourbakhsh, B. (2021). Serious side effects of amantadine: Rethinking the benefits and risks of medications for MS fatigue. *Multiple Sclerosis Journal*, *27*(14), 2290-2290. https://doi.org/10.1177/13524585211042341

Nourbakhsh, B., Revirajan, N., Morris, B., Cordano, C., Creasman, J., Manguinao, M., Krysko, K., Rutatangwa, A., Auvray, C., Aljarallah, S., Jin, C., Mowry, E., McCulloch, C., & Waubant, E. (2021). Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. *Lancet Neurology*, *20*(1), 38-48. https://doi.org/10.1016/s1474-4422(20)30354-9

O'Cathain, A., Hoddinott, P., Lewin, S., Thomas, K. J., Young, B., Adamson, J., Jansen, Y. J., Mills, N., Moore, G., & Donovan, J. L. (2015). Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. *Pilot Feasibility Stud*, *1*, 32. https://doi.org/10.1186/s40814-015-0026-y

Oyake, K., Baba, Y., Suda, Y., Murayama, J., Mochida, A., Ito, Y., Abe, H., Kondo, K., Otaka, Y., & Momose, K. (2021). Cardiorespiratory responses to exercise related to post-stroke fatigue severity. *Scientific Reports*, *11*(1), 12780. https://doi.org/10.1038/s41598-021-92127-w

Page, P., Hoogenboom, B., & Voight, M. (2017). Improving the reporting of therapeutic exercise interventions in rehabilitation research. *International Journal of Sports Physical Therapy*, *12*(2), 297-304.

Palotai, M., Cavallari, M., Healy, B. C., & Guttmann, C. R. (2020). A novel classification of fatigue in multiple sclerosis based on longitudinal assessments. *Multiple Sclerosis Journal*, *26*(6), 725-734. https://doi.org/10.1177/1352458519898112

Palotai, M., & Guttmann, C. R. (2020). Brain anatomical correlates of fatigue in multiple sclerosis. *Multiple Sclerosis Journal*, *26*(7), 751-764. https://doi.org/10.1177/1352458519876032

Patejdl, R., & Zettl, U. K. (2022). The pathophysiology of motor fatigue and fatigability in multiple sclerosis. *Frontiers in Neurology*, *13*, 891415. https://doi.org/10.3389/fneur.2022.891415

Patt, N., Kupjetz, M., Kool, J., Hersche, R., Oberste, M., Joisten, N., Gonzenbach, R., Nigg, C. R., Zimmer, P., & Bansi, J. (2023). Effects of inpatient energy management education and high-intensity interval training on health-related quality of life in persons with multiple sclerosis: A randomized controlled superiority trial with six-month follow-up. *Multiple Sclerosis and Related Disorders*, *78*, 104929. https://doi.org/10.1016/j.msard.2023.104929

Paul, F. (2023). Pathophysiology and Differentiation from Other Symptoms and Diseasess. In I.-K. Penner (Ed.), *Fatigue in Multiple Sclerosis: Background, Clinic, Diagnostic, Therapy* (pp. 27-39). Springer International Publishing. https://doi.org/10.1007/978-3-031-13498-2_3

Penner, I. K., Flachenecker, P., & Meissner, H. (2023). Cognitive Fatigue. In I. K. Penner (Ed.), *Fatigue in Multipe Sclerosis: Background, Clinic, Diagnostic, Therapy* (1 ed.). Springer Nature. https://doi.org/https://doi.org/10.1007/978-3-031-13498-2

Penner, I. K., & Paul, F. (2017). Fatigue as a symptom or comorbidity of neurological diseases. *Nature Reviews: Neurology*, *13*(11), 662-675. https://doi.org/10.1038/nrneurol.2017.117

Petajan, J. H., Gappmaier, E., White, A. T., Spencer, M. K., Mino, L., & Hicks, R. W. (1996). Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Annals of Neurology*, *39*(4), 432-441. https://doi.org/10.1002/ana.410390405

Pilutti, L. A., Platta, M. E., Motl, R. W., & Latimer-Cheung, A. E. (2014). The safety of exercise training in multiple sclerosis: a systematic review. *Journal of the Neurological Sciences*, *343*(1-2), 3-7. https://doi.org/10.1016/j.jns.2014.05.016

Pilutti, L. A., Sandroff, B. M., Klaren, R. E., Learmonth, Y. C., Platta, M. E., Hubbard, E. A., Stratton, M., & Motl, R. W. (2015). Physical Fitness Assessment Across the Disability Spectrum in Persons With Multiple Sclerosis: A Comparison of Testing Modalities. *Journal of Neurologic Physical Therapy*, *39*(4), 241-249. https://doi.org/10.1097/npt.0000000000000099

Pinarello, C., Elmers, J., Inojosa, H., Beste, C., & Ziemssen, T. (2023). Management of multiple sclerosis fatigue in the digital age: from assessment to treatment. *Frontiers in Neuroscience*, *17*, 1231321. https://doi.org/10.3389/fnins.2023.1231321

Powell, D. J. H., Liossi, C., Schlotz, W., & Moss-Morris, R. (2017). Tracking daily fatigue fluctuations in multiple sclerosis: ecological momentary assessment provides unique insights. *Journal of Behavioral Medicine*, *40*(5), 772-783. https://doi.org/10.1007/s10865-017-9840-4

Prosperini, L., & Castelli, L. (2018). Spotlight on postural control in patients with multiple sclerosis. *Degener Neurol Neuromuscul Dis*, *8*, 25-34. https://doi.org/10.2147/dnnd.S135755

Pust, G. E. A., Pottgen, J., Randerath, J., Lau, S., Heesen, C., Gold, S. M., & Penner, I. K. (2019). In search of distinct MS-related fatigue subtypes: results from a multi-cohort analysis in 1.403 MS patients. *Journal of Neurology*, *266*(7), 1663-1673. https://doi.org/10.1007/s00415-019-09311-2

Rademacher, A., Joisten, N., Proschinger, S., Bloch, W., Gonzenbach, R., Kool, J., Langdon, D., Bansi, J., & Zimmer, P. (2020). Cognitive Impairment Impacts Exercise Effects on Cognition in Multiple Sclerosis. *Frontiers in Neurology*, *11*, 619500. https://doi.org/10.3389/fneur.2020.619500

Riemenschneider, M., Hvid, L. G., Petersen, T., Stenager, E., & Dalgas, U. (2023). Exercise Therapy in Early Multiple Sclerosis Improves Physical Function But Not Cognition: Secondary Analyses From a Randomized Controlled Trial. *Neurorehabilitation and Neural Repair*, *37*(5), 288-297. https://doi.org/10.1177/15459683231159659

Riley, W. T., Rothrock, N., Bruce, B., Christodolou, C., Cook, K., Hahn, E. A., & Cella, D. (2010). Patient-reported outcomes measurement information system (PROMIS) domain names and definitions revisions: further evaluation of content validity in IRT-derived item banks. *Quality of Life Research*, *19*(9), 1311-1321. https://doi.org/10.1007/s11136-010-9694-5

Ritvo, P. G., Fischer, J. S., Miller, D. M., Andrews, H., Paty, D., & LaRocca, N. (1997). *Multiple sclerosis quality of life inventory: a user's manual*. National Multiple Sclerosis Society.

Robinson, W. H., & Steinman, L. (2022). Epstein-Barr virus and multiple sclerosis. *Science*, *375*(6578), 264-265. https://doi.org/10.1126/science.abm7930

Rocca, M. A., Valsasina, P., Colombo, B., Martinelli, V., & Filippi, M. (2021). Cortico-subcortical functional connectivity modifications in fatigued multiple sclerosis patients treated with fampridine and amantadine. *European Journal of Neurology*, *28*(7), 2249-2258. https://doi.org/https://doi.org/10.1111/ene.14867

Rommer, P. S., Eichstadt, K., Ellenberger, D., Flachenecker, P., Friede, T., Haas, J., Kleinschnitz, C., Pohlau, D., Rienhoff, O., Stahmann, A., & Zettl, U. K. (2019).

Symptomatology and symptomatic treatment in multiple sclerosis: Results from a nationwide MS registry. *Multiple Sclerosis*, *25*(12), 1641-1652. https://doi.org/10.1177/1352458518799580
Rooney, S., McWilliam, G., Wood, L., Moffat, F., & Paul, L. (2022). Oxygen Cost of Walking in People With Multiple Sclerosis and Its Association With Fatigue: A Systematic Review and Meta-analysis. *Int J MS Care*, *24*(2), 74-80. https://doi.org/10.7224/1537-2073.2020-128
Rooney, S., Wood, L., Moffat, F., & Paul, L. (2019). Is Fatigue Associated With Aerobic Capacity and Muscle Strength in People With Multiple Sclerosis: A Systematic Review and Meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *100*(11), 2193-2204. https://doi.org/10.1016/j.apmr.2019.06.014
Rouault, M., Pereira, I., Galioulline, H., Fleming, S. M., Stephan, K. E., & Manjaly, Z. M. (2023). Interoceptive and metacognitive facets of fatigue in multiple sclerosis. *European Journal of Neuroscience*. https://doi.org/10.1111/ejn.16048
Russell, N., Gallagher, S., Msetfi, R. M., Hayes, S., Motl, R. W., & Coote, S. (2022). Experiences of people with multiple sclerosis participating in a social cognitive behavior change physical activity intervention. *Physiotherapy Theory and Practice*, 1-9. https://doi.org/10.1080/09593985.2022.2030828
Sander, C., Voelter, H.-U., Schlake, H.-P., Eling, P., & Hildebrandt, H. (2017). Assessment of Fatigue in Multiple Sclerosis. *Neurology International Open*, *1*(02), E79-E85. https://doi.org/10.1055/s-0043-104752
Sandroff, B. M., & DeLuca, J. (2020). Will behavioral treatments for cognitive impairment in multiple sclerosis become standards-of-care? *International Journal of Psychophysiology*, *154*, 67-79. https://doi.org/https://doi.org/10.1016/j.ijpsycho.2019.02.010
Santinelli, F. B., Ramari, C., Poncelet, M., Severijns, D., Kos, D., Pau, M., Kalron, A., Meyns, P., & Feys, P. (2024). Between-Day Reliability of the Gait Characteristics and Their Changes During the 6-Minute Walking Test in People With Multiple Sclerosis. *Neurorehabilitation and Neural Repair*, *38*(2), 75-86. https://doi.org/10.1177/15459683231222412
Schlagheck, M. L., Bansi, J., Wenzel, C., Kuzdas-Sallaberger, M., Kiesl, D., Gonzenbach, R., & Zimmer, P. (2023). Complexity and pitfalls in maximal exercise testing for persons with multiple sclerosis. *European Journal of Neurology*, *30*(9), 2726-2735. https://doi.org/10.1111/ene.15875
Schlagheck, M. L., Joisten, N., Walzik, D., Wolf, F., Neil-Sztramko, S. E., Bansi, J., Rademacher, A., & Zimmer, P. (2021). Systematic Review of Exercise Studies in Persons with Multiple Sclerosis: Exploring the Quality of Interventions According to the Principles of Exercise Training. *Neurol Ther*, *10*(2), 585-607. https://doi.org/10.1007/s40120-021-00274-z
Seow, T. X. F., Rouault, M., Gillan, C. M., & Fleming, S. M. (2021). How Local and Global Metacognition Shape Mental Health. *Biological Psychiatry*, *90*(7), 436-446. https://doi.org/10.1016/j.biopsych.2021.05.013
Sim, J. (2019). Should treatment effects be estimated in pilot and feasibility studies? *Pilot Feasibility Stud*, *5*, 107. https://doi.org/10.1186/s40814-019-0493-7
Skivington, K., Matthews, L., Simpson, S. A., Craig, P., Baird, J., Blazeby, J. M., Boyd, K. A., Craig, N., French, D. P., McIntosh, E., Petticrew, M., Rycroft-Malone, J., White, M., & Moore, L. (2021). A new framework for developing

and evaluating complex interventions: update of Medical Research Council guidance. *BMJ*, *374*, n2061. https://doi.org/10.1136/bmj.n2061
Smedal, T., Myhr, K. M., Aarseth, J. H., Gjelsvik, B., Beiske, A. G., Glad, S. B., & Strand, L. I. (2011). The influence of warm versus cold climate on the effect of physiotherapy in multiple sclerosis. *Acta Neurologica Scandinavica*, *124*(1), 45-52. https://doi.org/10.1111/j.1600-0404.2010.01407.x
Smith, M., Barker, R., Williams, G., Carr, J., & Gunnarsson, R. (2020). The effect of exercise on high-level mobility in individuals with neurodegenerative disease: a systematic literature review. *Physiotherapy*, *106*, 174-193. https://doi.org/10.1016/j.physio.2019.04.003
Snook, E. M., & Motl, R. W. (2009). Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. *Neurorehabilitation and Neural Repair*, *23*(2), 108-116. https://doi.org/10.1177/1545968308320641
Sparasci, D., Gobbi, C., Castelnovo, A., Riccitelli, G. C., Disanto, G., Zecca, C., & Manconi, M. (2022). Fatigue, sleepiness and depression in multiple sclerosis: defining the overlaps for a better phenotyping. *Journal of Neurology*, *269*(9), 4961-4971. https://doi.org/10.1007/s00415-022-11143-6
Stephan, K. E., Manjaly, Z. M., Mathys, C. D., Weber, L. A., Paliwal, S., Gard, T., Tittgemeyer, M., Fleming, S. M., Haker, H., Seth, A. K., & Petzschner, F. H. (2016). Allostatic Self-efficacy: A Metacognitive Theory of Dyshomeostasis-Induced Fatigue and Depression. *Frontiers in Human Neuroscience*, *10*, 550. https://doi.org/10.3389/fnhum.2016.00550
Straudi, S., Martinuzzi, C., Pavarelli, C., Sabbagh Charabati, A., Benedetti, M. G., Foti, C., Bonato, M., Zancato, E., & Basaglia, N. (2014). A task-oriented circuit training in multiple sclerosis: a feasibility study. *BMC Neurology*, *14*(1), 124. https://doi.org/10.1186/1471-2377-14-124
Tang, W. K., Lu, J. Y., Chen, Y. K., Mok, V. C., Ungvari, G. S., & Wong, K. S. (2010). Is fatigue associated with short-term health-related quality of life in stroke? *Archives of Physical Medicine and Rehabilitation*, *91*(10), 1511-1515. https://doi.org/10.1016/j.apmr.2010.06.026
Taul-Madsen, L., Connolly, L., Dennett, R., Freeman, J., Dalgas, U., & Hvid, L. G. (2021). Is Aerobic or Resistance Training the Most Effective Exercise Modality for Improving Lower Extremity Physical Function and Perceived Fatigue in People With Multiple Sclerosis? A Systematic Review and Meta-analysis. *Archives of Physical Medicine and Rehabilitation*. https://doi.org/10.1016/j.apmr.2021.03.026
Terwee, C. B., Prinsen, C. A. C., Chiarotto, A., Westerman, M. J., Patrick, D. L., Alonso, J., Bouter, L. M., de Vet, H. C. W., & Mokkink, L. B. (2018). COSMIN methodology for evaluating the content validity of patient-reported outcome measures: a Delphi study. *Quality of Life Research*, *27*(5), 1159-1170. https://doi.org/10.1007/s11136-018-1829-0
Thabane, L., Ma, J., Chu, R., Cheng, J., Ismaila, A., Rios, L. P., Robson, R., Thabane, M., Giangregorio, L., & Goldsmith, C. H. (2010). A tutorial on pilot studies: the what, why and how. *BMC Medical Research Methodology*, *10*, 1. https://doi.org/10.1186/1471-2288-10-1
Theunissen, K., Plasqui, G., Boonen, A., Timmermans, A., Meyns, P., Feys, P., & Meijer, K. (2023). The increased perceived exertion during the six minute walking test is not accompanied by changes in cost of walking, gait characteristics or muscle fatigue in persons with multiple sclerosis. *Multiple*

Sclerosis and Related Disorders, *70*, 104479. https://doi.org/10.1016/j.msard.2022.104479

Thompson, A. J., Baranzini, S. E., Geurts, J., Hemmer, B., & Ciccarelli, O. (2018). Multiple sclerosis. *Lancet*, *391*(10130), 1622-1636. https://doi.org/10.1016/s0140-6736(18)30481-1

Torres-Costoso, A., Martínez-Vizcaíno, V., Reina-Gutiérrez, S., Álvarez-Bueno, C., Guzmán-Pavón, M. J., Pozuelo-Carrascosa, D. P., Fernández-Rodríguez, R., Sanchez-López, M., & Cavero-Redondo, I. (2022). Effect of Exercise on Fatigue in Multiple Sclerosis: A Network Meta-analysis Comparing Different Types of Exercise. *Archives of Physical Medicine and Rehabilitation*, *103*(5), 970-987.e918. https://doi.org/10.1016/j.apmr.2021.08.008

Valet, M., Stoquart, G., de Broglie, C., Francaux, M., & Lejeune, T. (2020). Simplified indices of exercise tolerance in patients with multiple sclerosis and healthy subjects: A case-control study. *Scandinavian Journal of Medicine and Science in Sports*, *30*(10), 1908-1917. https://doi.org/10.1111/sms.13756

Van Geel, F., Moumdjian, L., Lamers, I., Bielen, H., & Feys, P. (2020). Measuring walking-related performance fatigability in clinical practice: a systematic review. *European Journal of Physical and Rehabilitation Medicine*, *56*(1), 88-103. https://doi.org/10.23736/s1973-9087.19.05878-7

Van Geel, F., Veldkamp, R., Severijns, D., Dalgas, U., & Feys, P. (2020). Day-to-day reliability, agreement and discriminative validity of measuring walking-related performance fatigability in persons with multiple sclerosis. *Multiple Sclerosis*, *26*(13), 1785-1789. https://doi.org/10.1177/1352458519872465

Van Stan, J. H., Whyte, J., Duffy, J. R., Barkmeier-Kraemer, J. M., Doyle, P. B., Gherson, S., Kelchner, L., Muise, J., Petty, B., Roy, N., Stemple, J., Thibeault, S., & Tolejano, C. J. (2021). Rehabilitation Treatment Specification System: Methodology to Identify and Describe Unique Targets and Ingredients. *Archives of Physical Medicine and Rehabilitation*, *102*(3), 521-531. https://doi.org/10.1016/j.apmr.2020.09.383

Veauthier, C., Hasselmann, H., Gold, S. M., & Paul, F. (2016). The Berlin Treatment Algorithm: recommendations for tailored innovative therapeutic strategies for multiple sclerosis-related fatigue. *Epma j*, *7*(1), 25. https://doi.org/10.1186/s13167-016-0073-3

Venhorst, A., Micklewright, D., & Noakes, T. D. (2018). Perceived Fatigability: Utility of a Three-Dimensional Dynamical Systems Framework to Better Understand the Psychophysiological Regulation of Goal-Directed Exercise Behaviour. *Sports Medicine*, *48*(11), 2479-2495. https://doi.org/10.1007/s40279-018-0986-1

Ware, M., O'Connor, P., Bub, K., Backus, D., & McCully, K. (2022). The role of worry in exercise and physical activity behavior of people with multiple sclerosis. *Health Psychol Behav Med*, *10*(1), 786-805. https://doi.org/10.1080/21642850.2022.2112197

Wender, C. L. A., Manninen, M., & O'Connor, P. J. (2022). The Effect of Chronic Exercise on Energy and Fatigue States: A Systematic Review and Meta-Analysis of Randomized Trials. *Frontiers in Psychology*, *13*, 907637. https://doi.org/10.3389/fpsyg.2022.907637

Williams, G., Hill, B., Pallant, J. F., & Greenwood, K. (2012). Internal validity of the revised HiMAT for people with neurological conditions. *Clinical Rehabilitation*, *26*(8), 741-747. https://doi.org/10.1177/0269215511429163

Wolf, F., Eschweiler, M., Rademacher, A., & Zimmer, P. (2022). Multimodal Agility-Based Exercise Training for Persons With Multiple Sclerosis: A New Framework. *Neurorehabilitation and Neural Repair*, *36*(12), 777-787. https://doi.org/10.1177/15459683221131789

Wolf, F., Folkerts, A. K., Zimmer, P., & Nielsen, J. (2024). Experiences of fatigued persons with multiple sclerosis with multimodal agility-based exercise training and the ReFEx study protocol: a qualitative extension of a feasibility study. *BMJ Open*, *14*(2), e076333. https://doi.org/10.1136/bmjopen-2023-076333

Wolf, F., & Nielsen, J. (2022). *Influence of MS-fatigue questionnaire choice for identifying responders to treatment* 12th World Congress for Neurorehabilitation, Vienna. https://journals.sagepub.com/doi/abs/10.1177/15459683231159499

Wolf, F., Nielsen, J., Saliger, J., Hennecken, E., Eschweiler, M., Folkerts, A.-K., Karbe, H., & Zimmer, P. (2022). Randomised controlled pilot and feasibility study of multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve multiple sclerosis-related fatigue and fatigability during inpatient rehabilitation (ReFEx): study protocol. *BMJ Open*, *12*(9). https://doi.org/10.1136/bmjopen-2022-062160

Wolf, F., Nielsen, J., Saliger, J., Hennecken, E., Kröber, P., Eschweiler, M., Folkerts, A. K., Karbe, H., & Zimmer, P. (2023). Multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve multiple sclerosis-related fatigue and fatigability during inpatient rehabilitation: a randomized controlled pilot and feasibility study [ReFEx]. *BMC Neurology*, *23*(1), 388. https://doi.org/10.1186/s12883-023-03436-8

Wolf, F., Rademacher, A., Joisten, N., Proschinger, S., Schlagheck, M. L., Bloch, W., Gonzenbach, R., Kool, J., Bansi, J., & Zimmer, P. (2022). The aerobic capacity – fatigue relationship in persons with Multiple Sclerosis is not reproducible in a pooled analysis of two randomized controlled trials. *Multiple Sclerosis and Related Disorders*, *58*, 103476. https://doi.org/https://doi.org/10.1016/j.msard.2021.103476

Zimmer, P., Bloch, W., Schenk, A., Oberste, M., Riedel, S., Kool, J., Langdon, D., Dalgas, U., Kesselring, J., & Bansi, J. (2018). High-intensity interval exercise improves cognitive performance and reduces matrix metalloproteinases-2 serum levels in persons with multiple sclerosis: A randomized controlled trial. *Multiple Sclerosis*, *24*(12), 1635-1644. https://doi.org/10.1177/1352458517728342

8 Appendix (Full Text Publications)

Publication 1 could not be included in the electronic version of the dissertation:

Wolf, F., Rademacher, A., Joisten, N., Proschinger, S., Schlagheck, M. L., Bloch, W., Gonzenbach, R., Kool, J., Bansi, J., & Zimmer, P. (2022). The aerobic capacity – fatigue relationship in persons with Multiple Sclerosis is not reproducible in a pooled analysis of two randomized controlled trials. *Multiple Sclerosis and Related Disorders*, *58*, 103476. https://doi.org/https://doi.org/10.1016/j.msard.2021.103476

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Multimodal Agility-Based Exercise Training for Persons With Multiple Sclerosis: A New Framework

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Abstract

Introduction. Multimodal agility-based exercise training (MAT) has been described as a framework for fall prevention in the elderly but might also be a valuable concept for exercise training in persons with Multiple Sclerosis (pwMS). *The Problem.* Current recommendations advise pwMS to perform a multitude of different exercise training activities, as each of these has its separate evidence. However, pwMS struggle even more than the general population to be physically active. Additionally, Multiple Sclerosis often leads to co-occurring mobility and cognitive dysfunctions, for which simultaneous, time-efficient, and engaging training approaches are still limited in clinical practice and healthcare. *The solution.* The MAT framework has been developed to integratively improve cardiovascular, neuromuscular, and cognitive function by combining aspects of perception and orientation, change of direction, as well as stop-and-go patterns (ie, agility), in a group-training format. For pwMS, the MAT framework is conceptualized to include 3 Components: standing balance, dynamic balance (including functional leg strength), and agility-based exercises. Within these Components sensory, cognitive, and cardiovascular challenges can be adapted to individual needs. *Recommendations.* We recommend investigating multimodal exercise interventions that go beyond easily standardized, unimodal types of exercise (eg, aerobic or resistance exercise), which could allow for time-efficient training, targeting multiple frequent symptoms of persons with mild disability at once. MAT should be compared to unimodal approaches, regarding sensor-based gait outcomes, fatigue-related outcomes, cognition, as well as neuroprotective, and (supportive) disease-modifying effects.

Keywords

multiple sclerosis, agility, exercise, gait, balance

Introduction

Multimodal agility-based exercise training (MAT) refers to a framework aimed at integratively improving cardiovascular, neuromuscular, and cognitive function in a group-training format. "Agility-based" describes tasks, that require changes of direction, stop-and-go patterns, turns, and changing footwork strategies, with or without responding to a stimulus. The framework was first described by Donath et al[1] in the context of exercise-based fall prevention in the elderly. However, as discussed in this paper, several aspects make it valuable as a framework for exercise-based neurorehabilitation for persons with Multiple Sclerosis (pwMS).

Multiple Sclerosis (MS) is the most common, non-traumatic, neurological disorder among middle aged adults. Initially characterized as an inflammatory demyelinating disease of the central nervous system, neurodegenerative processes lead to progressive disability during later disease stages.[2] Importantly, the resulting lesions in the central nervous system often lead to co-occurring mobility and cognitive dysfunctions.[3]

Even though disease onset is most common in early adult life, pwMS fall more than older adults without MS.[2,4] Over 50% of pwMS fall once within 3 months, with falls occurring soon after disease onset and later increasing in

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frequency. Developing fear of falling can lead to decreased social participation and problems in the work environment, considering that many pwMS are in a working age.

Preceding falls, disease processes in MS lead to gait and balance deficits, along with muscle weakness, spasticity, impaired sensation, vestibular function, oculomotor, and visual impairments. This can also lead to limited walking distance, further aggravated by motor fatigability.[5]

However, there is also a high number of pwMS with only mild disability, demonstrating only subtle gait and balance deficits. According to the Reserve framework,[6] the best treatment for MS might be prevention of functional and structural decline. Aging plays a major role in a declining reserve and the development of a secondary progressive disease course, which entails marked increases in functional disability.[7] Thus, as described by others for drug treatments[7] and exercise,[8] actions should be taken early, that is, in patients that are typically younger, and with only mild functional disability. This "open window of opportunity" might be especially sensitive for the MAT framework that is discussed in this paper. As argued below, the MAT framework could provide multi-sensory challenges (eg, agility-like exercises, sensory, and cognitive challenges), resulting in central nervous system adaptations, that go beyond those elicited by "unimodal" approaches or traditional recommendations. Improving gait and balance as well as reestablishing high-level mobility functions (eg, running, jumping, agility-like functions)[9] could be regarded as the most proximal targets of MAT for pwMS, whereas improvement of central nervous system reserve would be the distal target.

By providing this conceptual basis of MAT for rehabilitation therapists working with pwMS, we want to facilitate the uptake of integrative exercise programs in clinical practice.

Problem

Prevalence of Subtle Gait and Balance Impairments in MS

Prevalence of gait and balance impairments in pwMS is high.[10] Gait impairments can be quantified via spatiotemporal gait characteristics (eg, gait speed, step length, cadence, stance phase etc.) measured using instrumented walkways, wireless inertial sensors, or 3D motion capture. A recent systematic review reported a positive linear relationship between spatiotemporal gait characteristics and disability (measured using the Expanded Disability Status Scale [EDSS]), as expected.[11] For example, according to the meta-regression, increasing from 2.0 to 3.0 on the 0 to 10 EDSS results in a reduction in comfortable or self-selected gait speed from 1.17 m/s (4.22 km/h) to 1.06 m/s (3.8 km/h). The meta-analysis also showed that being classified as a "faller" was significantly associated with slower gait speed. The authors further reported that individuals with low levels of disability had spatiotemporal gait characteristics very similar to the general population when walking in their comfortable gait speed. However, when instructed to walk as fast as possible for 6 minutes, persons with low EDSS (1.5-2.0) differed significantly from healthy controls in their mean gait speed, stride length, and stance phase time.[12] The use of technology has substantiated other subtle gait impairments. When looking at gait kinematics, pwMS with very mild disability (EDSS = 0.0-2.5) walk with less hip extension at toe-off and more hip flexion during swing than healthy controls.[13] Electromyography has also shown a decrease in gastrocnemius activity during walking over a 1-year period in pwMS with EDSS $\leq$ 3.0.[14] Taken together, technology-based measures have shown ample evidence of subtle gait impairments in persons with mild disability, which are not well quantified in routinely applied clinical tests.[15]

Similarly, several studies have detected subtle balance impairments using different devices, which are often neglected in clinical assessments, such as the EDSS.[16] For example, static posturography performed using a force plate showed significant differences between healthy controls and pwMS with EDSS 2.0 to 2.5 as well as EDSS 0.0 to 1.5 (which would be rated as no clinical disability with or without minimal signs of the disease).[17] Importantly, clinical assessments using more challenging tasks than conventional tests seem to better determine balance impairments in persons with low disability. In persons with a median EDSS of 1.0 dynamic balance during tandem walking on balance boards was worse compared to healthy controls.[18]

Several authors have also noted the influence of balance on gait performance.[4,11,13,18] Recently, Carpinella et al[19] showed that sensor-based outcomes recorded while walking with horizontal head turns (a task particularly challenging to maintain balance during walking) discriminated between healthy controls and "normal walking" pwMS (EDSS $\leq$ 2.5). This again draws a picture of subtle balance impairments in persons with low disability that can be "unmasked" by technology or more challenging tasks.[20]

There also is considerable evidence that cognition plays a primary role in balance, gait, and falls. A well described phenomenon is cognitive-motor interference, where a cognitive and a motor task interfere with each other when performed simultaneously.[21] Similarly, these types of dual-tasks have been reported to uncover deficits in balance via increased challenge in persons with clinically minimal balance and cognitive deficits.[21]

However, a recent study on cognitive-motor interference during gait did not find a dual-task condition (eg, subtracting sevens while stepping over obstacles) that was able to discriminate between healthy controls and pwMS, even though pwMS reported having more problems in dual-task situations in daily life.[22] Reasons for this might have been

the relatively short task duration of 60 seconds, potentially reducing the effects of fatigue, a small sample size, or type and difficulty of cognitive tasks.

Cognitive functions also play an important role in the construct of walking adaptability, which is necessary, when the complexity of the task exceeds the demands of basic stepping, such as uneven terrain, obstacles, turning, or negotiating a narrow path.[23] It also includes cognitive-motor dual-tasking while walking (eg, having a conversation while walking, scanning for an object while walking through a grocery store), but also motor-motor dual-tasking (eg, walking while throwing and catching). The concept of walking adaptability might comprise more aspects of real-life situations (including ambient demands, physical load, and time constrains) than highly standardized tasks mostly performed in MS trials on dual-task costs (of course, the downside of heightened ecological validity can be compromised reliability of assessments[23]). Unfortunately, the concept has been largely restricted to stroke research, so there is no data on differences in walking adaptability between healthy controls and pwMS.

As observable in this section, studies have applied different ranges of EDSS, when evaluating persons with "mild" disability. Currently, there is no clear definition of what constitutes mild disability in terms of EDSS, and the reported studies might have included persons with very different levels of "high-level mobility" (ie, mobility more advanced than independent level walking, such as running and jumping).[9] However, all ranges reported here have in common, that patients do not need an assistive device to ambulate and are mostly able to work full time.

Current Recommendations for Exercise Training in pwMS

Currently, authoritative recommendations for exercise training in pwMS with mild impairments (classified here as EDSS 0.0-4.5) include aerobic, resistance, flexibility (not discussed here), and neuromotor exercise.[24] In the following, we will determine aspects of these recommendations and current clinical practice that might benefit from a MAT framework.

First, some aspects could be improved with the integration of sensory (ie, visual, somatosensory, vestibular), and cognitive challenges. Aerobic exercise has been increasingly studied as a form of disease-modifying therapy for pwMS, investigating outcomes such as annual relapse rate, or global brain atrophy, with the treatment ingredient of interest being cardiovascular challenge.[25] However, these types of studies have often relied on stationary ergometer exercise, even in pwMS with mild disability, potentially providing low challenge to the sensory and cognitive system.[3] Greater specificity to mobility tasks, with a simultaneous cardiovascular stimulus could yield added benefits, even though this might challenge standardization in interventional trials.[26]

Regarding resistance exercise, we advocate targeting modes, positions, and muscles that are "functional" for gait, challenge balance, and do not solely focus on improving force production as noted by Mañago et al.[27] This, again, could mean reducing the amount of seated exercises (primarily in weight training machines) as their review showed that out of the 6 resistance exercise studies that improved gait, 4 implemented exercises in a standing position, and 2 used modes other than machines. The question of exactly how increased strength acquired from resistance training can be incorporated to gait kinetics seems to be very important.[28]

Besides this potential for increasing sensory challenge, there might be an equivalent potential for including cognitive challenges as stated before.[3,29]

Neuromotor training is a third type of exercise recommended for pwMS, specifically targeting fall prevention, postural stability, coordination, and, importantly in the present context, agility.[24] Referred modalities include a diverse range of pilates, dance, yoga, Tai chi, hippotherapy, virtual reality, and balance and motor control training. Even though there have been beneficial results on gait and balance improvement in these separate modalities, the range of modalities is so diverse, that it is hard to identify which treatment ingredients are specifically responsible for these improvements (eg, do pilates and virtual reality training decrease falls and improve postural stability via a common pathway?; what kind of ingredients are essential in a given pilates session to be successful?).[30] Studies on the modality of balance and motor control training have provided detailed treatment manuals and the challenges provided to pwMS can be regarded as quite specific.[26,31,32] However, the extent to which studies also included cognitive challenges differed. Even though agility has been named as a target for neuromotor training it has to be noted that studies on agility in pwMS are basically non-existent (a PubMed search with the search string "agility AND multiple sclerosis" performed in March 2022 retrieved only 6 hits). It is unclear what concept of agility is studied in the MS literature. As described in more detail in the later sections, we do not think that current trials on neuromotor training adequately target agility, as these trials do not specifically include start-stop, acceleration, and deceleration, turns etc., or responding to a stimulus. This is also the case for the core exercises of a recent complex multicomponent fall-prevention intervention that has been systematically developed and includes many of the other aspects already mentioned, but lacks any kind of agility exercises.[33] Interestingly, this high diversity of modalities in the neuromotor training section is similar to the gerontology literature. Nonetheless, within the field of gerontology, the agility framework has provided some common ground for a meta-analysis.[34] Thus, a framework for pwMS could provide some commonality as well.

Lastly, the most substantial benefits of a multimodal framework might lie in the lack of time-efficiency of current exercise recommendation for pwMS. The recommendations include 3 to 6 sessions of neuromotor, 2 to 3 aerobic, daily flexibility, and 2 to 3 resistance exercise sessions per week. Comparable to recommendations for older adults it seems time-consuming for pwMS to follow all these separate recommendations.[1,34] Especially, when considering the evidence for even lower physical activity in pwMS than in the general population, and the efforts being undertaken to get pwMS moving *at all*.[35]

There have been some interventions applying a combination of exercise approaches in pwMS.[36] However, components are often still split to different sessions or parts (ie, sessions target 1 component at each time). Studies mostly focus on the "classic" components of exercise training (eg, endurance, strength, balance). Aspects such as agility or the incorporation of cognitive challenges have been studied less frequently.

Taken together, there is evidence of subtle gait, and balance impairment in pwMS with clinically mild disability, but exercise interventions frequently lack sensory and cognitive challenge even though the impairment of central sensory integration has been described several times.[3,13,37] Agility has not been studied as a relevant component of fall-prevention in pwMS and is seldomly included in exercise intervention studies. A framework for time-efficient exercise training is lacking.

Solution

What is MAT for pwMS?

The MAT framework has been developed by Donath et al[1] to combine aspects of perception and orientation, change of direction and stop-and-go patterns (ie, agility), including reactive muscle work, with cardiovascular stimuli while at the same time adapting intensity, complexity, and cognitive challenge to individual needs in a group-training format.[34] As such, it could provide a valuable framework for multimodal exercise training in pwMS aiming to improve gait, balance, endurance, and strength. As many pwMS also exhibit problems with processing speed or attention and MAT also includes cognitive challenges, it could further provide a practical framework for combined motor and cognitive rehabilitation in pwMS.[29] This could lead to downstream positive effects on subjective fatigue via reduced effort perception. A recent network-level meta-analysis reported that balance exercises had the largest effect on fatigue compared to usual care among all other types of exercise and behavioral interventions.[38] Another recent study on vestibular function in pwMS postulated that correlations between posturography measures and processing speed might represent a shared utilization of central sensory processing by balance and cognitive pathways.[37]

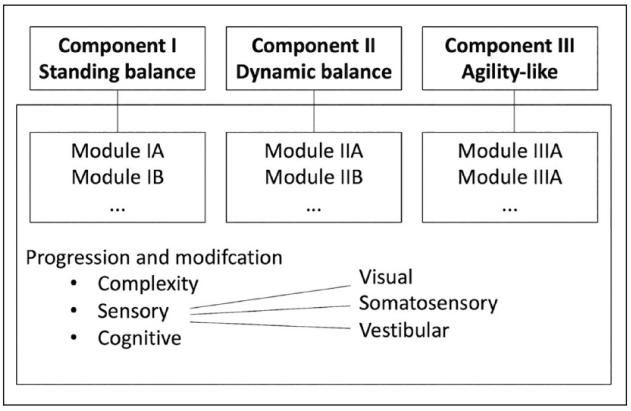

Figure 1. Structure of the MAT framework for pwMS.
Abbreviations: MAT, multimodal agility-based exercise training; pwMS, persons with Multiple Sclerosis.

In MAT for pwMS, agility-based exercises are 1 Component of 3: (I) standing balance, (II) dynamic balance (including functional leg strength), (III) agility-based exercises (see Figure 1 and Table 1). Components can be targeted in different modules, that describe the basic setting of a drill. Each drill can then be progressed via the complexity of the drill itself and via specific sensory (visual, somatosensory, vestibular) and cognitive (dual-tasks related to memory, attention, etc.) modifications. Whereas cognitive modifications target cognitive-motor dual-tasking, motor-motor dual-tasking is included in the progressions on task complexity. In every module, various options for progression exist by combining different aspects of complexity, sensory, or cognitive modifications. Components I and II mainly include content similar to other balance and motor control training studies,[26,32] whereas Component III is based on agility. As there have been reports on difficulties in replicating rehabilitation interventions, and translating research to clinical practice, besides describing theoretical aspects of the 3 Components, example Modules will be described for each Component (see Tables 2–4).[30,39]

Component I: Standing Balance

As described, pwMS exhibit deficits in the control of their center of mass during quiet stance. Furthermore, pwMS exhibit deficits in central sensory integration, that is, pwMS have problems integrating incoming sensory information through the visual, somatosensory, and vestibular channels.[40] Exercising in different sensory contexts (eg, eyes-closed, standing on a compliant surface, performing head turns) and different standing positions (eg, normal stance, feet together, tandem stance etc.) can provide a useful and clinically feasible way to improve standing balance and sensory integration.[1,40] Standing balance exercises can furthermore be easily progressed with secondary tasks such as catching an object, alone or with a partner, to provide external perturbations, and

Table 1. Definitions.

Standing balance represents all tasks where the base of support is not (or should not be) changing, even though there can be considerable movement of the center of mass.
Dynamic balance represents all tasks with changing base of support, such as in stepping, and locomotion.
Agility-based describes tasks, that require changes of direction, stop-and-go patterns, turns, and changing footwork strategies, with or without responding to a stimulus.

Table 2. Example Module Targeting Component I (Standing Balance).

Module	"Standing balance"
(basic setting)	Participants perform various exercises while standing.
Component	I (standing balance)
(main target)	
Progression	• Base of support (eg, feet together, semi-tandem stance, tandem stance, one-leg stance, half kneeling)
(task complexity)	• Catching and throwing (alone, with a partner)
	• Tools (number of objects for throwing, kind of objects)
Sensory modification	• Visual: eyes-closed
	• Somatosensory: various unstable support surfaces
	• Vestibular: head turns
Cognitive modification	• None
Concrete description of a sample task: "Stand with your feet together on the foam pad and exchange the ball with your partner."	

Table 3. Example Module Targeting Component II (Dynamic Balance).

Module	"Balancing on lines"
(basic setting)	Participants try to balance on lines on the gym floor (eg, basketball, volleyball lines)
Component	II (dynamic balance)
(main target)	
Progression	• Base of support (eg, narrow gait, tandem gait)
(task complexity)	• Direction of movement (forward, backward)
	• Speed of movement (eg, slow swing phase, 3 s)
	• Type of movement (high knees, lunges)
Sensory modification	• Visual: perform several steps with eyes-closed
	• Somatosensory: none
	• Vestibular: head turns
Cognitive modification	• Double-task: pairs of two, while balancing, trailing partner gives commands for stops or turns for leading partner
Concrete description of a sample task: "Balance on the lines on the gym floor in tandem gait backward with high knees, counting till 3 s for each swing phase. After you put down your right foot, slowly look to the right, after you put down your left foot, slowly look to the left."	

even cognitive-motor dual-tasking. As such, these exercises give the executing therapist good options for individualization to the needs of the participating individuals. Standing balance exercises should always be performed with sufficient challenge.[1,16,21,26,41] Providing the right amount of challenge can be regarded the primary objective of the therapist, especially if participants are inexperienced with this type of training, and if they have to perform movements, they normally tend to avoid.[26,32] Fear of falling and general deconditioning can result in reduced self-efficacy regarding balance.[21] Therefore, pwMS should be encouraged to exercise to their limits of stability,[16] while the therapist is responsible to monitor safety.

Component II: Dynamic Balance (Including Functional Leg Strength)

There is evidence for high task-specificity related to balance training in healthy individuals.[42] The capacity to balance is based more on the sum of specifically learned balance tasks, rather than on a general capacity that can be improved irrespective of the balance tasks that were trained

in the past.[42] Recent systematic reviews have advocated the adoption of ecologically relevant balance tasks.[16] Therefore, dynamic balance tasks, including stepping, and locomotion, play an important role in MAT besides standing balance. Importantly, depending on the configuration of the drill, challenges for reactive balance can and should also be incorporated (eg, when reacting to commands of the partner or the therapist, see Table 3). Reactive balance can be characterized by motor control strategies applied in response to postural perturbations such as trips. Impairment in reactive balance might be a major cause for falls. A recent meta-analysis has shown that pwMS have worse reactive balance compared to healthy controls across a range of measures (eg, shorter reactive step, more recovery steps needed), which might be caused by a considerably longer response time to initiate balance recovery.[43] Critically, the meta-analysis also indicated that adaptability of reactive balance is still intact in pwMS, mainly via improved "feedforward" mechanisms (ie, using prior knowledge to predict and fine tune motor commands).

Lastly, Component II can also include tasks that involve a higher demand for functional (eccentric) leg strength (eg, variations of lunging, that also provide reduced base of support), with a more conventional way of prescribing exercise such as repetitions and sets. For reasons already mentioned, no seated exercises or weight training machines are part of MAT.

Component III: Agility-Based Exercises

In the exercise sciences, agility has been defined as "a rapid whole-body movement with change of velocity or direction in response to a stimulus" by Sheppard and Young[44] (eg, an attacker evading a defender in football). This whole-body movement is connected to diverse footwork strategies at various speeds. It has received the most interest from the field of team-sports. Although there have been some inconsistencies, it is generally accepted that "agility has both movement and reactive elements."[45] Agility is different from "simple" change of direction tasks, as the movement is not executed pre-planned, but in response to a stimulus. On a playing field, it includes a high degree of complexity, variability, and unpredictability. Regarding fall prevention, agility seems to be critical, as situations predisposing a fall never occur pre-planned. In this context "perception-action coupling," (ie, feedback mechanisms[43]) might be as important to evade a fall, as it is to evade a defender in football. It has been shown that kinematic and kinetic variables differ when comparing planned versus unplanned side-stepping, suggesting different motor control strategies when reacting to a stimulus.[46] A key difference of conventional dual-task training and agility is, that dual-task training frequently involves performing predetermined tasks, like subtracting sevens while walking on a treadmill. Hence, the participant has prior knowledge of the task he is supposed to perform, and when to perform.

In the first meta-analysis related to MAT in older adults, studies were required to include at least 2 "traditional" training domains (strength, balance, endurance) plus mandatory agility-like exercises.[34] Agility-like exercises were described as comprising coordination or change of direction and velocity tasks. Thus, the authors did not require the agility-related tasks to include responding to a stimulus. Hence, to date it is still unclear to what extent agility-related exercises for older adults and pwMS should focus on responding to a stimulus, or whether "mere" change of direction training (including cutting maneuvers, turns, stop, and go patterns) can already be beneficial for these target groups.

In MAT for pwMS a clear separation of Component III from the first 2 Components exists in the speed of movement. Component III specifically includes fast locomotion, including fast gait, and running, if possible. Tasks here also involve the highest amount of reactive balance with demands for feedback control mechanisms (ie, exposure to

Table 4. Example Module Targeting Component III (Agility).

Module	"Cone tipping"
(basic setting)	Pairs of two: one participant starts surrounded by an assemble of cones. The partner outside of the cones says which cones must be touched by the participant.
Component	III (agility-based)
(main target)	
Progression	• Speed, duration (eg, walking, jogging, 1 round = 30 s)
(task complexity)	• Direction of movement (only forward, forward and backward)
	• Number of cones (eg, 4-8)
Sensory modification	• Visual: none
	• Somatosensory: none
	• Vestibular: none
Cognitive modification	• Spatial orientation and memory: directions are given by numbers, colors, or alphabet

Concrete description of a sample task: "Within 30 s try to touch as many cones as possible. Cones will be labeled clockwise according to the alphabet. The order of cones will be given to you by your partner. Try to change directions as fast as possible."

perturbations that remain highly unpredictable),[43] such as in passing and stopping a soccer ball with a moving partner. Further, the Modules also provide the highest cardiovascular challenge with an interval training-like stimulus, which can be regulated via the duration of a drill.

A Symbiosis? The MAT, PRIMERS, and Reserve Frameworks

Why is a skill originally developed in the context of team sports and the exercise sciences important for exercise training in pwMS? Are complex, variable, and unpredictable movements important at all for patients, never on a playing field? One answer could lie in the "Prevention Model of Reserve and Brain Maintenance in Multiple Sclerosis."[6] One premise of this model is, that the best treatment for MS might be prevention of decline. The concept of reserve was based on the observation that pwMS can have similar burden of disease but very different functional impairments.[47] Thus, there must be factors that protect one person against functional decline more than others. A patient will "enter" the disease with a certain amount of reserve in different categories. Besides cognitive reserve, as stated by Brandstadter et al,[6] there might be something like physical or motor reserve as well, protecting somebody with good premorbid balance from gait impairments for a longer time. Interestingly, like the concept of agility, the concept of brain maintenance has been taken from the aging literature to characterize the modulation of reserve over time through protective and risk factors. MAT might be a way for persons with mild disease to improve their functional reserve via processing and integrating multisensory exercise-related stimuli, which builds a bridge to another recently proposed exercise framework for pwMS: PRIMERS (PRocessing, Integration of Multisensory Exercise-Related Stimuli).[3] In 2018, Sandroff et al published this framework to answer the question "what is it about exercise, in particular, that might induce brain changes and secondary behavioral/performance improvements?" in pwMS. They framed exercise as a highly complex behavior involving the coordinated activation of nearly every physiological system in the human body. Among the implications of their framework, they state that exercise training interventions that involve a greater degree of neurophysiological sensorimotor demands should result in more robust brain and behavioral adaptations. MAT for pwMS could offer just that. The group-training format could further act as an enriched environment compared to exercising in isolation.[3]

Recommendations

Providing the MAT framework to the field of MS could act as a reference for future multimodal group-training studies and clinical practice. Especially, as standardized research methodology and innovative training programs directed toward meeting the demands of "real-life" situations are lacking for pwMS.[48] It might also serve to introduce the concept of agility to the field of MS, as it has been confined to the fields of athletic performance and aging. It could further provide a framework that is testable in clinical research and has a theoretical basis, potentially improving consistency of interventions in research studies.[4]

With respect to recommendations for practice, establishing MAT in routine care will necessitate the use of implementation methodology.[49] The group-training format requires the establishment of sound in- and exclusion criteria. At this point, we propose pwMS should be able to perform several steps in a jogging motion, be relatively pain-free, and without serious cognitive impairments, that interfere with understanding of the instructions. We would also consider age above 70 years for pwMS to be a barrier for participation, as the aging process on top of MS could be too much of a security risk when performing certain aspects of MAT and severe cognitive problems are more common. In our experience, the inclusion criteria mostly apply to pwMS still in a working age, who walk without an assistive device. However, there might occasionally be persons using a cane or walker in daily life, who are still able to participate when managed with close attention from the therapist. Due to the many possibilities of progression, there is no "upper limit" for inclusion. Regarding patient characteristics, that might be favorable for responding to MAT participation, in our experience, motivation and prior experience with exercise play an important role. If a patient has the goal to improve his or her balance or get back to high-level mobility tasks ("I want to run again") this psychological level could impact physical outcomes in MAT.

MAT might also be suitable as a framework for interventions in a group-setting with mixed neurological diagnoses. To maximize the use of resources, combining pwMS, stroke, and Parkinson's Disease in group-settings has recently been proposed as a promising approach for falls prevention research.[50] This might be equally useful when establishing MAT group-training in inpatient and outpatient neurological settings. Regarding equipment and staff, we recommend a group with a maximum of 8 participants in a room equivalent to 1 basketball court, to provide enough space for accelerating and decelerating etc. A skilled clinical exercise professional, that can progress and modify Modules according to participating individuals is a cornerstone of MAT. Again, we refer to the cautious gait pattern, low balance self-efficacy, and the avoidance of certain movements in many pwMS.[21,26,32] Targeting these aspects might require directly supervised training. While one goal of MAT is to challenge pwMS in multiple areas, inactive pwMS might be at risk of heightened fatigue, when starting MAT. Participants should be advised to take brakes and monitor their fatigue. Considering the higher risk for falls in the described population, especially for Component III an individualized dose is

Table 5. Research Milestones.

1. Determine feasibility of MAT in pwMS; acquire patient feedback and conduct assessments to questions such as:
• Are there specific aspects of MAT that pwMS tend to like or dislike?
• Does MAT induce an adequate amount of perceived exertion?
• What are the benefits of MAT as perceived by pwMS?
• Do pwMS adhere to a MAT program?
• Is MAT safe to perform in pwMS?
2. Determine efficacy of MAT to provide multi-systemic benefits, going from proximal (motor outcomes), to more distal (cognitive outcomes, imaging/biomarkers). Compare with unimodal/traditional approaches.
3. Determine a health care setting where MAT could be delivered on a regular basis and study effectiveness on larger scale. Acquire perspectives of therapists.

Abbreviations: MAT, multimodal agility-based exercise training; pwMS, persons with Multiple Sclerosis.

required to minimize falls but still achieve measurable benefits. If a participant has a high risk of falling, it is likely that he or she will experience benefits even if the complexity of agility-based tasks is reduced. Conversely, improvements will be less likely if individuals with higher gait stability do not receive the challenge they need.

With respect to recommendations for research, impact of MAT on several outcome measures will be worthwhile studying. Below, we will discuss some outcomes from proximal to more distal targets. As noted, sensor-based outcomes are appropriate to quantify spatiotemporal gait changes in milder disability.[11,15] Besides spatiotemporal measures, other sensor-based outcomes might be useful to quantify whether MAT improves the efficiency and economy of motor control. These include measures of complexity[51,52] or movement smoothness.[53] Another worthwhile measure would be the energetic cost of walking, which is based on oxygen consumption during walking.[54] Several studies have recently described associations of sensor-based outcomes during gait trials with perceived state fatigability (ratings of fatigue while performing a task),[55] objective motor fatigability (deterioration of objective performance during a motor task),[52] and trait fatigue (self-report of fatigue experienced over a longer time-period (eg, several weeks)).[12,52] Sensor-based and fatigue-related outcomes of intervention studies applying MAT should be compared to more traditional, unimodal types of exercise (ie, aerobic, or resistance exercise) to confirm that incorporating more sensory and cognitive stimuli is superior in affecting these outcomes, and potentially superior as a reserve-building activity. On the other hand, it will be important to study whether MAT for pwMS can provide similar neuroprotective stimuli as has been shown for endurance-type training with high cardiovascular demands.[56] Exercise has also been proposed has a (supportive) disease-modifying therapy.[57,58] Thus, MAT should also be compared to unimodal exercise programs that have been designed to study annual relapse rate and global brain atrophy derived from neuroimaging.[59]

Lastly, it will be important to show how MAT is able to improve "classic" fitness parameters, such as maximal strength, or cardiorespiratory fitness in comparison to unimodal approaches. Not providing adequate benefits would result in MAT having only compromised value for general health. Table 5 provides an overview on research milestones for MAT in pwMS.

Interestingly, multimodal agility-based exercise has also been conceptualized[60] and already performed in patients with Parkinson's Disease.[61,62] In several papers, Tollár et al[62,63] and Hortobágyi et al[64] applied similar aspects of training (eg, gait training, coordination training, balance exercises, including change of direction, and sensory integration) to the ones described here, while also incorporating exergaming (Xbox Kinect). They were able to show, that "supervised, high-intensity sensorimotor agility exercise" was able to improve motor outcomes, and quality of life, while also contributing to the least increase in levodopa intake with continued training over 6 years.[64] This also supports motor outcomes to be the most proximal targets of MAT for pwMS.

Regarding the concept of agility itself, debate of what constitutes agility in general is still ongoing. Thus, the aspects of agility, that are important for pwMS must be further elucidated (eg, change of direction, reacting to a stimulus, speed of movement, etc.). Similarly, the transferability of training effects to everyday function must be examined.[42] When considering MAT as a reserve-building activity, ongoing training may be needed to drive lasting neuroplasticity in pwMS.[65] Existing, evidence-based group-exercise programs such as FAME for stroke survivors can serve as a good example to develop MAT for pwMS.[66]

In conclusion, when considering the gait and balance deficits with several underlying causes of pwMS, and the difficulties of pwMS to be physically active, an approach of exercise training that (I) addresses these multifaceted motor control problems, (II) is fun, social, relevant to daily life, and (III) is time-efficient, seems to be promising.

As already stated by Motl et al,[29] several things can be learned from the gerontology literature and applied to pwMS. The MAT framework might be one of them.

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References

1. Donath L, van Dieen J, Faude O. Exercise-based fall prevention in the elderly: what about agility? *Sports Med*. 2016;46(2):143-149. doi:10.1007/s40279-015-0389-5
2. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. *Lancet*. 2018;391(10130):1622-1636. doi:10.1016/s0140-6736(18)30481-1
3. Sandroff BM, Motl RW, Reed WR, Barbey AK, Benedict RHB, DeLuca J. Integrative CNS plasticity with exercise in MS: the PRIMERS (PRocessing, Integration of Multisensory Exercise-Related Stimuli) conceptual framework. *Neurorehabil Neural Repair*. 2018;32(10):847-862. doi:10.1177/1545968318798938
4. Cameron MH, Nilsagard Y. Chapter 15 - Balance, gait, and falls in multiple sclerosis. In: Day BL, Lord SR, eds. *Handbook of Clinical Neurology*. Elsevier; 2018:237-250.
5. Severijns D, Zijdewind I, Dalgas U, Lamers I, Lismont C, Feys P. The assessment of motor fatigability in persons with multiple sclerosis: a systematic review. *Neurorehabil Neural Repair*. 2017;31(5):413-431. doi:10.1177/1545968317690831
6. Brandstadter R, Katz Sand I, Sumowski JF. Beyond rehabilitation: a prevention model of reserve and brain maintenance in multiple sclerosis. *Mult Scler*. 2019;25(10):1372-1378. doi:10.1177/1352458519856847
7. Kantarci OH. Phases and phenotypes of multiple sclerosis. *Continuum (Minneap Minn)*. 2019;25(3):636-654. doi:10.1212/con.0000000000000737
8. Riemenschneider M, Hvid LG, Stenager E, Dalgas U. Is there an overlooked "window of opportunity" in MS exercise therapy? Perspectives for early MS rehabilitation. *Mult Scler*. 2018;24(7):886-894. doi:10.1177/1352458518777377
9. Smith M, Barker R, Williams G, Carr J, Gunnarsson R. The effect of exercise on high-level mobility in individuals with neurodegenerative disease: a systematic literature review. *Physiotherapy*. 2020;106:174-193. doi:10.1016/j.physio.2019.04.003
10. Kister I, Chamot E, Salter AR, Cutter GR, Bacon TE, Herbert J. Disability in multiple sclerosis: a reference for patients and clinicians. *Neurology*. 2013;80(11):1018-1024. doi:10.1212/WNL.0b013e3182872855
11. Chee JN, Ye B, Gregor S, Berbrayer D, Mihailidis A, Patterson KK. Influence of multiple sclerosis on spatiotemporal gait parameters: a systematic review and meta-regression. *Arch Phys Med Rehabil*. 2021;102(9):1801-1815. doi:10.1016/j.apmr.2020.12.013
12. Müller R, Hamacher D, Hansen S, Oschmann P, Keune PM. Wearable inertial sensors are highly sensitive in the detection of gait disturbances and fatigue at early stages of multiple sclerosis. *BMC Neurol*. 2021;21(1):337. doi:10.1186/s12883-021-02361-y
13. Cofré Lizama LE, Khan F, Lee PV, Galea MP. The use of laboratory gait analysis for understanding gait deterioration in people with multiple sclerosis. *Mult Scler*. 2016;22(14):1768-1776. doi:10.1177/1352458516658137
14. Galea MP, Cofré Lizama LE, Butzkueven H, Kilpatrick TJ. Gait and balance deterioration over a 12-month period in multiple sclerosis patients with EDSS scores ≤ 3.0. *NeuroRehabilitation*. 2017;40(2):277-284. doi:10.3233/nre-161413
15. Vienne-Jumeau A, Quijoux F, Vidal P-P, Ricard D. Wearable inertial sensors provide reliable biomarkers of disease severity in multiple sclerosis: a systematic review and meta-analysis. *Ann Phys Rehabil Med*. 2020;63(2):138-147. doi:10.1016/j.rehab.2019.07.004
16. Comber L, Sosnoff JJ, Galvin R, Coote S. Postural control deficits in people with Multiple Sclerosis: a systematic review and meta-analysis. *Gait Posture*. 2018;61:445-452. doi:10.1016/j.gaitpost.2018.02.018
17. Inojosa H, Schriefer D, Klöditz A, Trentzsch K, Ziemssen T. Balance testing in Multiple Sclerosis—improving neurological assessment with static posturography? *Front Neurol*. 2020;11:135. doi:10.3389/fneur.2020.00135
18. Brandstadter R, Ayeni O, Krieger SC, et al. Detection of subtle gait disturbance and future fall risk in early multiple sclerosis. *Neurology*. 2020;94(13):e1395-e1406. doi:10.1212/WNL.0000000000008938
19. Carpinella I, Gervasoni E, Anastasi D, et al. Walking with horizontal head turns is impaired in persons with early-stage multiple sclerosis showing normal locomotion. *Front Neurol*. 2022;12:821640. doi:10.3389/fneur.2021.821640
20. Krieger SC, Antoine A, Sumowski JF. EDSS 0 is not normal: multiple sclerosis disease burden below the clinical threshold. *Mult Scler*. Published online July 13, 2022. doi:10.1177/13524585221108297
21. Prosperini L, Castelli L. Spotlight on postural control in patients with multiple sclerosis. *Degener Neurol Neuromuscul Dis*. 2018;8:25-34. doi:10.2147/dnnd.S135755
22. Veldkamp R, Kalron A, Baert I, et al. Differential effects and discriminative validity of motor and cognitive tasks varying in difficulty on cognitive-motor interference in persons with multiple sclerosis. *Mult Scler*. 2021;27(12):1924-1938. doi:10.1177/1352458520986960
23. Balasubramanian CK, Clark DJ, Fox EJ. Walking adaptability after a stroke and its assessment in clinical settings. *Stroke Res Treat*. 2014;2014:591013. doi:10.1155/2014/591013
24. Kalb R, Brown TR, Coote S, et al. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. *Mult Scler*. 2020;26(12):1459-1469. doi:10.1177/1352458520915629
25. Dalgas U, Stenager E, Hvid LG. Physical exercise in multiple sclerosis is not just a symptomatic therapy, it has a disease-modifying effect: commentary. *Mult Scler J*. 2022;28(6):863-864. doi:10.1177/13524585211072702
26. Callesen J, Cattaneo D, Brincks J, Kjeldgaard Jørgensen ML, Dalgas U. How do resistance training and balance and motor control training affect gait performance and fatigue impact in people with multiple sclerosis? A randomized controlled multi-center study. *Mult Scler*. 2020;26(11):1420-1432. doi:10.1177/1352458519865740

27. Mañago MM, Glick S, Hebert JR, Coote S, Schenkman M. Strength training to improve gait in people with multiple sclerosis: a critical review of exercise parameters and intervention approaches. *Int J MS Care*. 2019;21(2):47-56. doi:10.7224/1537-2073.2017-079
28. Hortobágyi T, Granacher U, Fernandez-Del-Olmo M, et al. Functional relevance of resistance training-induced neuroplasticity in health and disease. *Neurosci Biobehav Rev*. 2021;122:79-91. doi:10.1016/j.neubiorev.2020.12.019
29. Motl RW, Sandroff BM, DeLuca J. Exercise training and cognitive rehabilitation: a symbiotic approach for rehabilitating walking and cognitive functions in multiple sclerosis? *Neurorehabil Neural Repair*. 2016;30(6):499-511. doi:10.1177/1545968315606993
30. Van Stan JH, Whyte J, Duffy JR, et al. Rehabilitation treatment specification system: methodology to identify and describe unique targets and ingredients. *Arch Phys Med Rehabil*. 2021;102(3):521-531. doi:10.1016/j.apmr.2020.09.383
31. Hebert JR, Corboy JR, Manago MM, Schenkman M. Effects of vestibular rehabilitation on multiple sclerosis-related fatigue and upright postural control: a randomized controlled trial. *Phys Ther*. 2011;91(8):1166-1183. doi:10.2522/ptj.20100399
32. Hebert JR, Corboy JR, Vollmer T, Forster JE, Schenkman M. Efficacy of balance and eye-movement exercises for persons with multiple sclerosis (BEEMS). *Neurology*. 2018;90(9):e797-e807. doi:10.1212/WNL.0000000000005013
33. Comber L, Peterson E, O'Malley N, Galvin R, Finlayson M, Coote S. Development of the better balance program for people with multiple sclerosis: a complex fall-prevention intervention. *Int J MS Care*. 2021;23(3):119-127. doi:10.7224/1537-2073.2019-105
34. Morat M, Morat T, Zijlstra W, Donath L. Effects of multimodal agility-like exercise training compared to inactive controls and alternative training on physical performance in older adults: a systematic review and meta-analysis. *Eur Rev Aging Phys Act*. 2021;18(1):4. doi:10.1186/s11556-021-00256-y
35. Motl RW, Sandroff BM, Kwakkel G, et al. Exercise in patients with multiple sclerosis. *Lancet Neurol*. 2017;16(10):848-856. doi:10.1016/s1474-4422(17)30281-8
36. Sandroff BM, Bollaert RE, Pilutti LA, et al. Multimodal exercise training in multiple sclerosis: a randomized controlled trial in persons with substantial mobility disability. *Contemp Clin Trials*. 2017;61:39-47. doi:10.1016/j.cct.2017.07.016
37. Cochrane GD, Christy JB, Sandroff BM, Motl RW. Cognitive and central vestibular functions correlate in people with multiple sclerosis. *Neurorehabil Neural Repair*. 2021;35(11):1030-1038. doi:10.1177/15459683211046268
38. Harrison AM, Safari R, Mercer T, et al. Which exercise and behavioural interventions show most promise for treating fatigue in multiple sclerosis? A network meta-analysis. *Mult Scler*. 2021;27(11):1657-1678. doi:10.1177/1352458521996002
39. Page P, Hoogenboom B, Voight M. Improving the reporting of therapeutic exercise interventions in rehabilitation research. *Int J Sports Phys Ther*. 2017;12(2):297-304.
40. Gandolfi M, Munari D, Geroin C, et al. Sensory integration balance training in patients with multiple sclerosis: a randomized, controlled trial. *Mult Scler*. 2015;21(11):1453-1462. doi:10.1177/1352458514562438
41. Gunn H, Markevics S, Haas B, Marsden J, Freeman J. Systematic review: the effectiveness of interventions to reduce falls and improve balance in adults with multiple sclerosis. *Arch Phys Med Rehabil*. 2015;96(10):1898-1912. doi:10.1016/j.apmr.2015.05.018
42. Kümmel J, Kramer A, Giboin LS, Gruber M. Specificity of balance training in healthy individuals: a systematic review and meta-analysis. *Sports Med*. 2016;46(9):1261-1271. doi:10.1007/s40279-016-0515-z
43. Mohamed Suhaimy MSB, Okubo Y, Hoang PD, Lord SR. Reactive balance adaptability and retention in people with multiple sclerosis: a systematic review and meta-analysis. *Neurorehabil Neural Repair*. 2020;34(8):675-685. doi:10.1177/1545968320929681
44. Sheppard JM, Young WB. Agility literature review: classifications, training and testing. *J Sports Sci*. 2006;24(9):919-932. doi:10.1080/02640410500457109
45. Young W, Rayner R, Talpey S. It's time to change direction on agility research: a call to action. *Sports Med Open*. 2021;7(1):12. doi:10.1186/s40798-021-00304-y
46. Brown SR, Brughelli M, Hume PA. Knee mechanics during planned and unplanned sidestepping: a systematic review and meta-analysis. *Sports Med*. 2014;44(11):1573-1588. doi:10.1007/s40279-014-0225-3
47. Chard DT, Alahmadi AAS, Audoin B, et al. Mind the gap: from neurons to networks to outcomes in multiple sclerosis. *Nat Rev Neurol*. 2021;17(3):173-184. doi:10.1038/s41582-020-00439-8
48. Tacchino A, Veldkamp R, Coninx K, et al. Design, development, and testing of an app for dual-task assessment and training regarding cognitive-motor interference (CMI-APP) in people with multiple sclerosis: multicenter pilot study. *JMIR Mhealth Uhealth*. 2020;8(4):e15344. doi:10.2196/15344
49. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ*. 2021;374:n2061. doi:10.1136/bmj.n2061
50. O'Malley N, Clifford AM, Conneely M, Casey B, Coote S. Effectiveness of interventions to prevent falls for people with multiple sclerosis, Parkinson's disease and stroke: an umbrella review. *BMC Neurol*. 2021;21(1):378. doi:10.1186/s12883-021-02402-6
51. Yentes JM, Raffalt PC. Entropy analysis in gait research: methodological considerations and recommendations. *Ann Biomed Eng*. 2021;49(3):979-990. doi:10.1007/s10439-020-02616-8
52. Shema-Shiratzky S, Gazit E, Sun R, et al. Deterioration of specific aspects of gait during the instrumented 6-min walk test among people with multiple sclerosis. *J Neurol*. 2019;266(12):3022-3030. doi:10.1007/s00415-019-09500-z
53. Kiely J, Pickering C, Collins DJ. Smoothness: an unexplored window into coordinated running proficiency. *Sports Med Open*. 2019;5(1):43. doi:10.1186/s40798-019-0215-y
54. Theunissen K, Plasqui G, Boonen A, et al. The relationship between walking speed and the energetic cost of walking in persons with multiple sclerosis and healthy controls: a systematic review. *Neurorehabil Neural Repair*. 2021;35(6):486-500. doi:10.1177/15459683211005028

55. Ibrahim AA, Küderle A, Gaßner H, Klucken J, Eskofier BM, Kluge F. Inertial sensor-based gait parameters reflect patient-reported fatigue in multiple sclerosis. *J Neuroeng Rehabil*. 2020;17(1):165. doi:10.1186/s12984-020-00798-9
56. Joisten N, Rademacher A, Warnke C, et al. Exercise diminishes plasma neurofilament light chain and reroutes the kynurenine pathway in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(3):e982. doi:10.1212/NXI.0000000000000982
57. Dalgas U, Langeskov-Christensen M, Stenager E, Riemenschneider M, Hvid LG. Exercise as medicine in multiple sclerosis—time for a paradigm shift: preventive, symptomatic, and disease-modifying aspects and perspectives. *Curr Neurol Neurosci Rep*. 2019;19(11):88. doi:10.1007/s11910-019-1002-3
58. Proschinger S, Kuhwand P, Rademacher A, et al. Fitness, physical activity, and exercise in multiple sclerosis: a systematic review on current evidence for interactions with disease activity and progression. *J Neurol*. 2022;269(6):2922-2940. doi:10.1007/s00415-021-10935-6
59. Riemenschneider M, Hvid LG, Ringgaard S, et al. Study protocol: randomised controlled trial evaluating exercise therapy as a supplemental treatment strategy in early multiple sclerosis: the Early Multiple Sclerosis Exercise Study (EMSES). *BMJ Open*. 2021;11(1):e043699. doi:10.1136/bmjopen-2020-043699
60. King LA, Horak FB. Delaying mobility disability in people with Parkinson disease using a sensorimotor agility exercise program. *Phys Ther*. 2009;89(4):384-393. doi:10.2522/ptj.20080214
61. Jung SH, Hasegawa N, Mancini M, et al. Effects of the agility boot camp with cognitive challenge (ABC-C) exercise program for Parkinson's disease. *NPJ Parkinsons Dis*. 2020;6(1):31. doi:10.1038/s41531-020-00132-z
62. Tollár J, Nagy F, Kovács N, Hortobágyi T. Two-year agility maintenance training slows the progression of Parkinsonian symptoms. *Med Sci Sports Exerc*. 2019;51(2):237-245.
63. Tollár J, Nagy F, Kovács N, Hortobágyi T. A high-intensity multicomponent agility intervention improves Parkinson patients' clinical and motor symptoms. *Arch Phys Med Rehabil*. 2018;99(12):2478-2484.e1. doi:10.1016/j.apmr.2018.05.007
64. Hortobágyi T, Sipos D, Borbély G, et al. Detraining slows and maintenance training over 6 years halts Parkinsonian symptoms-progression. *Front Neurol*. 2021;12: 737726. doi:10.3389/fneur.2021.737726
65. Edwards EM, Fritz NE, Therrien AS. Cerebellar dysfunction in multiple sclerosis: considerations for research and rehabilitation therapy. *Neurorehabil Neural Repair*. 2022;36(2):103-106. doi:10.1177/15459683211065442
66. Eng JJ. Fitness and Mobility Exercise (FAME) Program for stroke. *Top Geriatr Rehabil*. 2010;26(4):310-323. doi:10.1097/TGR.0b013e3181fee736

BMJ Open

Randomised controlled pilot and feasibility study of multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve multiple sclerosis-related fatigue and fatigability during inpatient rehabilitation (ReFEx): study protocol

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ABSTRACT

Introduction Subjective fatigue and objectively assessed fatigability are common symptoms in persons with multiple sclerosis (pwMS). Recent work has suggested a positive effect of balance and motor control training (BMCT) in reducing fatigue. It is unclear whether this effect can also be attained during inpatient rehabilitation. Multimodal agility-based exercise training (MAT) has been developed as a framework that incorporates BMCT with added agility components but has not been applied to pwMS. Therefore, this study will evaluate the feasibility of a randomised controlled trial comparing MAT against strength and endurance training (SET) for the improvement of MS-related fatigue and fatigability in a German neurological rehabilitation centre.

Methods and analysis A total of 24 pwMS (Expanded Disability Status Scale ≤5.0, Fatigue Scale for Motor and Cognitive Functions ≥53) will be randomly assigned to either SET or land and water-based MAT for 4–6 weeks during inpatient rehabilitation. Assessments of subjective fatigue, motor and cognitive fatigability, cognitive and cardiorespiratory performance, and balance confidence will be performed at admission and discharge. Subjective fatigue will also be assessed at 1, 4 and 12 weeks after discharge. Feasibility outcomes will include patients' acceptance of study procedures and interventions, recruitment rate, retention rate, time needed to complete baseline assessments, intervention adherence and fidelity. All quantitative outcomes will be reported descriptively. A total of 12 pwMS (6 per group) will be interviewed to gain insights into participants' experiences during study participation.

Ethics and dissemination Ethical approval has been obtained from the Ethics Committee of the University of Bonn (reference number: 543/20). Dissemination of findings is planned via peer-reviewed journals, conferences and media releases.

Trial registration number DRKS00023943.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Comprehensive assessment of subjective fatigue, as well as objective cognitive and motor fatigability.
⇒ First application of agility-based exercise training to persons with multiple sclerosis.
⇒ Mixed-methods approach to acquire patient perspective and acceptance.
⇒ Clinical inpatient setting will challenge standardisation of study procedures.

INTRODUCTION

Fatigue, described as 'a subjective sensation of lack of energy and exhaustion' (p. E79)[1], was reported as the most common symptom (58%) among 35 000 patients from the German multiple sclerosis (MS) register.[2] It is also reported as one of the most disabling symptoms[3] with high socioeconomic relevance as 25% of persons with MS (pwMS) have impaired working capacity because of 'invisible symptoms' such as fatigue and impaired cognition.[4 5]

Data from the MS register also show that only 35% of fatigued pwMS receive any kind of treatment and among them only 15% receive pharmacological treatment to specifically handle fatigue symptoms.[2] No clear pathomechanisms for fatigue have been defined yet leading to the consequence of still limited pharmacotherapy options for the treatment of fatigue.[6]

According to the established taxonomy by Kluger *et al*[7] two concepts must be separated when considering fatigue: (1) the subjective experience of fatigue and (2) objective

performance fatigability during motor or cognitive tasks. Whether improvements in fatigability also transfer to subjective fatigue is still unclear. Interestingly, the association between the two constructs seems to be relatively weak.[8 9]

Next to distinguishing between 'fatigue' and 'fatigability', a further dichotomy exists with 'primary fatigue' resulting from pathophysiological processes of the disease itself (eg, central nervous system, immunological or endocrine changes) and 'secondary fatigue' resulting from mechanisms not directly related to the disease (eg, sleep, depression, medication).[10]

To reduce subjective fatigue, exercise interventions have been studied as a non-pharmacological treatment option. However, several methodological issues exist. As fatigue is frequently assessed as a secondary outcome variable, subjects are often not prescreened for fatigue symptoms at baseline and the intervention is not primarily designed to reduce fatigue.[11 12] Consequently, to date, there are few studies investigating the specific pathophysiological pathways of primary or secondary fatigue that are altered by exercise.[10]

In a recent meta-analysis, Moss-Morris *et al*[11] performed a detailed review of exercise intervention studies, that specifically aimed at fatigue reduction. Here, the authors reported variance in the effects of different types of exercise. For example, endurance exercise has been frequently investigated, as it can be easily standardised, but was reported to have only small effects on fatigue outcomes measured with self-report questionnaires.[13] If combined with other modalities such as resistance exercise, effects might be greater (eg, strength and endurance training (SET)). Lastly, types of exercise consisting primarily of stimuli targeting motor control (eg, balance and motor control training (BMCT)) were described as promising, due to their relatively large effect sizes and specification of a mechanistic pathway.

In the special setting of inpatient rehabilitation, the number of exercise studies for subjective fatigue reduction is very limited. In their review, Moss-Morris *et al*[11] identified only one study conducted in an inpatient rehabilitation setting. However, this trial was restricted from the meta-analysis because of methodological limitations, indicating the need for future systematic research on fatigue-specific therapy. This is also evident in the first German practice guideline for exercise therapy in pwMS, which highlights mobility rehabilitation but does not consider symptoms of fatigue or fatigability.[14]

Therefore, the ReFEx (Rehabilitation, Fatigue and Exercise) project aims to transfer the promising results of interventions focused on balance and motor control to inpatient rehabilitation and compare it with SET, which is considered the control group or 'usual care'. Importantly, we will adapt the existing approaches on BMCT to be based on the agility framework described by Donath *et al*.[15] Therefore, besides exercises focused on balance and sensory integration, the treatment manual will also include functional leg strength and agility-based exercises. This approach can be characterised as 'multimodal agility-based exercise training' (MAT)[16] and the ReFEx project will be the first to apply it to pwMS. In doing so, we not only expect to target subjective fatigue, but also other frequent MS-specific symptoms including performance fatigability as well as disturbed gait and balance. Applying the agility framework could further provide an opportunity for combined motor and cognitive rehabilitation,[17] that is fun, enjoyable and social.[15]

Referring to the pathophysiological framework by Langeskov-Christensen *et al*,[10] we hypothesise that the SET will improve secondary fatigue via improved aerobic capacity and motor function, while the MAT intervention will improve secondary fatigue via improved motor function and reduced cognitive effort in daily life (as hypothesised by Moss-Morris *et al*[11] and Callesen *et al*[18–21]). Based on the existing evidence, we expect greater benefits on secondary fatigue parameters from MAT than for SET. Regarding performance fatigability, we hypothesise, that MAT will be superior to SET in improving motor and cognitive fatigability.

In a first step, the pilot and feasibility study (PAFS) described in this protocol will be used to determine whether the adapted MAT and SET are feasible in the inpatient rehabilitation setting with a special emphasis on patients' acceptance. This will include both, a quantitative and qualitative evaluation.

METHODS AND ANALYSIS

Study design

The PAFS will be conducted at the Neurological Rehabilitation Centre (NRC) 'Godeshoehe' (Bonn; certified MS Rehabilitation Centre). It will have a two-armed, parallel-group, randomised-controlled design with 12 weeks follow-up, following a mixed-methods approach. Measurement time points are provided in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure (table 1).

Patient and public involvement

In our therapeutic work of several years in a specialised rehabilitation clinic for MS, the majority of pwMS report that fatigue is difficult to cope with and limits quality of life. These patient reports were the impetus for the conception of this study, especially as there are few evaluated therapy approaches. In the conception of this PAFS, it was important for us to appreciate the patient perspective and to include the affected persons as 'experts of their disease'. In particular, this takes the form of qualitative interviews, which we base on a constructivist paradigm that allows for the co-creation of knowledge by the participants and the researcher.[22]

Screening and recruitment

Individuals admitted to the NRC will be screened for pwMS. All pwMS will then be scheduled for neuropsychological examination the day after admission, according to

Table 1 SPIRIT figure depicting the schedule of enrolment, interventions and assessments for the pilot and feasibility study

	Study period						
	Enrolment	Allocation	Post-allocation				
Timepoint	$-T_0$	0	T_0	T_1	T_2	T_3	T_4
Enrolment:							
Eligibility screen	X						
Informed consent	X						
Stratified randomisation		X					
Interventions							
MAT			◆—	—◆			
SET			◆—	—◆			
Assessments:							
Fatigue (WEIMuS)	X			X	X	X	X
Fatigue (FSMC)	X			X	X	X	X
Cognitive fatigability (TAP-Alert)			X	X			
Motor fatigability (6MWT)	X			X			
Cognitive performance (CVLT, SDMT)			X	X			
Cardiorespiratory fitness (GXT)			X	X			
Motor function (T25FW, SSST, FGA)	X			X			
Balance confidence (ABC)	X			X			
Depression (CES-D)			X	X			
Feasibility outcomes	◆—	——	——	——	—◆		
Interview 1 (feasibility)				X			
Interview 2 (fatigue responder)					X		

0, after written informed consent; ABC, Activities-Specific Balance Confidence Scale; CES-D, Centre for Epidemiological Studies Depression Scale (German version); CVLT, California Verbal Learning Test; FGA, Functional Gait Assessment; FSMC, Fatigue Scale for Motor and Cognitive Functions; GXT, Graded Exercise Test; MAT, Multimodal Agility-based exercise Training; 6MWT, 6 min Walk Test; SDMT, Symbol Digit Modalities Test; SET, Strength and Endurance Training; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; SSST, Six Spot Step Test; $-T_0$, admission; T_0, postrandomisation; T_1, prior to discharge; T_2, 1–2 weeks after discharge; T_3, 4 weeks after discharge; T_4, 12 weeks after discharge; TAP-Alert, Test Battery of Attention Performance – Alertness; T25FW, Timed 25-foot Walk Test; WEIMuS, Würzburg Fatigue Inventory for Multiple Sclerosis.

usual practice. Here, patients will be asked to complete the Fatigue Scale for Motor and Cognitive Functions (FSMC). If a patient is classified as, at least, 'moderately fatigued' and the patient fulfils all other eligibility criteria (table 2), he or she will be informed about the study by his or her neuropsychologist (JN, JS and EH), verbally and in written form.

Randomisation

If patients provide the written informed consent to one of the study staff members within a maximum of 3 days, they will be randomly allocated (1:1) to the intervention or control group according to the minimisation procedure[23] and stratified by Expanded Disability Status Scale (EDSS, ≤3 or ≥3.5), Würzburg Fatigue Inventory for Multiple Sclerosis (WEIMuS, <38 or ≥38), age (<45 or ≥45) and MS disease course (relapsing-remitting or secondary-progressive). Randomisation will be provided by an independent researcher from the German Sport University Cologne using 'Randomisation-In-Treatment-Arms', Evident, Germany.

Sample size and duration

Data from the PAFS is planned to be pooled with data from the full trial in case no major changes of the study protocol will be necessary (see progression requirements). Acceptability of pooling will be evaluated according to components listed in the 'Acceptance checklist for clinical effectiveness pilot trials'.[24] As the primary aim of this trial is to evaluate the feasibility, no sample size calculation based on statistical assumptions will be performed. However, we consider a minimum of twelve recruited patients per study arm to be a reasonable sample size for this setting.[25]

The NRC treats about 100–120 pwMS per year. According to previous data collections for the German MS register no more than 25% of patients will have to be excluded, based on EDSS and FSMC screening (see eligibility criteria). We further predict no more than 10% of eligible patients to be unwilling to participate, based on previously conducted studies. Comparable studies have had high retention rates (95%)[26] but did not choose a primary endpoint after patients returned

Table 2 Eligibility criteria

Inclusion	Exclusion
1.MS disease course RR or SP	1. Unable to attend water therapy
2.Age 18–67	2. Comorbidities That prevent attending study therapies, chronic neurological conditions other than MS
3.EDSS ≤5.0	3. German language skills That interfere with understanding of testing and instructions
4.FSMC total score ≥53	4. Current fatigue medication Amantadine, Modafinil started <3 months
5.Written informed consent	

EDSS, Expanded Disability Status Scale; FSMC, Fatigue Scale for Motor and Cognitive Functions; MS, multiple sclerosis; RR, relapsing-remitting; SP, secondary-progressive.

home. Consequently, we plan with 80% retention from T_0 to T_2. This will result in a feasibility period of about six to 8 months. Retention rates will be used to inform the sample size calculation for the full randomised controlled trial (RCT).

Participants

PwMS will be eligible to participate in this trial according to the inclusion and exclusion criteria stated in table 2.

Interventions

The intervention period includes the time from admission to discharge, which usually comprises 4–6 weeks for this group of patients. Multidisciplinary inpatient rehabilitation can consist of various diagnostic and therapeutic components such as exercise training, occupational and physical therapy, health education, neuropsychological assessment, or assessment of working capacity. Thus, interactions between treatments as well as flexibility in the treatment schedule are common.[27] For this reason, we designed the schedules of the two study groups to ensure the following:

- Distinct differences in the amount of therapy targeting cognitive and sensory integration.
- Standardisation of treatment as strictly as possible within this specific clinical setting.
- Approximately equivalent amount of total therapy time.

See table 3 for an overview of intervention components. Reporting of the interventions will follow the modified Consensus on Exercise Reporting Template for Therapeutic Exercise Interventions.[28]

Standard treatment for both groups

Both groups will attend the 'MS group', a specific group for all pwMS, focusing on body awareness and relaxation techniques. It consists of maximum eight pwMS, lasts 30 min and is led by an exercise therapist. Both groups will also attend MS-specific lectures once a week. All other available therapies, which are not part of standard treatment, will be included only after individual consideration to maximise standardisation.

Table 3 Frequency, time and type of intervention components

MAT (intervention)	SET (control)
5x/wk, 30 min, 'MS group'	
5x/wk, 30 min, land-based MAT	5x/wk, 22 min, endurance training
3x/wk, 30 min, water-based MAT	3x/wk, 30 min, strength training

MAT, multimodal agility-based exercise training; SET, strength and endurance training.

Strength and endurance training

The combined SET programme will be considered the control condition. All endurance training sessions will be supervised by exercise therapists from the NRC. Strength training sessions will be supervised by exercise science students or therapists in one-on-one sessions. Students and therapists conducting the strength training will be instructed by FW and will follow a training protocol (see online supplemental file (Strength Protocol)).

Endurance training will be performed according to the standard protocol in this clinic, with 22 min per session (3 min of gradual increase, 17 min steady and 2 min cool-down) on a cycle ergometer (ergoselect 5, ergoline, Bitz, Germany) with continuous monitoring of power output and heart rate (ers.2 software, ergoline, Bitz, Germany). Endurance training will be performed in groups of maximum eight patients. In the first session, participants will start their training at an intensity that was rated 'light' to 'somewhat hard' by themselves during the baseline graded exercise test (GXT) (equivalent to 11–13 on the 6–20 Rated Perceived Exertion (RPE)—scale). In the following sessions, therapists will regulate the power output so that participants stay between 11 and 13 on the RPE-scale. If a pwMS is unable to complete the total duration, the session duration can be initially reduced and then progressed in the following sessions. The range of 11–13 was chosen based on recent evidence-based recommendations for pwMS with similar EDSS.[29]

Resistance training will be adapted from Callesen *et al*[18] to fit the inpatient setting. Each session will start with a 5 min warm-up on an elliptical trainer, treadmill or recumbent stepper, followed by 3–4 exercises targeting hip, knee, and ankle flexion and extension, as well as hip abduction. Exercises will be progressed as follows:

- Session 1–5: 3×10 repetitions with the 15 repetitions maximum (RM).
- Session 6-T_1 (T_1 will be around session 10–16): 3×12 repetitions with 12RM.

In detail, for every new exercise, therapists will initially determine the respective weight the participant is able to move no more than the intended RM. Therapists will be given the necessary room for individualisation but will be instructed to follow prespecified exercises (see online supplemental file (Strength Protocol)).

Multimodal agility-based exercise training

For the treatment manual see online supplemental file (MAT-Manual). All sessions will be guided by maximum three different exercise therapists (including FW) from the NRC, experienced with providing balance exercises on land and in the water in group settings. However, as MAT also comprises other/new elements, exercise therapists will be specifically trained by FW and instructed to follow the treatment manual.

Both parts (ie, water and land) will be installed within existing group therapies. Each group will consist of maximum eight participants. Empty spots will be filled with other patients from the NRC. The intervention programme will consist of three main components: (1) standing balance exercises, (2) dynamic balance exercises including functional leg strength, (3) agility-like exercises including change of direction and change of velocity.[16] Each main component will be represented in several modules. Each module is constructed as a basic setup, that can be progressed in terms of difficulty. Additionally, modifications on a cognitive (eg, memory, attention, inhibition) and sensory (ie, visual, somatosensory, vestibular) level are described. As stated by Callesen *et al*,[18] there is no consensus yet on how to define intensity or progression in balance and motor control exercises. Thus, for this intervention, therapists will be instructed to aim for a level of difficulty and complexity that keeps exercises manageable and safe for participants, but also provokes motor or cognitive errors. This is in line with recommendations for neurorehabilitation from basic science.[30]

For load management in the land-based therapy, there will be three sessions with higher physical strain (ie, agility-like components and functional leg strength) interspersed with two sessions with lower physical strain (ie, standing balance and exercises with a cognitive focus). Due to water immersion, physical strain in the water-based therapy should be lower in general.

Participants will be instructed to take individual breaks whenever they need to. They will also be advised to monitor their fatigue during their stay and skip a session when they need more time to recuperate.

Blinding

The neuropsychological staff conducting the cognitive tests will be blinded to the study groups. However, for organisational reasons and specifics of the study setting, blinding of participants, therapists conducting the interventions as well as personnel conducting the motor and cardiorespiratory fitness (CRF) tests and analysing the questionnaires will not be possible.

Outcomes

As depicted in table 1, assessments will be carried out at admission (ie, preintervention, T_0) and discharge (ie, postintervention, T_1), as well as after participants have returned home (ie, follow-up, T_2-T_4).

Baseline sample characteristics

Demographic data on age and sex will be taken from electronic records. Height will be self-reported from participants. Bodyweight at T_0 will be assessed with normal clothing, but without shoes, prior to GXT using a digital scale. The corresponding body mass index will then be calculated (kg/m^2).

Clinical data will include the following: MS disease course and time since diagnosis (years) will be taken from available medical records in the screening process. In case of an unspecified MS disease course, the participant and the treating physician will be contacted for any further information. EDSS, disease-modifying drugs, fatigue-specific drugs (amantadine, modafinil), and drugs decreasing heart rate will be assessed by the treating physician on the day of arrival and made available for the study staff in the electronic health record. Use of assistive devices for walking will be ascertained in conjunction with motor function testing.

Feasibility (quantitative)

To generate the quantitative feasibility outcomes, we adopted the categories described by Thabane *et al*[31] and promoted for exercise studies in MS by Learmonth and Motl[32] (see table 4).

Feasibility (qualitative)

The qualitative evaluation aims to (1) capture patients' views on acceptance, benefits, and satisfaction with study participation, (2) assess their experiences with the intervention methods and (3) identify necessary adaptions. For this purpose, we designed a semistructured interview. Six participants from each study arm will be interviewed face-to-face at T_1. The selection of participants will reflect the greatest possible diversity in terms of gender, age and EDSS.[33] The interview will include a total of 14 questions and will last approximately 20 min. Key topics of the interview are the concept of fatigue, experiences and demands of the interventions, personal relevance, and goal achievement. All interviews will be recorded digitally and transcribed verbatim by an independent transcription service.

Both interviewers (JN and FW) have several years of clinical experience with pwMS. A first draft of this interview was piloted with three pwMS prior to the start of the feasibility study to ensure that the questions allow valid insights into participants' experiences.

The interview will be supplemented by a customised questionnaire asking for prior knowledge of fatigue, prior experiences with MAT and SET, and comprehensibility of the study instructions and questionnaires. The questionnaire also asks about fun and relevance of training for

Table 4 Description of quantitative feasibility outcomes (adapted from Hubbard *et al*[57])

Classification	Outcome	Operationalisation	Importance for future RCT
Process	1. Eligibility rate	▶ No/rate of patients being eligible ▶ No/rate of negative cases for each eligibility criterium	Determines criteria that might produce too many non-eligible patients for the trial to be conducted in a reasonable timeframe
	2. Recruitment rate	▶ No of patients successfully randomised per month	Evaluates whether the no of participants randomised is high enough to allow for a time-efficient execution
	3. Refusal rate	▶ No/rate of patients eligible but unwilling to participate (with reasons)	Provides insights on possible barriers for participation, which might be counteracted by better study information and addressing these barriers.
	4. Retention rate	▶ No/rate of patients completing the intervention period ▶ No/rate of patients returning the WEIMuS at T_2	Provides information on the risk of subjects dropping out during the intervention period, which might necessitate adaptations to the interventions or the organisation of the study. Gives information on the feasibility of the primary outcome being assessed postdischarge and via an online platform.
	5. Adherence	▶ No of therapy sessions conducted relative to sessions scheduled	Gives information on how many sessions would normally be feasible to conduct during the inpatient stay
	6. Fidelity	▶ SET: training protocols will be reviewed to ensure that communicated principles were followed: (1) no of exercises performed each session, (2) total training load prescribed relative to actual training load per exercise (eg, target: 3 (sets) × 10 (repetitions) × 20 (weight)=600, moved: 3×10×15 = 450, percentage: 75%). The ers.2 software will document all endurance training sessions, which will provide measures of training duration and intensity (average heart rate, average power, 6–20 RPE) relative to the prescribed values. ▶ MAT: To quantify the degree of aerobic challenge, in the land-based sessions, patients will be wearing heart rate sensors (Verity Sense, Polar, Kempele, Finland). Average and maximum heart rate values for each session and patient will be tracked using software (Polar Team App). ▶ MAT: Components of each session will be coded by the operating therapist according to the MAT manual (standing balance, dynamic balance and functional leg strength, agility like) to get an approximate distribution.	Gives detailed information on whether subjects were able to perform the SET as planned. In the MAT, therapist's usage of the manual will be observable. This will allow for guided adaptations of the intervention protocols, if necessary.
Resources	Time	▶ No of days needed to complete baseline assessments ▶ Time requirements for (1) the first (T25FW, SSST, FGA, 6MWT) and second (GXT) physical testing blocks at T_0 and T_1, (2) preparation of MAT sessions	Evaluates whether baseline assessments can be scheduled in a timely manner before the start of the intervention period. Precise time requirements will allow for better scheduling of study-related appointments.
Management	Data	▶ No of missing items for FSMC and WEIMuS for all measurement time points ▶ No of missing outcomes for T_0 and T_1	Provides information on actions to take to ensure questionnaires will be fully completed and all assessments taken.
Scientific	1. Adverse events	▶ No and kind of adverse events related to study interventions	Establishes the safety of all interventions.
	2. Acceptability	▶ Perceived exertion: Session-RPE after each endurance, strength, and MAT session (Category Ratio (CR-10) RPE scale as developed by Foster *et al*.[58 59] After each session patients will be asked: 'How strenuous was the session as a whole?'. Patients will be instructed to provide a global rating of the complete session and not to focus on specific aspects. ▶ Fun during training and relevance of training for daily life: assessed at T_1 by using customised questions with a four-point Likert-type scale ranging from 'not at all' to 'very much'.[60]	Perceived exertion in both groups will determine whether the interventions are perceived to be too strenuous or too easy. Fun and relevance are important measures of motivation. In case of low values, additional actions will be necessary to ensure sufficient motivation.

FGA, Functional Gait Assessment; FSMC, Fatigue Scale for Motor and Cognitive Functions; GXT, Graded Exercise Test; MAT, Multimodal Agility-based exercise Training; 6MWT, 6 min Walk Test; RCT, randomised controlled trial; RPE, Rated Perceived Exertion; SET, Strength and Endurance Training; SSST, Six Spot Step Test; T_0, postrandomisation; T_1, prior to discharge; T_2, 1–2 weeks after discharge; T25FW, Timed 25-foot Walk Test; WEIMuS, Würzburg Fatigue Inventory for Multiple Sclerosis.

daily life (see table 4), and the motivation to continue a comparable training at home.

Primary outcome for the full RCT

Fatigue questionnaires presuppose internal averaging of the amount of fatigue experienced during a certain time frame.[1] This has been a problem for studies evaluating short-term interventions, as in some questionnaires patients are asked to evaluate their fatigue in timeframes of up to 4 weeks. As we are interested in the change in fatigue experienced in daily life from before the inpatient stay to afterwards, we (I) chose the WEIMuS[34] as the primary outcome measure to assess the fatigue experienced during the past week and (II) established the primary endpoint to be 1–2 weeks after participants have returned home (T_2). The WEIMuS has 17 items (scored 0–4) with higher total scores

indicating higher fatigue (range 0–68, cut-off for classification as fatigued: 32).

For fatigue screening (that is necessary for study eligibility), we will apply the FSMC. It is a 20-item Likert-type scale (1–5) with a total score (0–100) and two subscales relating to motor and cognitive fatigue.[35] The FSMC provides cut-off scores to classify cases of no (total score <43), mild (≥43), moderate (≥53) and severe (≥63) fatigue, which makes it especially suitable as a tool for classification of fatigue severity.[1 35]

Paper versions of both questionnaires will be handed out to participants. When at home, participants will be followed up via e-mail to fill out questionnaires on an online platform (Qualtrics) at timepoints T_2–T_4. Participants will be able to respond to the email request within 7 days.

Secondary outcomes for the full RCT

MS-fatigue is a multifactorial construct that requires assessment of other inter-related constructs.[7] This will include measures of cognitive (Test Battery of Attention Performance -Alertness[36]) and motor fatigability (6 min Walk Test, Distance Walked Index[37]), cognitive performance (California Verbal Learning Test, Symbol Digit Modalities Test[26 38]) and CRF (GXT on a cycle ergometer, protocol: start 25W, progression 10 W/min). Dynamic balance and motor function (Timed 25-Foot Walk Test,[39] Six Spot Step Test (SSST),[40] Functional Gait Assessment (FGA)[41]) will also be assessed as well as self-reported balance confidence (Activities-specific Balance Confidence scale[42]). Depression (Centre for Epidemiological Studies Depression Scale (German version)[43]) will be assessed as a confounder variable.

The subsequent full trial will also include qualitative data to explore the subjective experiences in participants showing a WEIMuS change of 6 or more points from T_0 to T_2 (positive or negative). These 'responders' will be contacted for a short telephone interview. Previous data has shown large differences in fatigue questionnaire change scores.[13] However, the scores do not provide any detail on individual circumstances, including, for example, social or work-related influences, that might be independent of intervention effects. Therefore, we decided to specifically ask participants:

> The analysis of your questionnaires shows a relevant positive/negative change of your fatigue symptoms, when comparing your scores from pre-rehab to the online questionnaire. What do you personally think is the reason for this?.

No minimal clinically relevant change scores have been established yet.[44] Thus, the relevant change score (≥6 or ≤−6) was chosen as a pragmatic value of 0.5 SD from the validation study.[45] A similar procedure has been described by Sander *et al*.[1]

Data analysis

Quantitative data analysis

Descriptive statistics will be used to summarise quantitative feasibility outcomes (table 4), and baseline sample characteristics. Retention, adherence, fidelity, adverse events and acceptability measures will be calculated per group. The results will be given as mean and SD for continuous data, median and IQR, or frequencies (number, %) for categorical data. The same will be applied to baseline and follow-up data for primary and secondary outcomes of the potential full trial. Change scores from baseline will be reported for these outcomes for each of the measurement timepoints. The frequency of participants in each group with a relevant change related to the WEIMuS total score (≥6 or ≤−6, as described above) will be calculated. However, hypothesis testing of within-group or between-group treatment effects will not be performed due to the inherent problems of hypothesis testing based on (small) pilot study data.[46 47] For the same reasons, no effect sizes will be presented, as they will have a high risk of under- or overestimating the 'true effect' of the interventions.[48]

All analyses will be performed using IBM SPSS Statistics in the most up-to-date version.

Qualitative data analysis

Coding of the interviews will be performed according to qualitative content analysis, using a combined model of deductive (a priori) and inductive coding (on the text material) to identify themes and subthemes.[49] Deductive coding will be based on preliminary considerations and hypotheses in the study planning and on reviews of relevant literature.[33 50–53] Coding will be carried out by at least two individuals (JN and FW) to ensure intercoder reliability.[54] The analysis will be supported by MAXQDA software in the most up-to-date version.[55] JN and FW will compile the themes emerging from the interview data and discuss these with the wider research team.

Progression requirements to full RCT

Falling short of the following feasibility values will necessitate changes to the protocol of the full RCT:

- Adherence: Average of at least 18 therapy sessions during the stay per group (equals 6×30 min sessions per week for 3 weeks (28 days admission to discharge minus 5 days for pretesting and post-testing)).
- Recruitment rate: 4 participants/month, <25% non-eligible pwMS, <10% eligible but unwilling to participate.
- Retention at T_1: >90% per group.
- Retention at T_2: >80% per group.
- Time requirements for baseline assessments: >80% able to complete all assessments within the first 3 days of therapy.
- Interview statements indicating that the interventions are perceived as relevant, comprehensible and pleasant.

Data management

The principal investigator (FW) will be responsible for data management. Demographic and clinical characteristics will be taken from the electronic health record. All other data will be collected on forms during the inpatient

stay and via an online tool for follow-up. Data will be entered into a secure internal network database by study personnel in the NRC. Entered data will be checked for plausibility and compared with the collection forms if necessary. Data will be collected and stored in accordance with the General Data Protection Regulation.

ETHICS AND DISSEMINATION

Written informed consent will be obtained from each participant. Ethical approval was obtained from the Ethics Committee at the Medical Faculty, University of Bonn (reference number: 543/20).

The results of this feasibility study will be disseminated regardless of the magnitude or direction of effect in peer-reviewed journals, conferences and the website and magazines of the German Sport University Cologne.

DISCUSSION

This PAFS will give relevant insights for conducting a future RCT in this special setting of inpatient rehabilitation for pwMS. Content-wise, it will (1) translate existing evidence on BMCT in pwMS to this setting, (2) add to this BMCT by introducing the framework of MAT and (3) apply a clear focus on fatigue as the primary outcome. Specifically, we see the potential of a relatively large training volume (eg, about eight therapy sessions per week) compared with studies in outpatient settings, and a high amount of supervised exercise, which should provide good adherence and fidelity. Having a therapist as a supervisor is especially important for a rather complex type of exercise as is MAT. For example, there are no simple 'numbers' like sets or repetitions one can follow. Quicker movements relating to agility, like changes of direction, acceleration and deceleration, frequently lie outside the 'comfort zone' of pwMS, which necessitates guidance of a therapist. Lastly, in the group format, a therapist is mandatory to provide modifications for pwMS with higher disability or very low disability.

We also anticipate certain issues in conducting this study. For example, scheduling of appointments for testing will be challenging, as there will be several testing blocks (ie, motor function, GXT, cognitive tests, interview), conducted in different departments of the NRC, which must be fitted into certain timeslots around admission and discharge. These appointments will compete against other study unrelated appointments (eg, ward rounds, urology assessments). Regarding the eligibility and randomisation criteria, it will be challenging to have all the correct data within the first 2 days as there can be delays in the admission process. Intervention duration can be regarded as a general limitation of this project, as it is restricted to the usual inpatient stay for this group of patients in the German national healthcare system (ie, 4–6 weeks). Land-based and water-based MAT might have different mechanisms of action, especially when considering the effect of body temperature on demyelinated axons, and the cooling effect present in water.[56] Still, water-based MAT was developed to allow for a greater amount of standardised MAT therapy time. As inpatients must receive a certain amount of therapy time during their stay, not including water-based MAT would have resulted in a greater amount of uncontrolled therapy in the intervention group. In a main trial, this would only permit conclusions to be drawn on the treatment effect of concomitant land-based and water-based MAT.

Lastly, analysis of blood-based biomarkers is planned to be part of the ReFEx study project. However, as these outcomes are connected to comparably high costs for materials and analysis, addition of blood sampling is postponed to the start of a full RCT. Nevertheless, information gathered during the feasibility study will be used to allow for smooth integration of blood draws and storage during assessments at admission and discharge. As the blood draws can be regarded as the most unpleasant part of the assessments for patients, feasibility of the interventions and patient acceptance should be established first.

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Contributors FW, JN, ME and PZ designed the overall study. FW and JN designed the feasibility study and wrote the protocol. FW, JN, JS and EH implemented the screening and assessment procedures. JS, EH, ME, A-KF, HK and PZ revised the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1 Sander C, Voelter H-U, Schlake H-P, *et al*. Assessment of fatigue in multiple sclerosis. *Neurology International Open* 2017;1:E79–85.
2 Rommer PS, Eichstädt K, Ellenberger D, *et al*. Symptomatology and symptomatic treatment in multiple sclerosis: results from a nationwide MS registry. *Mult Scler* 2019;25:1641–52.
3 Barin L, Salmen A, Disanto G, *et al*. The disease burden of multiple sclerosis from the individual and population perspective: which symptoms matter most? *Mult Scler Relat Disord* 2018;25:112–21.
4 Kobelt G, Langdon D, Jönsson L. The effect of self-assessed fatigue and subjective cognitive impairment on work capacity: the case of multiple sclerosis. *Mult Scler* 2019;25:740–9.
5 Nielsen J, Schnell R, Markett S. Are “invisible MS symptoms” (fatigue, cognitive dysfunction, depression) significant in the professional performance assessment of multiple sclerosis patients two years after the inpatient primary evaluation? *Zeitschrift für Neuropsychologie* 2020;31:11–25.
6 Manjaly Z-M, Harrison NA, Critchley HD, *et al*. Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2019;90:642–51.
7 Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology* 2013;80:409–16.
8 Behrens M, Broscheid K-C, Schega L. Taxonomie und Determinanten motorischer Performance Fatigability bei Multipler Sklerose [Taxonomy and determinants of motor performance fatigability in multiple sclerosis]. *Neurologie und Rehabilitation* 2021;27:3–12.
9 Loy BD, Taylor RL, Fling BW, *et al*. Relationship between perceived fatigue and performance fatigability in people with multiple sclerosis: a systematic review and meta-analysis. *J Psychosom Res* 2017;100:1–7.
10 Langeskov-Christensen M, Bisson EJ, Finlayson ML, *et al*. Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: a scoping review. *J Neurol Sci* 2017;373:307–20.
11 Moss-Morris R, Harrison AM, Safari R, *et al*. Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis. *Behav Res Ther* 2021;137:103464.
12 Motl RW, Sandroff BM, Kwakkel G, *et al*. Exercise in patients with multiple sclerosis. *Lancet Neurol* 2017;16:848–56.
13 Wolf F, Rademacher A, Joisten N, *et al*. The aerobic capacity - fatigue relationship in persons with Multiple Sclerosis is not reproducible in a pooled analysis of two randomized controlled trials. *Mult Scler Relat Disord* 2022;58:103476.
14 Tholen R, Dettmers C, Henze T. Bewegungstherapie zur Verbesserung der Mobilität von Patienten mit Multipler Sklerose : Konsensusfassung für die S2e-Leitlinie der DGNR in Zusammenarbeit mit Physio Deutschland – Deutscher Verband für Physiotherapie (ZVK) e.V.. *Neurologie und Rehabilitation* 2019;25:3–40.
15 Donath L, van Dieën J, Faude O. Exercise-Based fall prevention in the elderly: what about Agility? *Sports Med* 2016;46:143–9.
16 Morat M, Morat T, Zijlstra W, *et al*. Effects of multimodal agility-like exercise training compared to inactive controls and alternative training on physical performance in older adults: a systematic review and meta-analysis. *Eur Rev Aging Phys Act* 2021;18:4.
17 Motl RW, Sandroff BM, DeLuca J. Exercise training and cognitive rehabilitation: a symbiotic approach for rehabilitating walking and cognitive functions in multiple sclerosis? *Neurorehabil Neural Repair* 2016;30:499–511.
18 Callesen J, Cattaneo D, Brincks J, *et al*. How do resistance training and balance and motor control training affect gait performance and fatigue impact in people with multiple sclerosis? A randomized controlled multi-center study. *Mult Scler* 2020;26:1420–32.
19 Hebert JR, Corboy JR. The association between multiple sclerosis-related fatigue and balance as a function of central sensory integration. *Gait Posture* 2013;38:37–42.
20 Hebert JR, Corboy JR, Manago MM, *et al*. Effects of vestibular rehabilitation on multiple sclerosis-related fatigue and upright postural control: a randomized controlled trial. *Phys Ther* 2011;91:1166–83.
21 Hebert JR, Corboy JR, Vollmer T, *et al*. Efficacy of balance and eye-movement exercises for persons with multiple sclerosis (BEEMS). *Neurology* 2018;90:e797–807.
22 Wright MT. Was IST Partizipative Gesundheitsforschung? *Prävention und Gesundheitsförderung* 2013;8:122–31.
23 Scott NW, McPherson GC, Ramsay CR, *et al*. The method of minimization for allocation to clinical trials. A review. *Control Clin Trials* 2002;23:662–74.
24 Charlesworth G, Burnell K, Hoe J, *et al*. Acceptance checklist for clinical effectiveness pilot trials: a systematic approach. *BMC Med Res Methodol* 2013;13:78.
25 Ladlow P, Coppack RJ, Dharm-Datta S, *et al*. The effects of low-intensity blood flow restricted exercise compared with conventional resistance training on the clinical outcomes of active UK military personnel following a 3-week in-patient rehabilitation programme: protocol for a randomized controlled feasibility study. *Pilot Feasibility Stud* 2017;3:71.
26 Zimmer P, Bloch W, Schenk A, *et al*. High-Intensity interval exercise improves cognitive performance and reduces matrix metalloproteinases-2 serum levels in persons with multiple sclerosis: a randomized controlled trial. *Mult Scler* 2018;24:1635–44.
27 Voigt-Radloff S, Stemmer R, Korporal J. Forschung zu komplexen Interventionen in Der Pflege- und Hebammenwissenschaft und in den Wissenschaften Der Physiotherapie, Ergotherapie und Logopädie: ein forschungsmethodischer Leitfaden Zur Ermittlung, evaluation und implementation evidenzbasierter Innovationen. *Version* 2016;2.
28 Page P, Hoogenboom B, Voight M. Improving the reporting of therapeutic exercise interventions in rehabilitation research. *Int J Sports Phys Ther* 2017;12:297–304.
29 Kalb R, Brown TR, Coote S, *et al*. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. *Mult Scler* 2020;26:1459–69.
30 Nielsen JB, Willerslev-Olsen M, Christiansen L, *et al*. Science-Based neurorehabilitation: recommendations for neurorehabilitation from basic science. *J Mot Behav* 2015;47:7–17.
31 Thabane L, Ma J, Chu R, *et al*. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* 2010;10:1.
32 Learmonth YC, Motl RW. Important considerations for feasibility studies in physical activity research involving persons with multiple sclerosis: a scoping systematic review and case study. *Pilot Feasibility Stud* 2018;4:1.
33 Hersche R, Weise A, Michel G, *et al*. Three-week inpatient energy management education (IEME) for persons with multiple sclerosis-related fatigue: feasibility of a randomized clinical trial. *Mult Scler Relat Disord* 2019;35:26–33.
34 Flachenecker P, Müller G, König H, *et al*. ["Fatigue" in multiple sclerosis. Development and and validation of the "Würzburger Fatigue Inventory for MS"]. *Nervenarzt* 2006;77:165-6, 168-70, 172-4.
35 Penner IK, Raselli C, Stöcklin M, *et al*. The fatigue scale for motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* 2009;15:1509–17.
36 Dettmers C, Marchione S, Weimer-Jaekel A, *et al*. Cognitive fatigability, not fatigue predicts employment status in patients with MS three months after rehabilitation. *Mult Scler Relat Disord* 2021;56:103215.
37 Van Geel F, Veldkamp R, Severijns D, *et al*. Day-To-Day reliability, agreement and discriminative validity of measuring walking-related performance fatigability in persons with multiple sclerosis. *Mult Scler* 2020;26:1785–9.
38 Costa SL, Genova HM, DeLuca J, *et al*. Information processing speed in multiple sclerosis: past, present, and future. *Mult Scler* 2017;23:772–89.
39 Motl RW, Cohen JA, Benedict R, *et al*. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. *Mult Scler* 2017;23:704–10.
40 Nieuwenhuis MM, Van Tongeren H, Sørensen PS, *et al*. The six spot step test: a new measurement for walking ability in multiple sclerosis. *Mult Scler* 2006;12:495–500.
41 Thieme H, Ritschel C, Zange C. Functional gait assessment – Deutsche version. *Physioscience* 2009;5:5–11.
42 Schott N. [German adaptation of the "Activities-Specific Balance Confidence (ABC) scale" for the assessment of falls-related self-efficacy]. *Z Gerontol Geriatr* 2008;41:475–85.

43 Hautzinger M, Bailer M*Allgemeine Depressions Skala. Die Deutsche Version des CES-D*. Weinheim: Beltz, 1993.
44 Flachenecker P, Bures AK, Gawlik A, *et al*. Efficacy of an Internet-based program to promote physical activity and exercise after inpatient rehabilitation in persons with multiple sclerosis: a randomized, single-blind, controlled study. *Int J Environ Res Public Health* 2020;17. doi:10.3390/ijerph17124544. [Epub ahead of print: 24 06 2020].
45 Flachenecker P, König H, Meissner H. Fatigue in multiple sclerosis: Validation of the WEIMuS scale ("Würzburger Erschöpfungs-Inventar bei Multipler Sklerose"). *Neurologie und Rehabilitation* 2008;14:299–306.
46 Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *J Psychiatr Res* 2011;45:626–9.
47 Sim J. Should treatment effects be estimated in pilot and feasibility studies? *Pilot Feasibility Stud* 2019;5.
48 Kistin C, Silverstein M. Pilot studies: a critical but potentially misused component of interventional research. *JAMA* 2015;314:1561–2.
49 Kuckartz U*Qualitative Inhaltsanalyse. Methoden, Praxis, Computerunterstützung*. Weinheim: Beltz Verlagsgruppe, 2018.
50 Gunn H, Andrade J, Paul L, *et al*. Balance right in multiple sclerosis (BRiMS): a guided self-management programme to reduce falls and improve quality of life, balance and mobility in people with secondary progressive multiple sclerosis: a protocol for a feasibility randomised controlled trial. *Pilot Feasibility Stud* 2018;4:26.
51 Learmonth YC, Kinnett-Hopkins D, Motl RW. Capitalising on the opinions of persons with multiple sclerosis to inform the main trial - participant opinions from participation in a feasibility study, a qualitative extension study. *Disabil Rehabil* 2019;41:3071–8.
52 O'Cathain A, Hoddinott P, Lewin S, *et al*. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. *Pilot Feasibility Stud* 2015;1:32.
53 Smith M, Williams G, Barker R. Finding the right balance with participation in exercise and sport for individuals with multiple sclerosis: protocol for a pre and post intervention feasibility study. *BMJ Open* 2020;10:e035378.
54 Flick U. *Qualitative Sozialforschung: eine Einführung*. 6. Auflage. Reinbek bei Hamburg: Rowohlt Taschenbuch Verlag, 2014.
55 Rädiker S, Kuckartz U. *Analyse qualitativer Daten mit MAXQDA: Text, Audio und Video*. Wiesbaden: Springer VS, 2019.
56 Frohman AN, Okuda DT, Beh S, *et al*. Aquatic training in MS: neurotherapeutic impact upon quality of life. *Ann Clin Transl Neurol* 2015;2:864–72.
57 Hubbard EA, Motl RW, Elmer DJ. Feasibility and initial efficacy of a high-intensity interval training program using adaptive equipment in persons with multiple sclerosis who have walking disability: study protocol for a single-group, feasibility trial. *Trials* 2020;21:972.
58 Foster C, Florhaug JA, Franklin J, *et al*. A new approach to monitoring exercise training. *J Strength Cond Res* 2001;15:109–15.
59 Haddad M, Stylianides G, Djaoui L, *et al*. Session-RPE method for training load monitoring: validity, ecological usefulness, and influencing factors. *Front Neurosci* 2017;11:612.
60 Gooßes M, Saliger J, Folkerts A-K, *et al*. Feasibility of Music-Assisted Treadmill Training in Parkinson's Disease Patients With and Without Deep Brain Stimulation: Insights From an Ongoing Pilot Randomized Controlled Trial. *Front Neurol* 2020;11.

ReFEx Strength Protocol

Principles:	**Intensity:**	
• Frequency: 3x/week • Focus on leg strength/no balance training • 5min warm-up, 3-4 exercises/session	• Session 1-5: 3x10 repetitions at 15 RPM • Session 6 to T_1: 3x12 repetitions at 12 RPM • Break between sets: 1min	
Session-RPE:		
At the end of every training the participant is requested to provide a rating on perceived exertion (i.e., session-RPE) for the complete session		
Warm-up (5min):		
• Participants can choose between treadmill, cross trainer, stepper, and recumbent stepper		
Exercise pool: Always determine 15RPM before starting a new exercise!		
1 hip		
a) Extension Leg press (upper body upright) • Start: hip angle as small as possible	b) Flexion Standing knee raises (cable) • With balance support (chair)	c) Abduction Standing abduction (cable) • With balance support
2 knee		
a) Extension Leg press (supine)	b) Flexion Prone leg curls (cable) • End: >90° flexion	
3 foot		
a) Plantar flexion Calf raises on leg press • Large ankle ROM		

RPM = Repetition maximum; RPE = Rated perceived exertion; ROM = Range of motion

Manual for the land-based and water-based MAT (adapted from[1])

1. Land-based MAT

Standing balance			**SB**
Participants perform various exercises while standing.			
Progression: BOS	Progression: Catching & Throwing	Progression: Tools	
Narrow BOS	Alone	Number of objects for throwing	
Semi-tandem stance	With partner	Kind of objects (small sacks, balls, …)	
Tandem stance			
One leg stance (+movements of opposite leg)			
Half kneeling			
Sensory modification	Visual: closed eyes		
	Somatosensory: various unstable support surfaces		
	Vestibular: head turns (horizontal, vertical)		
Cognitive add-on	-		

"Chaosball"		**SB**
An object (e.g. ball) is passed in a group in a certain sequence, participants follow the sequence and recall certain attributes of the group members.		
Progression: Number of sequences/objects		
1 sequence (= 1 object)		
Switching: 2 sequences (= 2 objects)		
Simultaneously: 2 sequences (= 2 objects)		
Simultaneously: 3 sequences (= 3 objects)		
Sensory modification	Visual: -	
	Somatosensory: various unstable support surfaces	
	Vestibular: -	
Cognitive add-on (main focus)	Memory: Recall orders	
	Divided attention: more than one object	

Balancing on lines			**DB**
Participants follow the lines on the gym floor.			
Progression: BOS, DOM	Progression: Movement	Progression: Speed of movement	
Narrow gait	High knees	Slow swing phase (e.g., 3s)	
Tandem gait	Lunges		
Forwards, backwards			
Sensory modification	Visual: Perform several steps with eyes closed		
	Somatosensory: -		
	Vestibular: Upper body & head turns		
Cognitive add-on	Double-task: Pairs of two, trailing partner gives commands for stops or turns for leading partner		
	Double-task: Pairs of two, trailing partner has to move synchronously with leading partner		

Stepping			**DB**
Participants perform various forms of steps.			
Progression: DOM	Progression: Movement	Progression: Tools	
Forwards, backwards, sidewards	High knees	Stepping out of hoop	
Combination of directions	Lunges		
	Floor "touches"		
Sensory modification	Visual: closed eyes		
	Somatosensory: Various unstable support surfaces		
	Vestibular: Head turns (horizontal, vertical, diagonal)		
Cognitive add-on	Memory: Each direction gets a number (e.g. front = 1)		

"Transport chain"			**DB**
Over 5-10m each participant follows a line, but after each collective step an object is "transported" (e.g. thrown).			
Progression: BOS, DOM	Progression: Movement	Progression: Tools	
Narrow gait	High knees	Number of tools to be thrown	
Tandem gait	Lunges	Kind of objects (small sacks, balls, …)	
forwards, backwards			
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: Upper body & head turns (horizontal)		
Cognitive add-on	-		

"Commander"			**DB**
Pairs of two: one participant has to react to the commands of the other. Commands are different combinations of a step and simultaneous catch.			
Progression: Movement	Progression: Starting position	Progression: Number of commands	
Tasks for one side of body	On the floor	2 to 8	
Tasks for both sides of body (e.g. step left, catch right)	On the floor but inside a hoop		
	On unstable support surface		
	180° turn before step and catch		
Sensory modification	Visual: closed eyes (starting position)		
	Somatosensory: Various unstable support surfaces (starting position)		
	Vestibular: 180° turns before catch		
Cognitive add-on (main focus)	Memory: Recall pairs (movement+number / movement+color word / movement+number or color word)		
	Inhibition: command = stay in place		
	Reaction: commander minimizes time to react		

"Movement memory"		**DB**
Participants move through the gym while performing gait variations coded with various commands given by therapist.		
Progression: Movement	Progression: Number of pairs	
Tasks for one side of body	4 to 8	
Tasks for both sides of body (e.g. left knee up & right hand to left shoulder)		
Similarity of movements		
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on (main focus)	Memory: Recall pairs (movement+number / movement+color word / movement+number or color word)	
	Inhibition: command = stop	

"Remote control"		**DB**
Pairs of two: a participant is steered through the room with closed eyes via tactile cues of the partner.		
Progression: number of cues	Progression: movement	
3 to 6	Tandem walk, high knees	
Sensory modification	Visual: closed eyes	
	Somatosensory: -	
	Vestibular: turning in place	
Cognitive add-on	Spatial orientation: report location in space to partner (closed eyes)	

Walking with tasks			**AG**
Each participant performs various tasks (e.g. touch opposite knee while throwing an object left to right) while walking back and forth on a 20m lane.			
Progression: DOM, speed	Progression: movement	Progression: tools	
Forwards, backwards, sidewards	Tasks for one side of body	Kind of objects (small sacks, balls, …)	
walking, jogging	Tasks for both sides of body (e.g. left knee, right hand)		
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: Head turns (horizontal)		
Cognitive add-on	-		

Agility ladder			**AG**
Participants perform exercises in an agility ladder on the floor. Number and type of foot contacts in each field are varied.			
Progression: DOM, speed	Progression: complexity	Progression: tools	
Forwards, backwards, sidewards	Easier sequences (2 / 3 touches)	Kind of objects (small sacks, balls, …)	
	Harder sequences (1,2,3,2,1 / 2 forwards 1 back / 2 in 1 out)		
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: Head turns		
Cognitive add-on	Divided attention: Participants have to call numbers shown by therapist		
	Divided attention: Participants have to catch objects thrown by therapist		

Cone tipping		**AG**
Pairs of two: one participant starts surrounded by an assemble of cones. The partner outside of the cones says which cones have to be touched.		
Progression: speed, duration	Progression: number of cones	
Walking, jogging	4 to 8	
1 round = 30s		
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on	Spatial orientation & memory: directions are given by numbers, colors or alphabet	

Slalom			**AG**
Participants move through a slalom parcour.			
Progression: speed, duration	Progression: number of obstacles	Progression: competition	
Walking, jogging	4 to 8	Hit a target with an object at the end of slalom	
1 round = 60-90s			
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: -		
Cognitive add-on	-		

Soccer			**AG**
Participants move and pass a ball.			
Progression: speed, duration	Progression: number of players	Progression: change of direction	
Walking, jogging	1 to 4	Front - back	
1 round = 60-90s		Front - back and sideways	
		Random	
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: -		
Cognitive add-on	Attention: participants have to react to stop and change of direction signals by therapist		

"Suicide runs"		**AG**
The length of the gym is split into 3 sections. Participants cover each section in different speeds, accelerating and decelerating		
Progression: speed, duration	Progression: Stops at end of section	Progression: competition
Walking, jogging 1 round = 45-90s	touch a cone circle a cone stop - 2 steps back - accelerate forwards	Hit a target with an object at the end
Sensory modification	Visual: - Somatosensory: - Vestibular: -	
Cognitive add-on	-	

2. Water-based MAT

Standing balance		**SB**
Participants perform various exercises while standing in the pool.		
Progression: BOS	Progression: free leg	Progression: hands
Narrow BOS Semi-tandem stance Tandem stance One leg stance (+movements of free leg)	Floor "touches" Leg swings Number, amplitude, direction of swings	Inside water Outside water
Sensory modification	Visual: closed eyes Somatosensory: standing on kickboard Vestibular: head turns (horizontal, vertical)	
Cognitive add-on	-	

Gait and jump variations		**DB**
Participants perform gait and jump variations in a lane.		
Progression: BOS, DOM	Progression: movement	Progression: hands
Narrow gait Tandem gait Forwards, backwards, sidewards	High knees Lunges Hot steps, skipping gait Single-leg, two-legged jumps, hold landing position 3s jumping jack	Inside water Outside water
Sensory modification	Visual: closed eyes Somatosensory: walking with feet on 1-2 kickboard(s) Vestibular: head turns (horizontal, vertical, diagonal)	
Cognitive add-on	Memory: 4 variations of jumping jack	

"Movement memory"		**DB**
Participants move through the water while performing gait variations coded with various commands given by therapist.		
Progression: movement	Progression: number of pairs	
Only legs/only arms Combination of arms + legs, one-side of body Combination of arms + legs, both sides of body Similarity of movements	4 to 8	
Sensory modification	Visual: - Somatosensory: - Vestibular: -	
Cognitive add-on (main focus)	Memory: recall pairs (movement+number / movement+color word / movement+number or color word) Inhibition: command = stop	

"Commander"		**DB**
Pairs of two. One participant must respond to the commands of the partner. The commands consist of different combinations of a catch and step.		
Progression: movement	Progression: starting position	Progression: number of commands
Catch/step = same side of body Catch/step = diagonal	Floor standing on kickboard 180° turns before catching	2 to 8
Sensory modifications	Visual: starting position with closed eyes Somatosensory: kickboard (starting position) Vestibular: 180° turns (starting position)	
Cognitive add-on (main focus)	Memory: recall pairs (movement + number / movement + color / movement + number or color) Inhibition: command = stop Reaction: reduce response time	

"Circuit Training"		**DB**
Participants complete a circuit as pairs, consisting of various functional leg strength exercises.		
Progression: duration, speed		
45-60s per exercise, 2-3 rounds, 3-4 exercises per round Exercises include: running, swimming, jumping, step-ups		
Sensory modifications	Visual: - Somatosensory: - Vestibular: -	
Cognitive add-on	-	

"Chaosball"		**SB/AG**
Participants stand in a circle and throw a ball to each other in a certain order. Various attributes of other participants must be rememberd in the process.		
Progression: number of orders / objects		
1 order (= 1 object)		
Change: 2 orders (= 2 objects)		
Simultaneously: 2 orders (= 2 objects)		
Simultaneously: 3 orders (= 3 objects)		
Sensory modifications	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on (main focus)	Memory: recall orders	
	Divided attention: more than one object	
	Spatial orientation: comply with order, while participants no longer stand in a circle, but walk/run around in the pool	

"Waiter"		**AG**
Participants balance a ball on a kickboard and simultaneously perfom different exercises.		
Progression: DOM, speed	Progression: movement	
Walk, jog	Balance ball, throw & catch ball	
Forwards, backwards, turns	Change hands on kickboard	
	Throw & catch ball while changing hands	
Sensory modification	Visual: Move eyes away from ball	
	Somatosensory: -	
	Vestibular: throw & catch with 180°/360° turns	
Cognitive add-on (main focus)	Dual-task: walk/jog & balance ball & react to commands from therapist	
	Divided attention: balance ball while commands given by therapist include hand signs	
	Memory: commands from therapist are given via numbers or via a mix of numbers, hand signs, and/or clapping	
	Processing speed: react as fast as possible to commands given by therapist	

"Compass"		**AG**
Participants move in the directions given by therapist.		
Progression: speed, duration	Progression: number of directions	
Walking, jogging	4 to 8 (front, back, side, diagonal)	
1 round = 45-60s		
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on	Memory: recall pairs (direction+number / direction+color word)	
	Inhibition: therapist gives false cues	
	Processing speed: react as fast as possible to commands	

"Mirror"		**AG**
Pairs of two. One participant leads, the other follows while always keeping the same distance.		
Progression: speed, duration	Progression: fakes	
Walking, jogging, competition (shake off)	Leader fakes change of direction	
45-60sec.	Leader changes speeds	
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on	-	

"Beachball"		**AG**
Participants play with a beachball.		
Progression: number of players		
2 to whole group		
Sensory modification	Visual: -	
	Somatosensory: standing on kickboard	
	Vestibular: -	
Cognitive add-on	-	

MAT = multimodal agility-based exercise training; BOS = Base of support; DOM = Direction of movement

Components

- SB = Standing balance
- DB = Dynamic balance & functional leg strength
- AG = Agility

Each bracket represents a module. Each module targets one of the three components.

1. Callesen J, Cattaneo D, Brincks J, et al. How do resistance training and balance and motor control training affect gait performance and fatigue impact in people with multiple sclerosis? A randomized controlled multi-center study. *Mult Scler* 2020;26(11):1420-32. doi: 10.1177/1352458519865740 [published Online First: 20190724]

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RESEARCH Open Access

Multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve multiple sclerosis-related fatigue and fatigability during inpatient rehabilitation: a randomized controlled pilot and feasibility study [ReFEx]

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Abstract

Background Multimodal agility-based exercise training (MAT) is a group-based exercise training framework for persons with multiple sclerosis (pwMS) with a potential to impact fatigue and fatigability. In a mixed-methods design, this study evaluated the feasibility of implementing MAT in an inpatient rehabilitation setting and the feasibility of a randomized controlled trial (RCT) study protocol with 'traditional' strength and endurance training (SET) as an active control condition. Secondarily, preliminary outcome data was acquired.

Methods PwMS with low to moderate disability and self-reported fatigue were randomly allocated to either MAT or SET when starting inpatient rehabilitation (4–6 weeks). The MAT-participants exercised in a group following a MAT-manual (sessions were gym- (5x/week) and pool-based (3x/week)). SET-participants exercised individually 5x/week on a cycle ergometer, and 3x/week on strength training machines. Feasibility assessments focused on processes, resources, management, time, and scientific domains. Assessed clinical outcomes at admission and discharge included perceived fatigue, motor and cognitive fatigability, cognitive performance, motor function, and balance confidence. Perceived fatigue was reassessed 1, 4, and 12 weeks after discharge. Feasibility was determined regarding predetermined progression criteria.

Results Twenty-two participants were randomized. Both groups performed the minimum number of sessions (> 18), and retention was adequate (73–91%). SET-participants performed more sessions than MAT-participants (30.8 vs. 22.7) and stayed longer in the facility (34.2 vs. 31.6 days). Non-eligibility of admitted pwMS was high (74% non-eligible), mainly due to high EDSS and inability to attend pool-based sessions. Consequently, recruitment (1.8/month) was

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slower than the predetermined progression criterium. Baseline assessments took longer than required (only 50% completed within 3 days). Short-term fatigue reduction was similar for both groups. Motor fatigability also improved in both groups, whereas cognitive fatigability deteriorated. In MAT, average improvement in walking endurance (43.9 m) exceeded minimal important change values for individuals (> 26.9 m).

Conclusions Progressing to a definitive RCT necessitates adaptation of eligibility criteria. In the present design it will also be difficult to attain similar dosing of interventions. A multicenter RCT focused only on gym-based MAT might be another option to assess the effect of MAT. The primary outcome measure should be able to measure change in perceived fatigue more robustly.

Trial registration German Clinical Trials Register: DRKS00023943, date of registration: 23 September 2021.

Keywords Agility, Exercise, Fatigue, Multiple sclerosis, Rehabilitation

Background

Multiple Sclerosis (MS) is the most common, non-traumatic, neurological disorder among middle aged adults. Initially characterized as an inflammatory demyelinating disease of the central nervous system, neurodegenerative processes lead to progressive disability during later stages [1]. In Germany, persons with MS (pwMS) frequently attend inpatient rehabilitation facilities for several weeks to improve their ability to work in a multidisciplinary setting [2]. 'Visible' symptoms such as mobility impairments play an obvious role in pwMS's ability to participate in the job market. However, 25% of pwMS are limited in their professional participation due to 'invisible' symptoms such as fatigue [3, 4].

The definition and conceptualization of fatigue has been changing and expanding for years, including recent updates [5, 6]. For the purpose of this study the term 'fatigue' refers to the 'subjective sensation of lack of energy and exhaustion' (p. E79) [7], retrospectively self-reported for a period of at least one week by a pwMS (i.e., the trait component of fatigue). The term 'fatigability' refers to objectively measured performance decrements on motor or cognitive tasks, corresponding to the taxonomy of Kluger et al. [8].

Contrary to its impact, pharmacological treatment options for fatigue are limited [9]. Consequently, many exercise and behavioral interventions have been evaluated [10]. One of the results concerning exercise is that endurance exercise, although frequently investigated, seems to have only a small effect on fatigue [11, 12]. Interventions broadly focused on 'balance' are less prevalent, but potentially with a more pronounced effect [10, 11]. Among exercise studies that explicitly addressed fatigue, almost none were conducted in an inpatient rehabilitation setting [11], which is characterized by a multidisciplinary environment, including various diagnostic and therapeutic components such as exercise, occupational therapy, health education, or neuropsychological assessment and training. Additionally, interactions between treatments as well as flexibility in the treatment schedule are common [13, 14]. This leaves clinical practice with few results that could be applied directly to this setting.

We have recently described a group-based exercise training framework for pwMS (multimodal agility-based exercise training [MAT] [15]), which might comprise several aspects that have been proposed to be beneficial for fatigue reduction, e.g., (I) balance training for making 'navigating the environment' less effortful [11], (II) 'coordination of eye, head, and whole-body movements' to 'reduce the cognitive load associated with conscious compensatory strategies in dynamic environments' [16], and (III) 'improvement of sensory integration with a subsequent reduction of the cognitive load associated with motor processing' [17]. As the MAT approach also includes other aspects suitable for inpatient rehabilitation (i.e., group-based, applicable to other neurological conditions [18]) and is proposed to be beneficial for several symptoms, including fatigability [15], the ReFEx (Rehabilitation, Fatigue, and Exercise) project aims to compare MAT with a 'traditional' exercise approach, namely, strength and endurance training (SET) [19] during inpatient rehabilitation. Both, strength and endurance training can be considered standard elements in neurorehabilitation facilities in Germany (and for the current clinic) and are part of national-level MS exercise guidelines [20].

In a first step, the present feasibility study was conducted to determine whether all aspects of the trial were implementable in the clinical setting, and to inform the potential progression to a powered randomized controlled trial (RCT). Secondarily, preliminary clinical outcome data was acquired.

Methods

Design and setting

The study was located at the Neurological Rehabilitation Center (NRC) Godeshoehe GmbH in Bonn, Germany, which provides neurorehabilitation for all levels of disability. It is certified by the German MS Society as one of three MS rehabilitation centers in the state of North Rhine-Westphalia and treats around 120 pwMS each

year, 75% coming from within-state. All study-related sessions were implemented within existing therapy services of the NRC.

The study had a two-armed, parallel-group, randomized-controlled design with 12 weeks follow-up (Fig. 1), pursuing a mixed-methods approach. The qualitative part will be reported elsewhere. We intended to recruit 12 participants per group [14], but no sample size calculation was performed as the feasibility evaluation was the primary aim.

Ethical approval was obtained from the Ethics Committee of the University of Bonn (reference number: 543/20). The study was prospectively registered in the German Clinical Trials Register (ID: DRKS00023943) on 23rd September 2021. For more details we refer to the published feasibility protocol [14].

Screening and recruitment

New admissions were screened for MS and eligibility criteria were evaluated in a joint effort by the treating neuropsychologists (JN, JS, EH) and the principal investigator (FW). Inclusion criteria were a relapsing-remitting or secondary-progressive disease course (2017 McDonald criteria [21, 22]), age between 18 and 67 years (age for retirement in Germany), Expanded Disability Status Scale (EDSS) ≤ 5.0 [23], Fatigue Scale for Motor and Cognitive Functions (FSMC) ≥ 53 (cut-off for 'moderate fatigue') [24], and written informed consent. Exclusion criteria included the inability to attend aquatic therapy, comorbidities, that prevented attending study sessions, chronic neurologic conditions other than MS, insufficient German language skills, and specific fatigue medication (Amantadine, Modafinil) started less than 3 months ago. If deemed eligible, pwMS were informed about the study verbally and in written form.

Randomization and blinding

After written informed consent, pwMS were randomly allocated (1:1) to MAT or SET, according to the minimization procedure [25], stratified by EDSS (≤3 or >3), Würzburg Fatigue Inventory for Multiple Sclerosis (WEIMuS, <38 or ≥38) [26], age (<45 or ≥45), and MS disease course (relapsing-remitting or secondary-progressive). The WEIMuS acted as a stratification factor, as it was the potential primary outcome for a future RCT. Randomization was provided by an independent researcher from the German Sport University Cologne using RITA ('Randomization-In-Treatment-Arms', Evident, Germany).

The neuropsychological staff conducting the cognitive tests were blinded to the study groups. Participants, therapists, and staff conducting the physical tests and analyzing the questionnaires were not blinded regarding group allocation. However, participants were blinded regarding which of the groups was the experimental condition.

Interventions

The intervention period lasted from admission (T_0) to discharge (T_1), comprising 4 to 6 weeks (based on medical indications, determined by the treating physician). MAT-participants performed five 30 min sessions of gym-based MAT, and three 30 min sessions of pool-based MAT per week in a group setting (including other neurological patients). SET comprised five 22 min sessions of endurance training on cycle ergometers, and three 30 min sessions of individual strength training. Endurance training was provided on cycle ergometers and not on a treadmill to enable more pronounced differences regarding the demand for sensory integration between MAT and SET [27]. Furthermore, it is the standard modality for endurance training in this clinic. Importantly, participants from both groups also attended a group on body awareness and relaxation techniques, which is part of usual care for pwMS in this clinic and which provided some social contact in the SET-group as well [14].

MAT consisted of three components: (I) standing balance exercises, (II) dynamic balance exercises including functional leg strength, and (III) agility-like exercises. Agility-like exercises have been defined as '[…] tasks, that require changes of direction, stop-and-go patterns, turns, and changing footwork strategies, with or without responding to a stimulus' [15]. For load management in the gym-setting, three sessions with higher physical demands (i.e., agility-like components and functional leg strength) were interspersed with two sessions of lower physical strain (i.e., standing balance and exercises with a cognitive focus).

In SET, endurance training was performed with 3 min of gradual increase, 17 min steady and 2 min cool-down on a cycle ergometer (ergoselect 5, ergoline GmbH, Bitz, Germany) with continuous monitoring of power output (W) and heart rate (ers.2 software, ergoline GmbH, Bitz, Germany). The first session started with a power output participants had rated 'light' (=11) to 'somewhat hard' (=13) (6–20 Rating of Perceived Exertion [RPE] – scale) during the baseline graded exercise test (GXT, see Sect. 2.5.2 and Supplement) and then continued within this range. In detail, in each of the cycling sessions, therapists asked participants to rate their perceived exertion on the 6–20 RPE scale after 8 min and/or 15 min of cycling. Two timepoints were chosen in case perceived exertion changed during the session. If pwMS gave two different RPE ratings for each timepoint, the average score was documented. Therapists regulated the power output so that participants stayed between 11 and 13 on the RPE-scale. The new session always continued with the training load from the previous session. The range of 11–13 was chosen based on recent evidence-based recommendations for pwMS with similar EDSS [19].

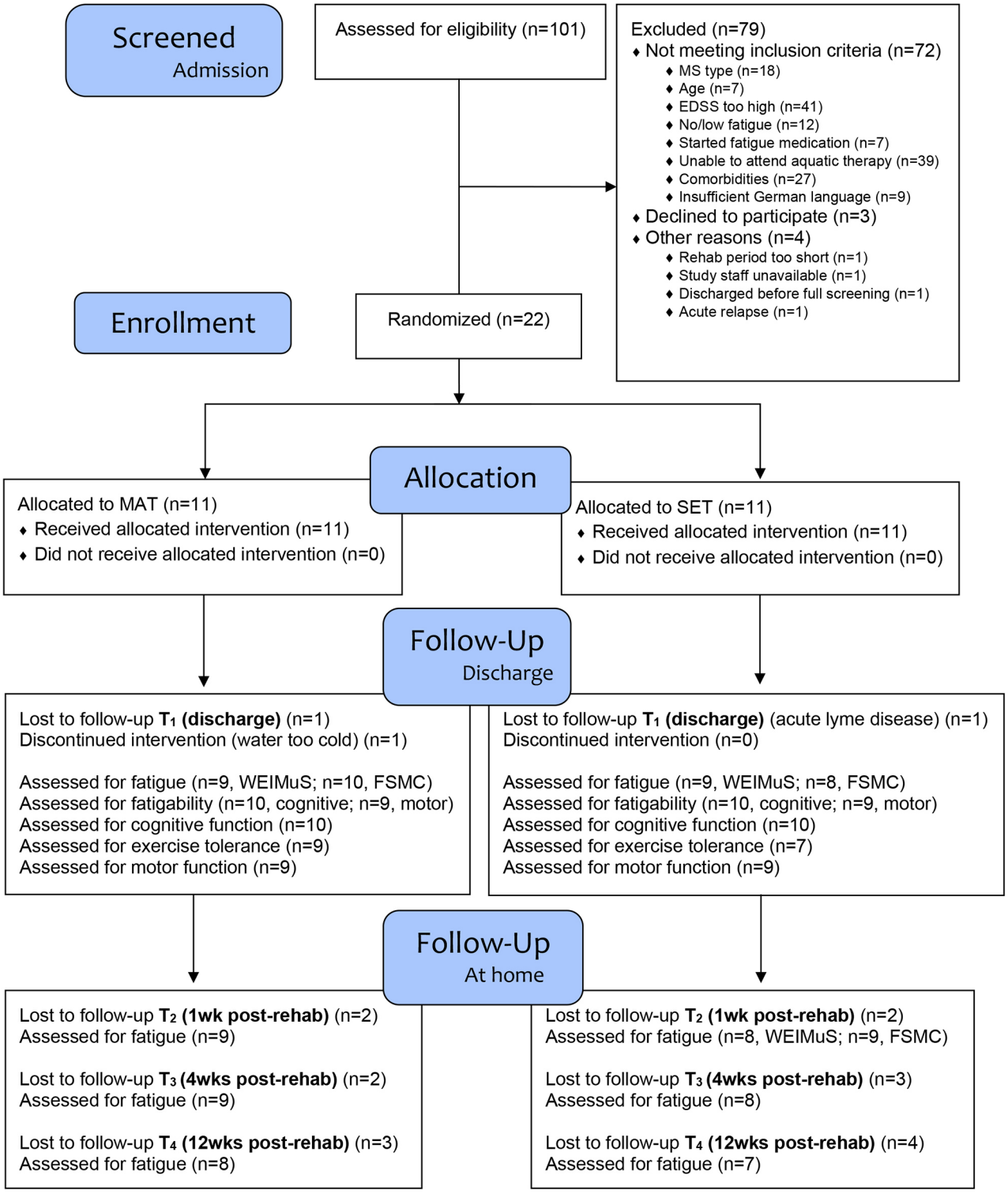

Fig. 1 CONSORT diagram. EDSS=Expanded Disability Status Scale; FSMC=Fatigue Scale for Motor and Cognitive Functions; MAT=multimodal agility-based exercise training; MS=multiple sclerosis; SET=strength and endurance training; WEIMuS= Würzburg Fatigue Inventory for Multiple Sclerosis

Strength training was adapted from published protocols [17]: each session started with a 5 min warm-up, followed by three to four lower extremity exercises. Sessions 1 through 5 included 3×10 repetitions (intensity: 15 repetitions maximum [RM]) and Session 6 through discharge included 3×12 repetitions (12RM). More details and treatment manuals are displayed in the protocol [14].

Outcomes

Feasibility

Feasibility domains were based on Thabane et al. [28] and evaluated according to prespecified progression criteria (Table 3). Evaluation of *processes* included the eligibility, recruitment, refusal, and retention rates, intervention adherence and fidelity. *Resources*-related outcomes focused on the number of days needed to complete baseline assessments, time requirements for the physical testing blocks at T_0 and T_1, and for the preparation of MAT sessions. *Data management* feasibility determined missing items from the WEIMuS and FSMC and missing assessments at T_0 and T_1. The *scientific* domain evaluated adverse events and perceived exertion. Adverse events were defined as events related to the interventions that led to early termination of a session. Perceived exertion was based on the session-RPE scale (0–10 scale, where 0 indicates 'rest', 10 indicates 'maximum' intensity) [29, 30]. See Table 4 in the protocol for details and rationales [14] and the Supplement for specifics of session-RPE application.

Six participants from each study arm were interviewed face-to-face at T_1 regarding feasibility objectives (will be reported elsewhere).

Potential clinical outcomes

Perceived fatigue was assessed with the WEIMuS [26] and FSMC [24] questionnaires at T_0 and T_1. Participants were followed up via e-mail to fill out online versions 1, 4, and 12 weeks after discharge (T_2-T_4, Fig. 1). Change in WEIMuS total score from T_0 to T_2 was evaluated as the potential primary endpoint for a future RCT [14].

Other potential clinical outcomes for a definitive RCT were assessed only at admission and discharge and included cognitive fatigability (circadian changes in tonic alertness measures, assessed with the Test Battery of Attention Performance – Alertness [TAP-Alert] [31, 32] before 11 a.m. and after 3 p.m.), motor fatigability (Distance Walked Index [DWI] [33]), cognitive performance (California Verbal Learning Test [CVLT], Symbol Digit Modalities Test [SDMT] [34]), exercise tolerance (GXT on a cycle ergometer, protocol: start 25 W, progression 10 W/min, for details, see [35] and Supplement), motor function (6-Minute Walk Test [6MWT] [36], Timed 25-Foot Walk Test [T25FW] [37], Six Spot Step Test [SSST] [38], Functional Gait Assessment [FGA] [39]), and balance confidence (Activities-specific Balance Confidence scale [ABC] [40]).

Data analysis

Descriptive statistics were used to summarize baseline sample characteristics, feasibility, and clinical outcomes, using IBM SPSS Statistics 29. Baseline differences between groups were examined using independent samples t-tests for normally distributed continuous variables or Mann-Whitney U tests for non-normally distributed and ordinal variables, and Fisher's Exact test for categorical variables, with $p<0.05$ indicating significant differences.

Change scores from baseline were calculated for clinical outcomes for each of the measurement timepoints, as was the frequency of participants in each group with a relevant improvement related to the WEIMuS (≤-6) [14] and FSMC (≤-10) [41] total scores at T_2. Since this was a small-scale feasibility study, hypothesis testing of within- or between-group treatment effects was not performed [42, 43]. For the same reasons, no effect sizes were estimated [44]. However, we compared the feasibility data to the prespecified progression criteria (Table 3).

Results

Participants

Flow of participants is depicted in the CONSORT diagram (Fig. 1). Due to maintenance work of the pool starting in October 2022 we had to reduce the sample size from 24 to 22 participants. Baseline sociodemographic and clinical characteristics are described in Table 1.

Feasibility

Results regarding the *a priori* defined progression requirements are shown in Table 3.

Processes

Twenty-five of 101 (26%) patients screened were eligible and three of 25 (12%) declined to participate. Two were interested but overwhelmed with their current situation or wanted to focus on their own primary goals. One declined because not wanting to be restrained to one intervention. 'EDSS' and 'able to attend aquatic therapy' produced the most negative cases regarding eligibility, followed by comorbidities and disease course (Fig. 1, Table S1). It took 12 months (11/2021 to 11/2022) to randomize 22 participants, equaling 1.8 randomizations per month, which is below the progression requirement (Table 3).

Retention between T_0 and T_1 was 91% for each group. One MAT-participant dropped out during the intervention period, because of the pool being too cold. One SET-participant was excluded from the follow-up analysis as he developed acute lyme disease and was unable to attend

Table 1 Baseline sociodemographic and clinical characteristics

	MAT (n = 11)	SET (n = 11)	*p*-value
Age mean (SD, min-max)	45.6 (10.1, 26–56)	53.3 (9.3, 31–64)	**0.019**[a]
Sex f:m	10:1	8:3	0.586[b]
BMI mean (SD, min-max)	25.0 (5.0, 20.0–36.9)	28.9 (7.6, 21.6–48.0)	0.116[a]
Work status (n)	• Unfit for work (1) • Retired (3) • 3-6 h/d (3) • > 6 h/d (4)	• Unfit for work (1) • Retired (5) • 3-6 h/d (3) • > 6 h/d (2)	0.921[b]
MS type RR:SP	9:2	9:2	1.000[b]
TSD mean (SD, min-max)	9.5 (7.0, 2–28)	9.7 (8.6, 0–27)	0.699[a]
EDSS median (min-max)	3.0 (1.5–4.5)	2.5 (2.0–4.5)	0.748[a]
Walking device (n)	0	0	1.000[b]
CES-D mean (SD, min-max)	24.7 (11.7, 4–40)	25.7 (8.1, 13–39)	0.818[c]
DMT (n)	• None (4) • Glatiramer acetate (1) • Natalizumab (1) • Ofatumumab (1) • Teriflunomide (1) • Cladribine (1) • Fingolimod (1) • Siponimod (1)	• None (2) • Glatiramer acetate (2) • Natalizumab (1) • Ofatumumab (1) • Teriflunomide (2) • Dimethyl fumarate (1) • Interferone beta-1b (1) • Ocrelizumab (1)	0.929[b]
Fatigue medication (n)	• Amantadine (1)* • None (10)	• None (11)	1.000[b]

[a]Mann-Whitney U test, [b]Fisher's Exact test, [c]Independent samples t-test, bold = significant difference between groups. BMI = Body Mass Index; CES-D = Centre for Epidemiological Studies Depression Scale (German version); DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; f = female; m = male; MAT = multimodal agility-based exercise training; max = maximum value; min = minimum value; MS = multiple sclerosis; n = number of patients; RR = relapsing-remitting multiple sclerosis; SD = standard deviation; SET = strength and endurance training; SP = secondary progressive multiple sclerosis; TSD = time since diagnosis in years

*this patient had started taking Amantadine more than three months ago and therefore, was not excluded

Table 2 Adherence results are shown for MAT, SET and both groups combined ('total'). Results are also given separately for gym/pool sessions and strength/endurance sessions

	Total n = 20	MAT n = 10	Gym n = 10	Pool n = 10	SET n = 10	Strength n = 10	Endurance n = 10
No. appointments (completed/scheduled (rate attended))	535/596 (90%)	228/270 (84%)	148/165 (90%)	80/105 (76%)	308/327 (94%)	117/123 (95%)	191/204 (94%)
Average completed sessions/participant (min-max)	26.8 (12–38)	22.7 (12–33)	14.8 (9–20)	8.0 (3–14)	30.8 (18–38)	11.7 (8–14)	19.1 (10–25)

MAT = multimodal agility-based exercise training; SET = strength and endurance training

most of the sessions and follow-up assessments. At T_2, nine (82%, MAT-group) and eight (73%, SET-group) participants completed the WEIMuS, respectively. Thus, retention-related progression requirements were mostly fulfilled (Table 3).

Average length of stay in the rehabilitation facility were 31.6 (SD = 5.2, min-max = 25–41, n = 10) full days for the MAT-group and 34.2 (SD = 6.2, min-max = 22–41, n = 10) full days for the SET-group and both groups managed to attain the required minimum number of sessions (Table 3). However, on average, the SET-group performed more sessions than the MAT-group and adherence for the pool-based training was lower (76%) than for all other sessions (90–95%) (Table 2).

Regarding fidelity, a total of 122 gym-based and 76 pool-based MAT-sessions were logged and analyzed for MAT-components, as noted by the respective therapists. In an average week, 18.5%/17.9% (gym/pool) of training content targeted standing balance, 46.2%/50.1% dynamic balance/functional leg strength, and 35.3%/30.2% targeted agility-like exercises, showing that therapists provided all three MAT components. Average heart rate during all tracked gym-based sessions was 93.7 bpm (SD = 11.3, min-max = 78.8-114.1, n = 11), average maximum heart rate was 116.9 bpm (SD = 11.8, min-max = 99.1-132.3, n = 11).

In SET, strength sessions included an average 2.8 exercises (goal: three), and participants performed an average 99.5% of the prescribed load. Endurance sessions lasted for an average 21min26s (goal: 22 min) and average heart rate corresponded to 107.1 bpm (SD = 14.4, min-max = 90.5-127.9, n = 10). The average prescribed training intensity for cycling sessions was 57.5 W (SD = 24.2, min-max = 35–120, n = 10), while average actual load was

Table 3 *A priori* progression requirements [14] and results

Requirement	Results
quantitative	
1. Adherence	
Average of at least 18 therapy sessions completed during the stay per group	+ MAT: 22.7 (12–33) + SET: 30.8 (18–38)
2. Recruitment	
4 participants/month	− 1.8/month
< 25% non-eligible pwMS	− 74% non-eligible
< 10% eligible but unwilling to participate	− 12%
3. Retention	
T_1 > 90% per group	+ 91% (both groups)
T_2 > 80% per group	+ 82% (MAT) − 73% (SET)
4. Time	
> 80% able to complete all baseline assessments within the first 3 days of therapy	− 50%
qualitative	
5. Interviews	
Statements indicate that the interventions and study processes are acceptable	There were no major acceptability issues. Still, some adaptations to the study protocol were identified and will be reported separately.

Adherence data is presented as mean (min-max); + =requirement fulfilled; - =requirement not fulfilled; MAT=multimodal agility-based exercise training; pwMS=persons with multiple sclerosis; SET=strength and endurance training; T_1=discharge; T_2=one-week post-discharge

53.5 W (SD=34.2, min-max=24.5-139.6, n=10), corresponding to an average 88% completion of the prescribed load (SD=20, min-max=54–116, n=10). Average RPE (6-20) during cycling was 12.8 (SD=0.5, min-max=11.7–13.2, n=10) (goal: 11–13).

Resources

Days needed to complete the baseline assessments were 4.1 (SD=1.5, min-max=3–9, n=22) and 50% of participants completed all assessments within the first 3 days of therapy, which is below the required 80% (Table 3).

At T_0 and T_1, average time requirements for the physical assessments were 45 min (T_0) and 43 min (T_1) for motor function, and 30 min (T_0) and 33 min (T_1) for the GXT. To prepare MAT-sessions, therapists needed an average 3.7 min (gym-based, min-max=1–12, n=102 sessions) and 2.6 min (pool-based, min-max=1–12, n=62 sessions).

Data management

Data management revealed no missing items for WEIMuS and FSMC questionnaires and no missing assessments at T_0. At T_1, 7/22 (32%) participants had at least one missing assessment, with the GXT missing the most (six participants).

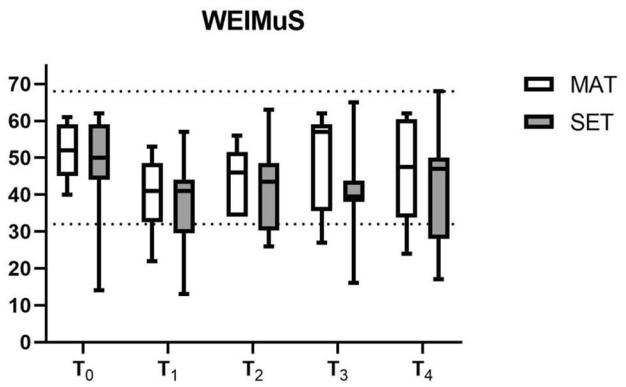

Fig. 2 WEIMuS total scores for both groups. Lower scores indicate less fatigue. Box plot: line=median, whiskers=min-max. Upper dotted line=maximum WEIMuS total score (=68); lower dotted line=cut-off for fatigue (=32); MAT = multimodal agility-based exercise training; SET = strength and endurance training; T_0=admission; T_1=discharge; T_2=1 week post-discharge; T_3=4 weeks post-discharge; T_4=12 weeks post-discharge

Scientific

No adverse events occurred in the MAT-group. During the cycling sessions, therapists noted six minor adverse events occurring in three participants (knee pain, severe fatigue, dizziness, low blood pressure).

Average session-RPE was 4.7 (gym-based, min-max=2.3–6.8, n=11, 141 sessions), 3.6 (pool-based, min-max=2.3–5.4, n=11, 61 sessions), 4.0 (strength, min-max=1.7–5.4, n=10, 105 sessions), and 3.8 (endurance, min-max=2.1–5.8, n=9, 136 sessions), respectively. According to the session-RPE scale a score of 3 indicates 'moderate' intensity, 4 is 'somewhat hard', and 5 is 'hard' [30].

Clinical outcomes

Fatigue

Both groups showed a comparable median reduction in WEIMuS total scores at T_1 and T_2 (Fig. 2, scores are reported in Table S2 as Supplement), with the MAT group having a higher percentage of participants with a relevant improvement at T_2 (7/9, 78% [MAT] vs. 5/8, 63% [SET]). At T_3, the MAT group displayed a sharp rise in scores, which dropped again at T_4. From T_0 to T_4, individual WEIMuS trajectories showed an increasing variability for participants with a full data set (Fig. 3).

FSMC total scores are reported in the Supplement (Figure S1, Table S2). The proportion of participants with a relevant improvement at T_2 was considerably lower than for the WEIMuS (0/9, 0% [MAT] vs. 3/9, 33% [SET]).

Fatigability

Of the whole sample, three MAT- and two SET-participants revealed clinically relevant (i.e., at least −10% decrease in meters walked between the first minute of

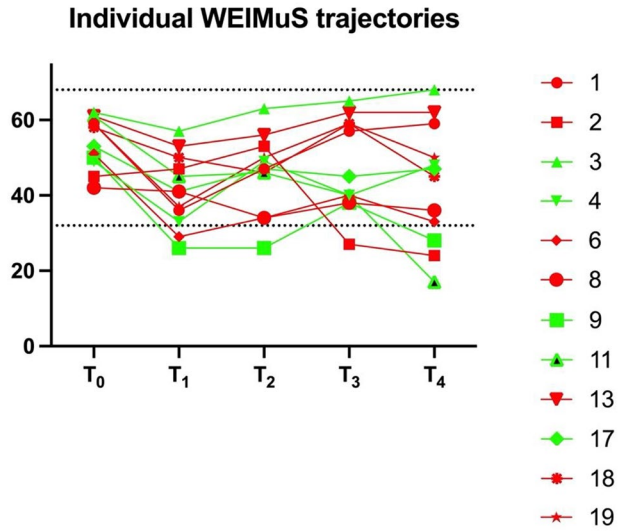

Fig. 3 Individual WEIMuS total score trajectories for participants with a full data set from T_0 to T_4 (n = 12). A decrease in scores indicates less fatigue. Red = multimodal agility-based exercise training; green = strength and endurance training; upper dotted line = maximum WEIMuS total score (68); lower dotted line = indicates cut-off for fatigue [32]; T_0 = admission; T_1 = discharge; T_2 = 1 week post-discharge; T_3 = 4 weeks post-discharge; T_4 = 12 weeks post-discharge

the 6MWT and the last minute) [33] walking fatigability at T_0 and T_1, respectively. Both groups improved their DWI (i.e., less drop-off in meters walked between minute 1 and 6, Table 4) with several participants showing substantial improvements (e.g., +14.6%). However, as most participants also walked further at T_1, some also showed a worse DWI at T_1.

Cognitively, tonic alertness reaction times increased in both groups between morning and afternoon assessments at T_0 and T_1, reflecting cognitive fatigability [45]. Unexpectedly, in both groups, afternoon alertness measures deteriorated between admission and discharge, as did the difference between morning and afternoon assessments. Only in the SET reaction times in the morning were faster at T_1. Overall, variability was high.

Other clinical outcomes

Peak power output in the GXT increased in both groups, with higher change scores in SET. Validity criteria [46] for cardiorespiratory fitness testing were mostly not attained, except for perceived exertion (Supplement). Therefore, we changed our terminology to 'exercise tolerance' [47].

All motor function measures also increased in both groups. For the 6MWT, improvements (43.9 m [MAT], 26.3 m [SET]) exceeded measurement error on group-level (≥11.1 m) and in the MAT also substantially exceeded minimal important change values for patients with mild disability (≥26.9 m) [48].

Discussion

This study examined the feasibility of a trial comparing a 'new' group-based exercise framework for pwMS (MAT) [15] with 'traditional' exercise (SET) in an inpatient rehabilitation setting. Main clinical outcomes of interest for a definitive RCT were fatigue and fatigability [8].

Among the four predefined quantitative progression categories, one category was fulfilled (adherence), one was mixed, but approached a positive value (retention), and two were negative (recruitment, time). Therefore, changes to the study design are necessary.

Descriptively, favorable changes in fatigue were observable in both groups at the end of rehabilitation. Mobility related outcomes also improved in both groups, with the most pronounced changes in walking endurance, where MAT elicited clinically relevant changes.

Feasibility

Advantages of inpatient rehabilitation include the high frequency of exercise sessions and high retentions rates, as patients are on-site. However, pwMS are also embedded in a multidisciplinary setting, with study-unrelated appointments possibly interfering with study-related sessions. Adherence rates were lower than the ones described by Zimmer et al. [49] (100%, n = 57) in a similar setting, but this trial also included fewer study-related sessions/week (3–5/week for 3 weeks vs. 8/week for >4 weeks). Thus, the present results on adherence still indicate that a high frequency of sessions was possible on an organizational level and regarding the capacities of this (fatigued) patient collective. One exception was the pool session (only 76% adherence), which should be moved to a spot with a longer break from lunch, as indicated by pwMS in the interviews.

Another option would be to cut the pool-based sessions to (I) allow for more time to recover, (II) increase recruitment (as eligibility for pool-based sessions was low), (III) avoid the mix-up of effects from gym- and pool-based MAT, and (IV) lower the barrier for replication, without the need for a pool.

Even though both groups performed the minimum number of sessions, the SET-group attended substantially more sessions (228 [MAT] vs. 308 [SET]), as appointments were much more flexible due to individual scheduling. Consequently, MAT had considerably lower 'dosing'. This is interesting, as one hypothesis of the MAT framework is that it might be more time-efficient [15]. Still, to evaluate differences in treatment effects it is important to ensure similar amounts of sessions performed, first [50].

Only about 1.8 participants were randomized per month instead of the intended four. There are examples of other trials conducted in similar settings, reporting equally low eligibility [49, 51]. If 'able to attend aquatic

Table 4 Descriptive data on clinical outcomes at admission, discharge, and change scores (T_1-T_0).

Domain	Outcome	MAT		SET	
		Mean (SD)	Min-max	Mean (SD)	Min-max
Fatigability	**DWI (%)**				
	T_0 [a]	-7.8 (6.5)	-17.6–0.0	-7.6 (5.8)	-20.0–3.3
	T_1 [a]	-6.5 (5.2), n = 9	-15.5–0.0	-5.4 (5.3), n = 9	-11.6–3.1
	T_1-T_0 (change) ↑	1.7 (8.5)	-9.8–14.6	3.4 (4.3)	-2.0–9.6
	TAP-Alertness (afternoon-morning difference, ms)				
	T_0 [b]	12.2 (60.2)	-108–119	8.2 (79.7)	-62–240
	T_1 [b]	36.2 (136.3), n = 10	-97–364	10.6 (50.7), n = 10	-26–148
	T_1-T_0 (change) ↓	22.6 (130. 9)	-154–332	25.6 (56.2)	-19–167
Cognitive performance	**CVLT (n words)**				
	T_0 [c]	56.9 (10.7)	37–71	53.0 (10.0)	28–65
	T_1 [c]	53.0 (12.5), n = 10	38–74	53.7 (11.3), n = 10	36–70
	T_1-T_0 (change) ↑	-3.9 (7.5)	-18–3	0.8 (11.4)	-20–22
	SDMT(n pairs)				
	T_0 [d]	49.7 (9.1)	30–62	49.2 (9.3)	35–63
	T_1 [d]	52.9 (10.6), n = 10	36–67	52.0 (8.8), n = 10	38–69
	T_1-T_0 (change) ↑	1.2 (5.8)	-10–9	3.6 (6.1)	-5–13
Exercise tolerance	**GXT (W_{peak})**				
	T_0 [c]	106.8 (37.1)	55–175	110.5 (42.7)	55–225
	T_1 [c]	101.7 (32.8), n = 9	65–165	130.7 (51.6), n = 7	95–245
	T_1-T_0 (change) ↑	2.2 (6.7)	-10–10	14.3 (16.1)	0–40
Motor function & confidence	**6MWT (m)**				
	T_0 [c]	499.0 (90.1)	366–631	511.5 (89.6)	315–648
	T_1 [c]	544.8 (101.9), n = 9	399–700	537.1 (87.0), n = 9	365–660
	T_1-T_0 (change) ↑	43.9 (30.0)	-25–77	26.3 (32.8)	-14–81
	T25FW (s)				
	T_0 [d]	5.20 (0.99)	4.05–7.10	4.98 (0.98)	3.90–7.05
	T_1 [d]	5.01 (0.79), n = 9	3.95–6.5	4.80 (0.55), n = 9	4.35–6.10
	T_1-T_0 (change) ↓	-0.10 (0.40)	-0.61–0.65	-0.30 (0.61)	-1.10–0.50
	SSST (s)				
	T_0 [d]	8.19 (2.42)	4.95–11.37	7.48 (1.80)	5.52–11.62
	T_1 [d]	7.55 (2.21), n = 9	4.91–10.72	6.58 (1.33), n = 9	4.90–8.85
	T_1-T_0 (change) ↓	-0.51 (1.12)	-2.45–1.52	-0.92 (1.07)	-2.77–0.43
	FGA(total score)				
	T_0 [c]	23.0 (18.0–26.0)*	14–28	24.0 (23.0–27.0)*	12–28
	T_1 [c]	24.0 (19.0–26.5), n = 9	14–30	25.0 (23.0–28.0), n = 9	15–29
	T_1-T_0 (change) ↑	2.0 (-1.5–4.5)	-4–6	2.0 (0.0–2.0)	-1–3
	ABC (total score)				
	T_0 [c]	70.5 (21.3)	24.1–99.1	75.8 (14.9)	55.0–95.6
	T_1 [c]	67.8 (19.4), n = 10	33.4–97.2	72.1 (13.2), n = 8	57.5–96.3
	T_1-T_0 (change) ↑	0.2 (7.2)	-12.5–10.3	-2.6 (6.8)	-16.4–5.6

All outcomes had n = 11 at T_0, sample size for each outcome at T_1 is reported in the table. All scores are presented as mean (SD, min-max), except for the FGA, presented as median (interquartile range). Arrows indicate direction for improvement. [a] = scores closer to zero indicate less fatigability; [b] = lower scores indicate smaller increase in fatigability from morning to afternoon; [c] = higher scores are favorable; [d] = lower scores are favorable; * FGA scores are presented as median (interquartile range); 6MWT = 6-Minute Walk Test; ABC = Activities-specific Balance Confidence scale; CVLT = California Verbal Learning Test; DWI = distance walked index; FGA = Functional Gait Assessment; GXT = graded exercise test; MAT = multimodal agility-based exercise training; SDMT = Symbol Digit Modalities Test; SET = strength and endurance training; SSST = Six Spot Step Test; T25FW = Timed 25-Foot Walk Test; TAP = Test Battery of Attention Performance; T_0 = admission; T_1 = discharge; W_{peak} = peak power output

therapy' and 'relapsing-remitting/secondary-progressive disease course' would be excluded as criteria, eligibility could be increased from 26 to 35%. Still, this would not be sufficient. A preliminary sample size calculation for a clinically relevant difference regarding the WEIMuS retrieved a sample size of n = 66, which would take about 46 months to recruit with the present results, or about 32 months with the adapted inclusion criteria. A multicenter trial might be an option to progress in a more efficient amount of time. A limitation of the eligibility assessment could have been the COVID-19 pandemic, which might have resulted in fewer applications for rehabilitation from pwMS with lower EDSS, because of COVID-19 restrictions.

Interestingly, gym-based MAT elicited the highest ratings of session-based perceived exertion, which on

average approached the rating of 'hard' - despite the fact, that average heart rate values were low. This warrants several considerations. First, the present heart rate values only give a very broad impression regarding intensity as they do not take maximum heart rate into account. As age differed between groups, heart rates indicating relative intensity would also be different. Furthermore, it is important to consider that even 'high physical strain' gym-based MAT sessions have many standing breaks, e.g., while the therapist gives demonstration and instructions, which profoundly reduces average heart rate for a complete session and leads to a more interval-like training stimulus. Values of average maximum heart rate might also be misleading, as 'low physical strain' MAT sessions blunted maximum values from the 'high physical strain' sessions. For example, four MAT-participants had individual gym-sessions with maximum heart rates above 150 bpm. Lastly, what we can only describe anecdotally is that MAT-participants repeatedly differentiated their session-based perceived exertion between physical and cognitive exertion (but were then prompted to give an overall score). Supposedly, this could reflect the unique content of MAT, and cognitive elements might increase session-RPE scores.

Clinical outcomes

Regarding the performed assessments, this study is among the first which broadly focused on balance/motor control and conducted several follow-up measurements for fatigue [10]. Retention from end-of-treatment to 3 months follow-up was acceptable in both groups (78–89%), suggesting the online fatigue assessment to be a viable option for future follow-up assessments.

Observed (descriptive) changes in fatigue (i.e., WEIMuS) from admission to discharge/1 week after discharge were higher than for short-term treatment with fampridine, for example [52]. The reason for the rise in scores at T_3 for MAT is unclear, but could be attributed to the small sample size, as scores dropped again at T_4.

Proper assessment of fatigue seems to be one of the biggest challenges regarding the development of treatment strategies. The WEIMuS and FSMC differed in their classification of responders 1 week after discharge and clinically relevant change values have not been rigorously determined for these measures [7]. Therefore, switching to one of the 'new generation' questionnaires (e.g., PROMIS Fatigue (MS) 8a [53]) might be considered for a future trial [53, 54].

Similarly, no gold standard exists to quantify walking fatigability in pwMS [55]. Assessment of DWI is one option and was easily implementable in the present setting. Nevertheless, instrumented walking fatigability assessment has been advocated recently as another option and might be selected for a future RCT [55, 56].

Unexpectedly, cognitive fatigability tended to be worse at T_1. A reason for this might be that the cognitive load between the morning/afternoon assessments was not rigorously standardized. In addition, it has been shown that a number of other disease-specific factors (e.g., daytime sleepiness, hand motor impairment), personality-related behavioral factors in dealing with performance situations (e.g., energy management, test anxiety), or psychometric aspects of test use (e.g., practice effects) could contribute directly or indirectly to this relationship, complicating interpretation [57].

Limitations

As mentioned, advantages of inpatient rehabilitation are the high volume and frequency of exercise sessions and high retentions rates. However, some general disadvantages of the inpatient rehabilitation setting should be reconsidered. First, the intervention duration is restricted and, as MAT is a group-based, therapist-led intervention (i.e., no home-based or digital training) [15], the setting precludes the possibility of evaluating long-term MAT effects. If MAT is framed as a reserve-building activity long-term studies are needed [15, 58], which would favor an outpatient setting. Second, the multidisciplinary setting might affect some of the outcome measures. As it would be unethical to withhold a certain kind of therapy, patients can receive, for example, varying degrees of complementary computerized cognitive training, making it challenging to distill the effect of the study-related training. This feeds into the wider discussion on the 'black box' of usual care and treatment components in rehabilitation [59]. Third, the length of stay in a neurorehabilitation facility in Germany is not fixed but is determined during the stay by the treating physician based on medical indications and can vary between 4 and 6 weeks. Therefore, intervention duration was not matched. However, this allows the design to reflect the actual clinical setting and the same follow-up periods post-discharge. Lastly, all results from the present feasibility study, must be seen in light of the small sample size, and potentially 'delivery agent bias' [60], i.e., the newly evaluated intervention (MAT) was partially provided by a developer (FW) [14], which might have increased its effects and compromised blinding.

Conclusions

Substantial changes to the study design are needed, especially to increase recruitment. Going forward, a multicenter trial focused on gym-based MAT might be another option. 'New generation' fatigue questionnaires, instrumented motor fatigability, and alertness assessments with a standardized cognitive load are candidates for improved outcome assessments.

List of Abbreviations

6MWT	6-Minute Walk Test
ABC	Activities-specific Balance Confidence scale
CVLT	California Verbal Learning Test
DWI	Distance Walked Index
FGA	Functional Gait Assessment
FSMC	Fatigue Scale for Motor and Cognitive Functions
GXT	Graded exercise test
MAT	Multimodal agility-based exercise training
NRC	Neurological Rehabilitation Center
ReFEx	Rehabilitation, Fatigue, and Exercise
pwMS	Persons with multiple sclerosis
RPE	Rating Perceived Exertion
SET	Strength and endurance training
SDMT	Symbol Digit Modalities Test
SSST	Six Spot Step Test
T25FW	Timed 25-Foot Walk Test
TAP-Alert	Test Battery of Attention Performance – Alertness
WEIMuS	Würzburg Fatigue Inventory for Multiple Sclerosis

Supplementary Information

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Supplementary Material 1

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Authors' contributions
FW, JN, ME and PZ designed the overall study. FW and JN designed the feasibility study. FW, JN, JS and EH implemented the screening and assessment procedures. PK assisted with data collection and strength sessions. FW conducted statistical analysis and drafted the manuscript. All authors read and revised the manuscript.

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Data Availability
The raw data were generated at the Neurological Rehabilitation Center Godeshoehe GmbH. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Ethics Committee of the University of Bonn (reference number: 543/20). Participants were informed about the study verbally and in written form and all provided written consent. All methods were carried out in accordance with relevant guidelines and regulations in the declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
FW: none. JN: received honoraria from the MS Society Vienna, Austria, and grants from the Pharos Foundation, Dortmund, Germany JS: none. EH: none. PK: none. ME: none. A-KF: none. HK: none. PZ: received grants from the German Multiple Sclerosis Society NRW.

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References

1. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet. 2018;391(10130):1622–36.
2. Dettmers C, Schmidt R, Jöbges M. Fatigue und fatigability bei Multipler Sklerose – Leistungsbeurteilung. Die Rehabilit. 2020;59:327–9.
3. Kobelt G, Langdon D, Jönsson L. The effect of self-assessed fatigue and subjective cognitive impairment on work capacity: the case of multiple sclerosis. Mult Scler. 2019;25(5):740–9.
4. Nielsen J, Schnell R, Markett S, Saliger J, Arling V, Karbe H. Are invisible MS symptoms (fatigue, cognitive dysfunction, depression) significant in the professional performance assessment of multiple sclerosis patients two years after the inpatient primary evaluation? Z Neuropsychol. 2020;31(1):11–25.
5. Behrens M, Gube M, Chaabene H, Prieske O, Zenon A, Broscheid KC, et al. Fatigue and human performance: an updated Framework. Sports Med. 2023;53(1):7–31.
6. Enoka RM, Almuklass AM, Alenazy M, Alvarez E, Duchateau J. Distinguishing between fatigue and fatigability in multiple sclerosis. Neurorehabil Neural Repair. 2021;35(11):960–73.
7. Sander C, Voelter H-U, Schlake H-P, Eling P, Hildebrandt H. Assessment of fatigue in multiple sclerosis. Neurol Int Open. 2017;1(02):E79–E85.
8. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. Neurology. 2013;80(4):409–16.
9. Nourbakhsh B, Revirajan N, Morris B, Cordano C, Creasman J, Manguinao M, et al. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. Lancet Neurol. 2021;20(1):38–48.
10. Harrison AM, Safari R, Mercer T, Picariello F, van der Linden ML, White C, et al. Which exercise and behavioural interventions show most promise for treating fatigue in multiple sclerosis? A network meta-analysis. Mult Scler. 2021;27(11):1657–78.
11. Moss-Morris R, Harrison AM, Safari R, Norton S, van der Linden ML, Picariello F, et al. Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis. Behav Res Ther. 2021;137:103464.
12. Wolf F, Rademacher A, Joisten N, Proschinger S, Schlagheck ML, Bloch W, et al. The aerobic capacity – fatigue relationship in persons with multiple sclerosis is not reproducible in a pooled analysis of two randomized controlled trials. Mult Scler Relat Disord. 2022;58:103476.
13. Voigt-Radloff S, Stemmer R, Korporal J, Horbach A, Ayerle G, Schäfers R et al. Forschung zu komplexen Interventionen in der Pflege- und Hebammenwissenschaft und in den Wissenschaften der Physiotherapie, Ergotherapie und Logopädie: ein forschungsmethodischer Leitfaden zur Ermittlung, Evaluation und Implementation evidenzbasierter Innovationen; Version 2. 2016.
14. Wolf F, Nielsen J, Saliger J, Hennecken E, Eschweiler M, Folkerts A-K et al. Randomised controlled pilot and feasibility study of multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve multiple sclerosis-related fatigue and fatigability during inpatient rehabilitation (ReFEx): study protocol. BMJ Open. 2022;12(9).
15. Wolf F, Eschweiler M, Rademacher A, Zimmer P. Multimodal Agility-based Exercise training for persons with multiple sclerosis: a New Framework. Neurorehabil Neural Repair. 2022;36(12):777–87.
16. Hebert JR, Corboy JR, Vollmer T, Forster JE, Schenkman M. Efficacy of Balance and Eye-Movement exercises for persons with multiple sclerosis (BEEMS). Neurology. 2018;90(9):e797–e807.
17. Callesen J, Cattaneo D, Brincks J, Kjeldgaard Jørgensen ML, Dalgas U. How do resistance training and balance and motor control training affect gait performance and fatigue impact in people with multiple sclerosis? A randomized controlled multi-center study. Mult Scler. 2020;26(11):1420–32.

18. O'Malley N, Clifford AM, Conneely M, Casey B, Coote S. Effectiveness of interventions to prevent falls for people with multiple sclerosis, Parkinson's Disease and Stroke: an umbrella review. BMC Neurol. 2021;21(1):378.
19. Kalb R, Brown TR, Coote S, Costello K, Dalgas U, Garmon E, et al. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the Disease course. Mult Scler. 2020;26(12):1459–69.
20. Tholen R, Dettmers C, Henze T, Höthker S, Flachenecker P, Lamprecht S, et al. Bewegungstherapie zur verbesserung der mobilität von patienten mit multipler sklerose: konsensusfassung für die s2e-leitlinie der dgnr in zusammenarbeit mit physio deutschland – Deutscher verband für physiotherapie (ZVK) e. V. Neurol Rehabil. 2019;25(1):3–40.
21. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83(3):278–86.
22. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.
23. Andreu-Caravaca L, Ramos-Campo DJ, Chung LH, Rubio-Arias J. Dosage and effectiveness of aerobic training on Cardiorespiratory Fitness, Functional Capacity, Balance, and fatigue in people with multiple sclerosis: a systematic review and Meta-analysis. Arch Phys Med Rehabil. 2021;102(9):1826–39.
24. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult Scler. 2009;15(12):1509–17.
25. Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials. A review. Control Clin Trials. 2002;23(6):662–74.
26. Flachenecker P, König H, Meissner H, Müller G, Rieckmann P. Fatigue in multiple sclerosis: validation of the WEIMuS scale (Würzburger Erschöpfungs-Inventar Bei Multipler Sklerose). Neurol Rehabil. 2008;14:299–306.
27. Sandroff BM, Motl RW, Reed WR, Barbey AK, Benedict RHB, DeLuca J. Integrative CNS plasticity with Exercise in MS: the PRIMERS (PRocessing, integration of Multisensory Exercise-related stimuli) conceptual Framework. Neurorehabil Neural Repair. 2018;32(10):847–62.
28. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol. 2010;10:1.
29. Foster C, Florhaug JA, Franklin J, Gottschall L, Hrovatin LA, Parker S, et al. A new approach to monitoring exercise training. J Strength Cond Res. 2001;15(1):109–15.
30. Haddad M, Stylianides G, Djaoui L, Dellal A, Chamari K. Session-RPE Method for Training load monitoring: validity, ecological usefulness, and influencing factors. Front Neurosci. 2017;11:612.
31. Neumann M, Sterr A, Claros-Salinas D, Gütler R, Ulrich R, Dettmers C. Modulation of alertness by sustained cognitive demand in MS as surrogate measure of fatigue and fatigability. J Neurol Sci. 2014;340(1–2):178–82.
32. Claros-Salinas D, Bratzke D, Greitemann G, Nickisch N, Ochs L, Schröter H. Fatigue-related diurnal variations of cognitive performance in multiple sclerosis and stroke patients. J Neurol Sci. 2010;295(1–2):75–81.
33. Van Geel F, Veldkamp R, Severijns D, Dalgas U, Feys P. Day-to-day reliability, agreement and discriminative validity of measuring walking-related performance fatigability in persons with multiple sclerosis. Mult Scler. 2020;26(13):1785–9.
34. Strober L, DeLuca J, Benedict RH, Jacobs A, Cohen JA, Chiaravalloti N, et al. Symbol Digit modalities Test: a valid clinical trial endpoint for measuring cognition in multiple sclerosis. Mult Scler. 2019;25(13):1781–90.
35. Schlagheck ML, Bansi J, Wenzel C, Kuzdas-Sallaberger M, Kiesl D, Gonzenbach R, et al. Complexity and pitfalls in maximal exercise testing for persons with multiple sclerosis. Eur J Neurol. 2023;30(9):2726–35.
36. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Mult Scler. 2008;14(3):383–90.
37. Motl RW, Cohen JA, Benedict R, Phillips G, LaRocca N, Hudson LD, et al. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. Mult Scler. 2017;23(5):704–10.
38. Nieuwenhuis MM, Van Tongeren H, Sørensen PS, Ravnborg M. The six spot step test: a new measurement for walking ability in multiple sclerosis. Mult Scler. 2006;12(4):495–500.
39. Thieme H, Ritschel C, Zange C. Functional Gait Assessment – deutsche version. Physioscience. 2009;5:5–11.
40. Schott N. [German adaptation of the activities-specific balance confidence (ABC) scale for the assessment of falls-related self-efficacy]. Z Gerontol Geriatr. 2008;41(6):475–85.
41. D'Hooghe M, Van Gassen G, Kos D, Bouquiaux O, Cambron M, Decoo D, et al. Improving fatigue in multiple sclerosis by smartphone-supported energy management: the MS TeleCoach feasibility study. Mult Scler Relat Disord. 2018;22:90–6.
42. Sim J. Should treatment effects be estimated in pilot and feasibility studies? Pilot Feasibility Stud. 2019;5:107.
43. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. J Psychiatr Res. 2011;45(5):626–9.
44. Kistin C, Silverstein M. Pilot studies: a critical but potentially misused component of Interventional Research. JAMA. 2015;314(15):1561–2.
45. Harrison AM, das Nair R, Moss-Morris R. Operationalising cognitive fatigability in multiple sclerosis: a Gordian knot that can be cut? Mult Scler. 2017;23(13):1682–96.
46. Langeskov-Christensen M, Langeskov-Christensen D, Overgaard K, Moller AB, Dalgas U. Validity and reliability of VO(2)-max measurements in persons with multiple sclerosis. J Neurol Sci. 2014;342(1–2):79–87.
47. Valet M, Stoquart G, de Broglie C, Francaux M, Lejeune T. Simplified indices of exercise tolerance in patients with multiple sclerosis and healthy subjects: a case-control study. Scand J Med Sci Sports. 2020;30(10):1908–17.
48. Baert I, Freeman J, Smedal T, Dalgas U, Romberg A, Kalron A, et al. Responsiveness and clinically meaningful improvement, according to disability level, of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. Neurorehabil Neural Repair. 2014;28(7):621–31.
49. Zimmer P, Bloch W, Schenk A, Oberste M, Riedel S, Kool J, et al. High-intensity interval exercise improves cognitive performance and reduces matrix metalloproteinases-2 serum levels in persons with multiple sclerosis: a randomized controlled trial. Mult Scler. 2018;24(12):1635–44.
50. Hecksteden A, Faude O, Meyer T, Donath L. How to Construct, Conduct and analyze an Exercise Training Study? Front Physiol. 2018;9:1007.
51. Flachenecker P, Meissner H, Frey R, Guldin W. Neuropsychological training of attention improves MS-Related fatigue: results of a Randomized, Placebo-Controlled, double-blind pilot study. Eur Neurol. 2017;78(5–6):312–7.
52. Broicher SD, Filli L, Geisseler O, Germann N, Zörner B, Brugger P, et al. Positive effects of fampridine on cognition, fatigue and depression in patients with multiple sclerosis over 2 years. J Neurol. 2018;265(5):1016–25.
53. Kamudoni P, Johns J, Cook KF, Salem R, Salek S, Raab J, et al. A comparison of the measurement properties of the PROMIS fatigue (MS) 8a against legacy fatigue questionnaires. Mult Scler Relat Disord. 2022;66:104048.
54. Watson C, Scippa K, Barlev A, Kresa-Reahl K, Cole JC. Results from patient interviews on fatigue in Progressive multiple sclerosis and evaluation of fatigue patient-reported outcome (PRO) Instruments. Neurol Ther. 2022;11(2):725–39.
55. Van Geel F, Moumdjian L, Lamers I, Bielen H, Feys P. Measuring walking-related performance fatigability in clinical practice: a systematic review. Eur J Phys Rehabil Med. 2020;56(1):88–103.
56. Broscheid KC, Behrens M, Bilgin-Egner P, Peters A, Dettmers C, Jöbges M et al. Instrumented Assessment of Motor Performance Fatigability during the 6-Min Walk Test in mildly affected people with multiple sclerosis. Front Neurol. 2022;13.
57. Weinrich JO, Saliger J, Eschweiler M, Karbe H, Kalbe E, Nielsen J. The relationship between diurnal measures of Tonic alertness and self-reported fatigue in persons with multiple Sclerosis-A Retrospective Data Analysis. Arch Clin Neuropsychol. 2023.
58. Brandstadter R, Katz Sand I, Sumowski JF. Beyond rehabilitation: a prevention model of reserve and brain maintenance in multiple sclerosis. Mult Scler. 2019;25(10):1372–8.
59. Arienti C, Buraschi R, Pollet J, Lazzarini SG, Cordani C, Negrini S, et al. A systematic review opens the black box of usual care in Stroke rehabilitation control groups and finds a black hole. Eur J Phys Rehabil Med. 2022;58(4):520–9.
60. Beets MW, von Klinggraeff L, Weaver RG, Armstrong B, Burkart S. Small studies, big decisions: the role of pilot/feasibility studies in incremental science and premature scale-up of behavioral interventions. Pilot Feasibility Stud. 2021;7(1):173.

Publisher's Note

Multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve multiple sclerosis-related fatigue and fatigability during inpatient rehabilitation: a randomized controlled pilot and feasibility study [ReFEx].

Authors: Florian Wolf, Jörn Nielsen, Jochen Saliger, Eva Hennecken, Philipp Kröber, Mareike Eschweiler, Ann-Kristin Folkerts, Hans Karbe, Philipp Zimmer

Supplement

Detailed description of the graded exercise test (GXT)

Due to the clinical setting, measuring cardiorespiratory fitness with the gold standard of spirometry was not possible for this pilot study. Nevertheless, we applied the formula described by Valet, Stoquart (1) to predict the peak oxygen consumption, using the peak power attained in the GXT on a cycle ergometer (ERGO-FIT Cycle 4000 med; ERGO-FIT GmbH & Co. KG, Pirmasens, Germany) (see Table S3). According to Valet, Stoquart (1) validity and reliability of this method was very good in pwMS (intraclass correlation coefficient = 0.75)(1). The protocol of the GXT was based on previous protocols, as currently, standard disease specific protocols do not exist(2). Specifically, it was based on a protocol, used for several other studies performed in a similar inpatient rehabilitation setting(2), with some slight differences due to the present participant sample: (a) workload always started at 25W, (b) it was increased by 10W/min for all participants until volitional exhaustion. The cool-down period consisted of 3min of light pedaling at 0-25W. Heart rate was continuously monitored using a Polar Verity Sense (Polar, Kempele, Finland) connected to an iPad (Apple, Cupertino, USA) with the Polar Team App. At the end of each minute, participants were asked to rate their perceived exertion using the 6-20 Rating of Perceived Exertion (RPE) – scale. Before starting the GXT, instructions regarding the RPE-scale were read to the participants according to Borg (3). Right after volitional exhaustion, participants were asked to pick a reason for test termination (Table S4).

Detailed description of assessing the session-RPE

The session-RPE gives a rating of perceived exertion for a complete session. Specifically, the modified Category Ratio (CR-10) RPE scale as developed by Foster, Florhaug (4) was used to quantify session-RPE.

Endurance training (cycling): Before the first session, participants received a ‘diary’, and were instructed to note their session-RPE right after finishing each of the cycling sessions. The diary also included: (I) the question participants were supposed to answer: “Overall, how strenuous was the cycling session today?”, (II) written instructions (“please do not rate how you feel overall today, or how much fun you had during cycling. Instead, only rate how strenuous the cycling was. There is no right or wrong. This is only about your personal impression”), (III) the session-RPE scale (in German). The diary form was chosen for the endurance training to reduce study-related obligations for the therapists.

All other sessions (strength, gym, pool): session-RPE was directly ascertained and documented by the respective therapist after finishing a session. Participants were specifically instructed to rate the complete session and not specific exercises.

Table S1 Eligibility criteria, positive and negative cases.

Criteria	n/total	Percentage
Disease course (RR/SP)		
Info missing	1/101	1%
Eligible	82/100	82%
Non-eligible	18/100	18%
Age (18-67)		
Info missing	0/101	0%
Eligible	94/101	93%
Non-eligible	7/101	7%
EDSS (up to 5.0)		
Info missing	3/101	3%
Eligible	57/98	58%
Non-eligible	41/98	42%
FSMC (53 and up)		
Info missing	25/101	25%
Eligible	41/76	84%
Non-eligible	12/76	16%
Fatigue medication (not started less than 3 months ago)		
Info missing	1/101	1%
Eligible	93/100	93%
Non-eligible	7/100	7%
Water therapy		
Info missing	0/101	0%
Eligible	62/101	61%
Non-eligible	39/101	39%
Comorbidities		
Info missing	1/101	1%
Eligible	73/100	73%
Non-eligible	27/100	27%
Language		
Info missing	0/101	0%
Eligible	92/101	91%
Non-eligible	9/101	9%

EDSS=Expanded Disability Status Scale; FSMC=Fatigue Scale for Motor and Cognitive Functions; RR=relapsing-remitting; SP=secondary-progressive.

Table S2 WEIMuS and FSMC total scores.

	T_0	T_1	T_2	T_3	T_4
WEIMuS					
MAT	n=11	n=9	n=9	n=9	n=8
Median	52 (40 – 61)	41 (22 – 53)	46 (34 – 56)	57 (27 – 62)	47.5 (24 – 62)
Change from T_0		-14 (-24 – 2)	-12 (-17 – 8)	-2 (-18 – 6)	-7.5 (-21 – 9)
SET	n=11	n=9	n=8	n=8	n=7
Median	50 (14 – 62)	41 (13 – 57)	43.5 (26 – 63)	39.5 (16 – 65)	47 (17 – 68)
Change from T_0		-12 (-30 – -1)	-13 (-15 – 1)	-10.5 (-27 – 3)	-5 (-44 – 6)
FSMC					
MAT	n=11	n=10	n=9	n=9	n=8
Median	83 (61 – 93)	77.5 (74 – 89)	80 (74 – 91)	82 (68 – 92)	80 (68 – 98)
Change from T_0		-4 (-18 – 6)	-3 (-8 – 4)	-4 (-16 – 9)	1 (-16 – 10)
SET	n=11	n=8	n=9	n=8	n=7
Median	78 (65 – 100)	82 (65 – 91)	72 (55 – 94)	78 (56 – 92)	75 (68 – 99)
Change from T_0		3.5 (-9 – 7)	-7 (-15 – 4)	-5.5 (-14 – 6)	-1 (-18 – 5)

Values present median (min-max). Decrease in scores indicates less fatigue. FSMC=Fatigue Scale for Motor and Cognitive Functions; MAT=multimodal agility-based exercise training; SET=strength and endurance training; T_0=admission; T_1=discharge; T_2=1 week post-discharge; T_3=4 weeks post-discharge; T_4=12 weeks post-discharge; WEIMuS=Würzburg Fatigue Inventory for Multiple Sclerosis;

Table S3 Morning and afternoon data of the alertness assessment and supplementary data from the graded exercise test.

	MAT	SET
TAP-Alertness (ms)		
Morning		
T_0[a]	306.8 (97.2, 230 – 572)	299.7 (84.6, 194 – 463)
T_1[a]	365.8 (193.8, 247 – 872), n=10	278.7 (46.4, 216 – 373), n=10
T_1-T_0 (change) ↓	53.9 (95.8, -13 – 300)	-23.0 (56.5, -143 – 32)
Afternoon		
T_0[a]	319.0 (109.3, 216 – 590)	307.9 (113.6, 195 – 520)
T_1[a]	402.0 (193.8, 247 – 872), n=10	289.3 (71.6, 198 – 453), n=10
T_1-T_0 (change) ↓	76.5 (126.4, -69 – 341)	2.6 (82.6, -155 – 158)
$W_{peak/kg}$		
T_0[b]	1.50 (0.57, 0.74 – 2.41)	1.39 (0.59, 0.70 – 2.76)
T_1[b]	1.45 (0.48, 0.83 – 2.22), n=9	1.60 (0.71, 0.93 – 3.09), n=7
T_1-T_0 (change) ↑	0.04 (0.09, -0.14 – 0.16)	0.17 (0.18, -0.03 – 0.47)
$_pVO_{2peak}$ (ml/min)		
T_0[b]	1422.0 (370.3, 875.1– 2040.4)	1496.8 (409.2, 1079.2 – 2572.0)
T_1[b]	1369.3 (336.8, 971.3 – 1947.3), n=9	1718.0 (497.5, 1319.2 – 2742.9), n=7
T_1-T_0 (change) ↑	15.1 (68.0, -93.1 – 98.5)	129.0 (158.4, -31.6 – 394.1)

All scores had n=11 at T_0, sample size for each outcome at T_1 is reported in the table. All scores are presented as mean (SD, min-max). Arrows indicate direction for improvement. [a]=lower scores are favorable; [b]=higher scores are favorable; MAT=multimodal agility-based exercise training; $_pVO_{2peak}$=predicted[#] peak oxygen uptake; SET=strength and endurance training; T_0=admission; T_1=discharge; TAP=Test Battery of Attention Performance; $W_{peak/kg}$=peak power output relative to bodyweight.

[#] $_pVO_{2peak}$=9.39*W_{peak} + 7.70*weight (kg) – 5.88*age (years) + 136.7 ml/min, according to Valet, Stoquart (1).

Results of GXT validity criteria(5)

1. Heart rate at W_{peak} within 90% of predicted maximum heart rate (208 – 0.7*age)?

- T_0 Yes=3/22 (13.6%)
- T_1 Yes=2/16 (9.1%)

2. Rating of perceived exertion (RPE 6-20) at W_{peak} ≥17?

- T_0 Yes=22/22 (100%), mean (SD): 19.18 (0.73)
- T_1 Yes=16/16 (100%), mean (SD): 19.44 (0.52)

Table S4 Reasons for termination of the graded exercise test.

Reason	T_0	T_1
Breathing	3/22 (17.6%)	2/16 (12.5%)
Leg weakness	**17/22 (77.3%)**	**14/16 (87.5%)**
Pain	1/22 (4.5%)	0/16 (0.0%)
Sensory issues	0/22 (0.0%)	0/16 (0.0%)
Dizziness	1/22 (4.5%)	0/16 (0.0%)

Data are presented as n/total (percentage). T_0=admission; T_1=discharge.

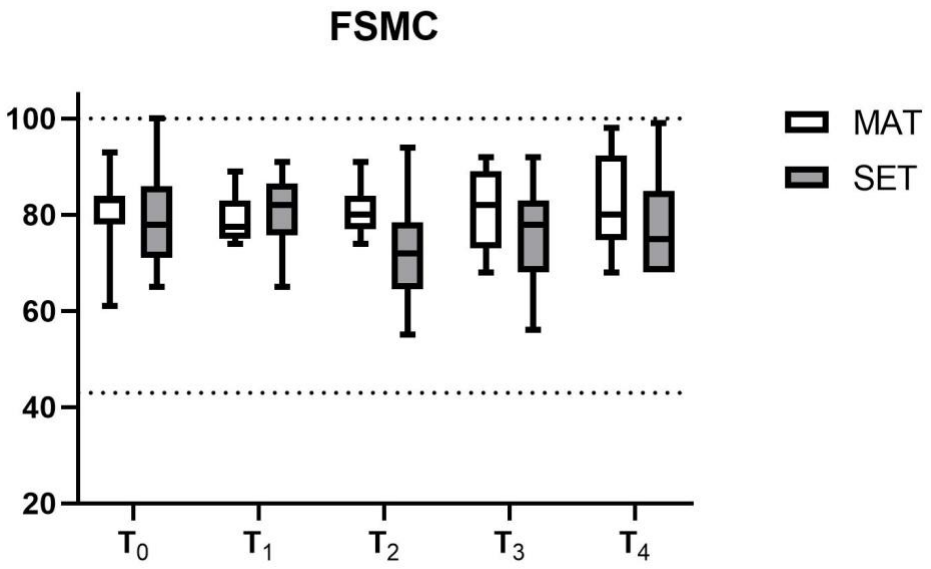

Figure S1 FSMC total scores for both groups. Box plot: line=median, whiskers=min-max. Upper dotted line=maximum FSMC total score (=100); lower dotted line=cut-off for fatigue (=43); FSMC=Fatigue Scale for Motor and Cognitive Functions; T_0=admission; T_1=discharge; T_2=1 week post-discharge; T_3=4 weeks post-discharge; T_4=12 weeks post-discharge.

References

1. Valet M, Stoquart G, de Broglie C, Francaux M, Lejeune T. Simplified indices of exercise tolerance in patients with multiple sclerosis and healthy subjects: A case-control study. Scand J Med Sci Sports. 2020;30(10):1908-17.

2. Schlagheck ML, Bansi J, Wenzel C, Kuzdas-Sallaberger M, Kiesl D, Gonzenbach R, et al. Complexity and pitfalls in maximal exercise testing for persons with multiple sclerosis. Eur J Neurol. 2023;30(9):2726-35.

3. Borg G. Anstrengungsempfinden und körperliche Aktivität. Dtsch Arztebl International. 2004;101(15):A-1016.

4. Foster C, Florhaug JA, Franklin J, Gottschall L, Hrovatin LA, Parker S, et al. A new approach to monitoring exercise training. J Strength Cond Res. 2001;15(1):109-15.

5. Langeskov-Christensen M, Langeskov-Christensen D, Overgaard K, Moller AB, Dalgas U. Validity and reliability of VO(2)-max measurements in persons with multiple sclerosis. J Neurol Sci. 2014;342(1-2):79-87.

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Experiences of fatigued persons with multiple sclerosis with multimodal agility-based exercise training and the ReFEx study protocol: a qualitative extension of a feasibility study

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ABSTRACT

Objectives (1) To explore experiences of fatigued persons with multiple sclerosis (pwMS) with a new multimodal agility-based exercise training (MAT) framework and (2) to investigate the demands of the Rehabilitation, Fatigue, and Exercise (ReFEx) study protocol, which compares high-frequency MAT and 'traditional' strength and endurance training (SET) to identify possible adaptations for a powered randomised controlled trial (RCT).

Design A qualitative interview study nested within a feasibility RCT, comparing MAT and SET.

Setting Neurological inpatient rehabilitation centre in Germany.

Participants Twenty-two pwMS were recruited for the feasibility study. Six were selected from MAT and SET, respectively, for semistructured face-to-face interviews prior to discharge, following a purposive sampling strategy. Participants had low physical disability but were at least moderately fatigued.

Interventions During inpatient rehabilitation (4–6 weeks) MAT participants attended group-based and manual-based MAT sessions in the gym (5×/week, 30 min) and the pool (3×/week, 30 min). SET participants exercised individually on a cycle ergometer (5×/week, 22 min) and on strength training machines (3×/week, 30 min).

Results Three key categories emerged from the interviews: (1) *facilitators* regarding MAT were variety and playfulness, group setting and challenging exercises. *Barriers* regarding MAT were feeling overburdened, feeling pressured in the group setting and the wish to perform 'traditional' strength training (not part of MAT). (2) MAT *benefits* were of physical and psychological nature, with improved balance stated the most. (3) *Demands* described the perceived exertion during MAT and SET, reflecting that there is no accumulation of fatigue during the intervention.

Conclusions MAT is appreciated by pwMS and includes facilitators less attainable with 'traditional' SET. Evaluation of MAT in a powered RCT is indicated, if rest breaks postsession, and screening for negative self-evaluation and social comparison are considered. Future (qualitative) research should investigate the important factors of inpatient rehabilitation contributing to fatigue reduction in pwMS.

Trial registration number DRKS00023943; German Clinical Trials Register.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This was a qualitative extension of a randomised controlled feasibility study, including persons with multiple sclerosis who were at least moderately fatigued.
⇒ The real-world inpatient rehabilitation environment in Germany makes it applicable to clinical practice.
⇒ Coding of the interviews was based on relevant topics from the literature and emerging data from the transcripts, following an integrated deductive–inductive approach.
⇒ Due to the feasibility stage, the sample size was small, no participant validation was performed, and no independent coders were used.

INTRODUCTION

In many countries, multiple sclerosis (MS) is the leading cause of non-traumatic, neurological disorder among young adults.[1] In Germany, persons with MS (pwMS) frequently attend inpatient rehabilitation facilities, for example, to improve their working capacity.[2] Notably, 25% of pwMS have impaired working capacity because of 'invisible' symptoms such as fatigue.[3 4]

Fatigue can be defined as 'a subjective sensation of lack of energy and exhaustion',[5] while the term fatigability refers to objectively measurable performance decrements (eg, during walking).[6 7] Contrary to its impact, pharmacological treatment options for fatigue are limited.[8] Consequently, many exercise interventions have been evaluated, including aerobic, resistance, flexibility, balance, general (ie, no primary fitness target, such as yoga) and combined exercise, with some being conducted in an aquatic environment.[9] Most interventions had a duration of 12 weeks or less, but some lasted for up to 26 weeks.[9 10] A meta-analysis found 13 exercise studies that were explicitly targeted

at fatigue,[11] but only one small study was based in an inpatient rehabilitation setting.[12] In general, interventions broadly focused on 'balance' have shown large effects[13–15] but the number of existing studies is small.[9 11]

Recently, a group-based exercise training framework for pwMS (multimodal agility-based exercise training (MAT)[16]) was described, which might comprise several aspects proposed to be beneficial for fatigue reduction, for example, (1) balance training for making 'navigating the environment' less effortful,[11] (2) 'coordination of eye, head and whole-body movements' to 'reduce the cognitive load associated with conscious compensatory strategies in dynamic environments'[15] and (3) 'improvement of sensory integration with a subsequent reduction of the cognitive load associated with motor processing'.[13] These aspects are not the focus of 'traditional' exercise approaches, such as strength and endurance training (SET), which might be a reason why balance training had stronger effects in meta-analysis.[11 14 15] Still, SET is clearly beneficial to improve other aspects of functioning and is part of established guidelines.[17] As there have been few head-to-head comparisons of different types of exercise,[9] the Rehabilitation, Fatigue, and Exercise (ReFEx) protocol compares MAT and SET in an inpatient rehabilitation setting, regarding fatigue reduction.

As a first step, a pilot and feasibility study was conducted to identify problems that might undermine the acceptability of MAT and SET or the conduct of the evaluation. The feasibility study included MAT performed in a gym as well as in an aquatic setting and it applied a quantitative and qualitative assessment. This kind of mixed-methods design is part of established guidelines for evaluating complex interventions.[18 19]

For the qualitative feasibility assessment, several relevant topics were identified from the existing literature. First, the present study was one of few exercise studies, which required participants to report at least moderate fatigue at baseline (using an established cut-off score[11]). It is well described that a 'cyclical relationship' exists between exercise and fatigue[20] and fatigue is seen as an adverse short-term consequence of and a barrier to exercise by pwMS.[20] Therefore, it was important to ascertain from participants how the high-frequency training (8 sessions/week), and overall rehabilitation schedule affected their fatigue and ability to recover. As MAT has not been applied to pwMS and is designed to challenge motor as well as cognitive aspects[16]—which both are domains of fatigue experience[6]—it was particularly important to ensure that MAT was not perceived as too fatiguing. Second, the type of exercise has been reported as one of the most common facilitators for exercise adherence/participation, and it should match the persons' capabilities and preferences.[20] As the study compared two types of exercise, of which one was based on a framework not previously applied in pwMS (ie, MAT), we were especially interested in the participants' experiences with this new framework. Third, perceived consequences are central to pwMS regarding exercise participation.[20] Thus, perceived consequences of MAT were planned to be ascertained.

This resulted in the overall objectives of (1) exploring experiences of fatigued pwMS with MAT and (2) investigating the demands of the ReFEx study protocol to identify possible adaptations for a powered randomised controlled trial (RCT).

METHODS

Context of the qualitative study

The qualitative study focused on semistructured face-to-face interviews, conducted prior to discharge from the Neurological Rehabilitation Centre 'Godeshoehe' (NRC, Bonn, Germany) and was an extension of a randomised controlled feasibility study with 22 pwMS, described in detail in the protocol,[21] and the quantitative results paper.[22] In brief, eligible pwMS were informed about the study, and after consent, were randomised to perform either MAT or SET during their inpatient stay (4–6 weeks, individually determined by the treating physician based on medical indications). Participants were assessed for perceived fatigue, fatigability and further secondary outcomes at admission and discharge (ie, preintervention and postintervention). A 12-week follow-up period consisted of online fatigue questionnaires.

Interventions (MAT and SET)

The MAT group exercised 5x/week for 30 min in the gym and 3x/week for 30 min in the pool, both in a group setting of maximum eight participants. The group followed a MAT-manual (see protocol),[21] based on the three components of MAT[16]: (1) standing balance exercises, (2) dynamic balance exercises including functional leg strength and (3) agility-like exercises (eg, change of direction, change of velocity); each with defined sensory modifications and cognitive challenges. For load management in the gym-setting, three sessions with higher physical demands (ie, agility-like components and functional leg strength) were interspersed with two sessions on standing balance or exercises with a cognitive focus. The group was open to patients with other neurological conditions (mostly stroke), but similar mobility capacity. Group leaders were author FW, and two female exercise therapists, trained by FW.

In the SET, individuals performed moderate intensity (ie, 'light' to 'somewhat hard' on the 6–20 Rated Perceived Exertion (RPE) scale) endurance training, 5x/week for 22 min on a cycle ergometer, and strength training, 3x/week for 30 min on machines (predetermined lower extremity exercises with progression).[21] Cycle ergometer sessions were running all day in the clinic. Thus, the SET participants had flexible schedules and trained together with around five other patients from the NRC, who did not participate in the study. Due to the flexible scheduling, participants in the cycling sessions were changing from day-to-day, and therefore, the cycling sessions for the SET participants did not occur in a closed group. During the

Table 1 Daily schedules for MAT and SET

MAT	SET
10.30 gym-based MAT (5 x/week)	*flexible* cycle ergometer (5 x/week)
12.00 lunch break	12.00 lunch break
13.30 pool-based MAT (3 x/week)	*flexible* strength training (3 x/week)
14.15 'MS-group' (5 x/week)	14.15 'MS-group' (5 x/week)

MAT, multimodal agility-based exercise training; SET, strength and endurance training.

endurance training, a therapist monitored RPE. Strength training was provided 1:1, with a trained exercise science student or therapist (FW).

All participants also attended the 'MS group' 5x/week for 30 min—a group for pwMS focusing on relaxation and body awareness, which is 'usual care' in this clinic. Daily schedules of MAT and SET are depicted in table 1.

Other rehabilitation-related appointments (eg, neuropsychology, occupational therapy) are not displayed but could be scheduled anywhere between 7.15 and 16.30.

Selection of interview participants

Six of 11 participants per group were selected face-to-face for the interviews in a joint decision by authors FW and JN, reflecting the greatest possible diversity in terms of gender, age and Expanded Disability Status Scale (EDSS), relying on a purposive sampling strategy, similar to previous studies.[23 24] The number of cases was based on reported sample sizes for qualitative research in feasibility studies.[19] None of the approached pwMS refused to participate in the interviews.

Notable inclusion criteria from the overall feasibility study were a relapsing–remitting or secondary-progressive disease course, age between 18 and 67 (age for retirement in Germany), EDSS ≤5.0, Fatigue Scale for Motor and Cognitive Functions (FSMC)≥53 (total score 20–100, cut-off scores classify no (<43), mild (≥43), moderate (≥53) and severe (≥63) fatigue[25]), and written informed consent.

Data collection

Development of the interview guide and complementary survey

Based on prior knowledge (see the Introduction section), and existing guidance on qualitative research for feasibility studies,[18 19] FW and JN separately drafted initial interview questions and thematic blocks. Thematic blocks were used to structure the questions in the interview guide, regarding different overall topics.[26] After discussion, this resulted in 32 questions and six thematic blocks. After each author had piloted the questions with one pwMS, respectively, questions were revised. A guide containing 24 questions and five thematic blocks was then discussed with an independent third researcher (ÜSS, see the Acknowledgments section). This resulted in several questions being transferred to a survey format, reducing the number of final interview questions to 14 in three thematic blocks (1-fatigue concept, 2-experiences and demands, 3-personal relevance and goal achievement; interview guide in online supplemental file 1). Block 1 (fatigue concept) was unrelated to the feasibility objectives and, therefore, was not analysed in this paper. The complementary survey had 4-point Likert type, or binary scale questions and was distributed to all participants in the study at one of the physical assessments prior to discharge.

Interviews

Because participants were consecutively discharged from the clinic, individual, face-to-face interviews, conducted 1–2 days prior to discharge, were considered most appropriate. JN conducted all interviews in an office at the NRC (see Consolidated criteria for reporting qualitative research (COREQ)[27] in online supplemental file 2. Interviews were scheduled for maximum 30 min. All interviews were audio-recorded.

Analysis

After completion of all interviews, audio files were transcribed verbatim (in German) by an independent transcription service and imported into MAXQDA2022. The qualitative analysis used a constructivist paradigm, described as an approach that allows for the cocreation of knowledge by the participants and the researchers.[28] The respondents are considered experts in their lifeworld, that is, experts in their experience, but not necessarily experts in understanding that experience, which is why the researcher brings in his or her prior theoretical knowledge.[29] Coding of the interviews was based on *focused analysis* as described by Rädiker and Kuckartz,[26] and entailed a combined model of deductive (*a priori*) and inductive coding (on the text material). Initial codes were deductively developed from the questions in the interview guide (online supplemental file 1) and, therefore, reflected the preliminary considerations from relevant literature. With these initial codes, all interviews were coded once by FW, while adapting and adding codes emerging from the text material. Next, one interview was coded by FW and JN together to ensure mutual understanding. This contributed to improved code definitions, which FW applied in a second round of coding all transcripts. Subsequently, in a joint discussion between authors FW, JN and AKF, a decision was made to focus on statements from the MAT group, only adding content from the SET group regarding the demands of the protocol, as there was more uncertainty regarding the MAT, and SET participants' feedback was less rich in content. The further process of analysis was critically accompanied by discussions among the investigators, about how to group the findings, whereupon a final coding system was agreed on (ie, investigator triangulation). This resulted in three final key categories. Coded segments per category were compiled to establish

subcategories. These steps were completed while continuously rereading the transcripts to stay close to the data. Finally, FW translated quotes for the manuscript from German to English.

Researcher characteristics and reflexivity

Most, but not all participants met the interviewer (JN) in his role as a neuropsychologist and part of the research team, prior to the interviews. However, JN was not involved in the exercise sessions or assessments, except for handing out questionnaires at baseline. This was important, as it facilitated that the participants were able to speak freely about their experiences. JN is a certified systemic therapist and counsellor with many years of experience in patient-centred communication. Participants were informed that MS and the topic of the study were one of the researchers' preferred research areas and that the study was designed by the research team to gain a better understanding of fatigue and to find therapeutic ways to improve fatigue.

Patient and public involvement

We acquired perspectives of the participants in the trial, but we did not include patient representatives while constructing the interview guide, or in the analysis process. This was due to limited staff and time resources. However, results of the interview study will be used to guide the design of a future RCT.

RESULTS

Participant characteristics are shown in table 2. None of the participants used a mobility aid. Median FSMC total scores were 82.5 and 76 for the MAT and SET interviewees, respectively (ie, both indicating severe fatigue). Median interview length per group was 15:42 min (MAT) and 09:31 min (SET).

Three key categories emerged from the analysis (box 1). The first two encapsulate *Facilitators and barriers* as well as *Benefits* for participating in MAT. *Demands* reflects MAT participants', and SET participants' perceived exertion during, and perceived fatigue after the sessions, recovery as well as overall impact on fatigue. As mentioned in the Methods section, analysis of the SET group was restricted to the last theme (*Demands*). Participants are identified via their ID (table 2) in the supporting quotes.

Facilitators for MAT

Overall, variety and playfulness of the training content, the group setting, and the feeling of being challenged by the exercises emerged as facilitators.

Three participants mentioned appreciating the variety of the training content, which changed from day to day. As described, MAT was based on three exercise components and each had various modules, which were prespecified in the MAT manual. PwMS enjoyed the alterations between these different components, as exemplified in this statement by MAT3:

> I thought this was very good, very diversified, so we partially had therapies, which were exclusively challenging endurance and sometimes strength, which means, you were able to also push yourself a little, and I liked that. And sometimes it was also coordination or balance and sometimes also leg strength (MAT3).

All three participants mentioning the variety of the training schedule noted in conjunction, that they thought training was often playful, which made it feel more fun, or even led to training 'unconsciously', as described here by MAT6:

> On the one hand it was sometimes very playful. This was fun, because you did not notice at all that you were training and still you were really getting benefits. I executed the first running steps, because I wanted to win at a game, and I did not notice, it was not like: 'Oh, it's working now!'—instead, it just worked (MAT6)

Fun of training is supported by the results of the complementary survey, and six of nine MAT participants indicated an interest in continuing a training like MAT in their community (table 3).

Two participants (among those who also appreciated variety and playfulness) expressed feeling positive about being challenged by some of the exercises, particularly in areas where they knew they had some deficits. The following statement is especially interesting, as MAT3 describes the challenge she experienced when having to perform motor-cognitive dual tasks, which she recognised as a task she usually struggles with:

> The connection between movement and cognitive performance, like where you had to do both, move in a coordinated way, but also think because this is especially challenging for me. There were these variations with the lunges left, right and the catching, catch both balls and so on, and this felt good to me, because I see my biggest deficits there (MAT3).

MAT2 and MAT4 were more ambivalent about being challenged by the level of difficulty in the exercises, making statements such as feeling proud after finishing a session or liking the experience of boundaries, but at the same time, sometimes felt disappointed about their own performance, when they were unable to match their expectations (see the Barriers section).

All six participants also had positive reflections regarding the group setting, including it being motivating, pleasant, and stimulating:

> A great group. You were motivating each other. You were also happy for each other, if there was somebody performing better, and who enjoyed that, so this collective joy. Yes, and noticing that everybody was improving, not only you (MAT6).

Table 2 Individual and group characteristics of the interview participants

ID	Sex	Age range(years)	Working capacity†	EDSS	MS type	TSD range(years)
MAT1	f	46–50	3–6 hour/d	2.0	RR	6–10
MAT2	f	46–50	Retired	3.5	RR	26–30
MAT3	f	26–30	3–6 hour/d	4.0	RR	11–15
MAT4	f	51–55	Retired	2.0	SP	0–5
MAT5	m	26–30	>6 hour/d	2.0	RR	6–10
MAT6	f	51–55	3–6 hour/d	3.0	RR	6–10
MAT Group	f:m 5:1	48‡		2.5‡	RR:SP 5:1	7.5‡
SET1	f	61–65	>6 hour/d	2.5	RR	21–25
SET2	f	31–35	Retired	3.5	RR	6–10
SET3	f	61–65	3–6 hour/d	2.0	RR	11–15
SET4	m	51–55	On disability	2.0	RR	26–30
SET5	f	51–55	3–6 hour/d	3.0	SP	6–10
SET6	m	56–60	On disability	2.0	RR	6–10
SET Group	f:m 4:2	54‡		2.25‡	RR:SP 5:1	10.5‡

*Higher scores indicate more fatigue.
†Describes the capacity to work as determined during inpatient rehabilitation.
‡Values present the group median.
EDSS, Expanded Disability Status Scale; f, female; FSMC, Fatigue Scale for Motor and Cognitive Functions; m, male; MAT, multimodal agility-based exercise training; RR, relapsing-remitting; SET, strength and endurance training; SP, secondary-progressive; TSD, time since diagnosis.

However, two participants also noted barriers regarding the group setting (see below).

Barriers against MAT

Barriers regarding MAT were pre-existing expectations on the benefit of 'traditional' strength training, feeling overburdened, and feeling pressured in the group setting.

A barrier for MAT adherence in the context of the present trial (ie, comparing MAT with SET) might occur in persons wanting to perform 'traditional' strength training, as they have specific expectations regarding this kind of training. For example, despite being positive about several aspects of the MAT group (see above), MAT3 explicitly stated that she would have liked to perform more strength training:

> Sure, I enjoyed both therapy sessions, but I also don't have any comparisons. But I said right away, that I also have deficits with my strength, especially on the left, so, frequently while walking I bend on my left, especially if I'm not feeling well, or I have severe problems with arm strength, hand strength and so on. […] And I didn't have that, I could say this over the whole process, that I was really missing that (MAT3).

BOX 1 FINAL CATEGORY SYSTEM.

Facilitators and barriers (MAT)
⇒ Facilitators for MAT.
⇒ Barriers against MAT.
Benefits of MAT
Perceived demands of MAT and SET
⇒ Exertion.
⇒ Fatigue.

Supporting stronger prior expectations regarding SET were the survey results showing that only 22% of SET participants did not have any prior experience with SET, but 67% of MAT participants stated not having any prior experience with exercise similar to MAT (table 3).

Two MAT participants (MAT2 and MAT4) reported being dissatisfied with their own performance. MAT4 even stated feeling overburdened. This occurred especially in situations where the MAT demanded cognitive performance:

> But the feeling of sadness, this occurred very fast for me, because you are confronted with it, that you are not concentrated, even though you have already done it once or twice before (MAT4).

The same two MAT participants sometimes felt pressured in the group, as they compared their own with the others performance, even though they mentioned feeling motivated by the group setting at the same time, as recorded here from MAT2:

> Yes, because there just is more stimulation, because you do have to adapt to the other. This is a demand on yourself, instead of just doing it alone, even

Table 3 Results of the customised complementary survey, distributed to all study participants

Question (translated)	Answer	MAT (n=9) (n)	SET (n=9) (n)
Did you have any previous experience with strength and endurance training?	Both	n.a.	6
	Only strength	n.a.	0
	Only endurance	n.a.	1
	None	n.a.	2
Did you have any previous experience with exercise/therapy similar to MAT?	Yes	3	n.a.
	No	6	n.a.
How much fun did you have during both of the study therapies?	A lot of fun	4	1
	Fun most of the time	5	7
	Little fun	0	1
	No fun	0	0
If you had the opportunity to continue with a group similar to MAT close to your home, would you take up this offer?	Yes, more than 1 x/week	1	n.a.
	Yes, 1 x/week	5	n.a.
	Maybe	3	n.a.
	No	0	n.a.
Would you participate in this study again?	Yes	9	8
	No	0	1

A total of 18 study participants completed the survey (nine from each group). Of the remaining four participants, two had dropped out, while another two did not complete the survey.
MAT, multimodal agility-based exercise training; n.a., not applicable; SET, strength and endurance training.

though this is … Well, to see that others are able to do it is sometimes sad. Well, that's how it is (MAT2).

Benefits of MAT

Five of the six MAT participants stated that they had experienced improvements in balance. Some used certain situations occurring during the day to verify this improvement.

> I actually notice that when I walk through the hallway. In the beginning I always had to be careful and keep contact to the wall and always monitor whether there was somebody approaching. This has very much improved. So, my walking has become more secure and also when taking the stairs, in the beginning, I always had to use the handrail, but now I don't need it this often (MAT2)

Besides balance, which was directly ascertained, participants in the MAT group mentioned improvements in the following physical domains: endurance, leg strength and gait function (mostly in context with the functional leg training). Several also described improvements related to the unique content of MAT, for example, improvement of complex movements:

> I also do have this problem with coordinating movement: Once I've started to run, I run, then it's fine, but if I really do slow movements and especially if I turn my head, then sometimes I really look like I'm drunk. And I think, I was able to do this a little better. It's not gone, but it has definitely helped (MAT3).

Psychologically, participants described a sense of accomplishment after finishing a session, and effects related to self-efficacy to continue exercising at home (see MAT1 below). Two also mentioned that experiencing boundaries while being challenged helped them to increase their body awareness.

> But I have to say, in my case it's like, that movement-wise it has improved. Which I am also very happy for, that I am out of this fatigue loop and that I can really do something. I did do something before, but probably too much or too little. Here it's exactly the right dose. That's it, or also the combination. So, I do have a good base now to carry on. Now I also have more self-confidence and so on (MAT1).

Participants did not describe any worsening of symptoms at the end of the training period.

Perceived demands of MAT and SET

Exertion

Overall, four participants indicated that exertion in the gym-based MAT can be high, and all MAT participants agreed that perceived exertion was higher in the gym than in the pool, as intended by the training schedule design. MAT6 makes this comparison in the following statement, while highlighting the importance of the session scheduling through the course of the day:

> And the order is good as well because the gym-session really is with your whole bodyweight. And some are fighting right there because they don't have the reserve in strength. And following that they were able

to participate in the pool-session because the body is lighter. So, the other way round it would definitely not be a good idea (MAT6).

Despite the high perceived exertion in the gym, participants, such as MAT1, were able to turn this into a feeling of accomplishment after the session:

> Actually, very strenuous, like today, so this was actually strenuous, but in a way that you were feeling good afterwards. So, sometimes you were like: 'Oh, no, not today again.' But it actually is paradoxical, because it does feel good then, even in a way that makes you go out with a feeling of: 'Oh yes, today I accomplished that'. And this is really awesome, and I'm feeling good (MAT1)

MAT3, among the two youngest participants (age 27), was the only participant, who did not rate exertion to be high in the gym. Instead, she emphasised in several statements, that mostly after the session was finished, she noticed the demands of the session (ie, fatigue), and this especially happened after she had been cognitively challenged (one of her self-described deficits, as already mentioned).

In the SET, participants stated overall that their exertion during the sessions was rather moderate, and none reported that it felt hard or too hard. Three of the six SET participants stated that their day-by-day condition and the time of day influenced how strenuous the sessions felt, as described here by SET5 for the training on the cycle ergometer:

> […] I noticed that the time of day played a role in how strenuous it felt. There certainly were days where I thought they could easily add another fifty watts, and there were days where actually fifty watts were already too much (SET5).

Fatigue

Regarding the acute impact on fatigue after a session, three MAT participants experienced reduced motor function, primarily confined to the lower extremities. The following quote is an example of this experience after participating in a gym-based MAT session:

> Most of the time it's like I can't get my legs up, so I kind of sluggishly climb up the stairs and I really think: 'Oh god, this is too much!' […] I don't even take the stairs, but the elevator, actually very uncommon for me, but it is too much right then (MAT1).

One participant from each group also described sensory symptoms in terms of tingling in the legs postexercise. Training in the gym (MAT) and strength training (SET) seemed to elicit more fatigue postexercise for most participants, opposed to aquatic MAT and endurance training. Interestingly, acutely after training, in total, four participants from both groups felt more energised while or directly after training:

> This very intense feeling of tiredness was getting better while training on the ergometer. Just because of the movement I had the feeling the tiredness was decreasing as well (SET5)

MAT3 even used this energy to go for a walk outside after the exercise session:

> But if I had reached a higher heart rate (in the session), I was full of energy and I directly used this and went to the forest, or I walked up and down the hill, and that was good (MAT3).

To recover after and in between study-related training sessions, pwMS reported timespans from 5 min up to 60 min. Resting in bed in their room after the sessions was one of the measures participants described to refuel. However, they also reported that sometimes there were so many other appointments that they were unable to recover. Subsequently, one issue expressed frequently in the MAT group was that training in the pool always occurred after lunch time, when many were low on energy. Still, none of the participants indicated that they had been unable to attend the second training session or the sessions on the next day. Yet, it did occur that a participant skipped a study-unrelated appointment, because of fatigue. MAT1 commented on this situation and noted, importantly, that this possibility of 'skipping' was not an option when being at home:

> So, yesterday it occurred again, I can reconstruct that regarding yesterday, that I was really tired afterwards (the MAT session), I also did not go to another therapy session. This was really exhausting for me. But other than that I would say, because you are not doing anything else, it did feel good to me, so that I was not that fatigued, as if I would do additional stuff at home (MAT1)

In total, five participants from both groups reported reduced fatigue at the end of their stay in the interviews and attributed this reduction to being out of their home environment and not related it to effects arising from the exercise sessions. SET4 and MAT5 gave examples on this phenomenon here:

> Yes, well, now I've calmed down in general, this has had a positive influence. It is hard to determine how this is going if you return to your normal environment (SET4).
>
> But other than that I would say, as you are not doing anything else, it did feel good to me, that I wasn't that fatigued, than when I do other stuff at home as well (MAT1)

DISCUSSION

Key objectives of the qualitative extension were to explore experiences with MAT, and to ascertain perceived

demands of participating in the trial from fatigued pwMS. This should inform adaptations to a future RCT. To our knowledge, this is the first qualitative study assessing barriers and facilitators regarding MAT in pwMS, and regarding the demands of high-frequency exercise during inpatient rehabilitation.

Our results showed that facilitators regarding MAT were variety and playfulness, the group setting and the feeling of being challenged by the exercises, whereas pre-existing expectations on the benefit of 'traditional' strength training, feeling overburdened and feeling pressured in the group were barriers. A physical benefit highlighted by the participants was improved balance, while psychologically experiencing a sense of accomplishment was emphasised. As expected, some participants from MAT and SET acutely experienced fatigue after the sessions, while occasionally being unable to recover for the next appointment. However, this did not result in being unable to attend the second study-related session of the day or sessions on the following day. None stated experiencing an accumulation of fatigue, instead, improved fatigue was reported prior to discharge (ie, the time of the interview).

Barriers of MAT

It is known that pwMS tends to avoid exercising among 'healthy' people.[30] Despite our patient collective having low physical disability and exercising among other pwMS (or persons with other neurological diseases), feelings of underperformance did occur in the MAT group. This is in line with another group-based exercise intervention, describing upward and downward social comparisons in pwMS[31] and points to a deliberate selection of exercise content by the leading therapists, with current group characteristics in mind. More similar levels of motor performance of participating individuals might be warranted, as PwMS have stated that exercising with individuals who have similar difficulties can improve learning and encouragement.[32] For a future study, an additional postsession self-rating will be helpful to match pwMS' individual performance levels and needs (eg, 'I felt not challenged enough/overburdened/just right'; in case of feeling overburdened, the therapist should seek further discussion with the participant and might adapt future sessions and re-evaluate the training fit). However, as part of the benefits category, some participants also described a sense of accomplishment after finishing a session, and effects related to self-efficacy to continue exercising at home. As we did not perform interviews preintervention, we do not have a detailed understanding on how participants' issues with self-esteem or self-efficacy regarding exercise changed during the intervention. Russell *et al*[31] reported improvements in these domains after a 10-week social cognitive behaviour change physical activity intervention, indicating that incorporating workshops on principles of social cognitive theory in the programme might be beneficial. Nevertheless, the current psychological benefits already support that the exercise content felt relevant to pwMS, which will assist compliance in the future.

Like previous research,[20 33 34] exercising in a group also felt motivating and stimulating to pwMS. These perceptions emerged despite of the group not being as 'closed' as in research performed in community or academic settings. The rehabilitation centre puts patients in a new environment and the MAT-programme probably provided a regular opportunity for patients to socialise with other patients and might have played an even more important role. Finally, as differing expectations regarding MAT and SET could influence exercise effects,[35] a better description of MAT in the study information sheet might be a possibility to reduce this effect, as SET might be more familiar to pwMS.

Fatigue and the study protocol

The possibility of high-frequency exercise in this fatigued MS-collective is complemented by acquired quantitative data, showing an average adherence of 90% for both groups (596 sessions analysed).[22] Still, participants' statements indicated the importance of installing rest breaks for 30 min to 60 min, especially after the gym-sessions, as study-unrelated appointments might influence participants' ability to recover. Indeed, rest period allowing for fatigue was a common exercise facilitator in the studies reviewed by Motl and Learmonth.[20] Male pwMS in the study by Smith *et al*[36] mentioned how heat could influence their fatigue levels and limit their ability to exercise. As only one of our interviewees was present during the summer, this did not show up in our data, but should be kept in mind, especially regarding accelerated climate change in Europe and Germany.[37] Similarly, a positive cooling effect of aquatic training has been reported recurringly,[38] which was not detected in the present study. Heat might not only heighten fatigue levels but also negatively impact balance control, as reported by pwMS.[39] Therefore, future studies should monitor in advance, whether the training locations are susceptible to heat, whether there are options for cooler environments or time of training during the day (eg, morning hours) and how exercise will be adapted in case of heightened fatigue and lowered balance control due to heat.

Several participants from both groups described being energised right after the exercise sessions. This is in contrast to previously described negative short-term consequences of exercise on fatigue,[20] but in accordance with a more recent thematic synthesis, which summarised three studies where pwMS reported the need to exercise when they felt tired to increase their energy levels.[40]

Overall, inpatient rehabilitation could be an environment that allows pwMS to break through a vicious circle as it frees up capacities otherwise occupied by work, caring and other duties, and facilitates experiencing the positive effects of exercise. Appropriately, in a recent comprehensive qualitative study, Ghaidar *et al*[41] reported factors contributing to the decision of pwMS to attend inpatient rehabilitation in Germany. These included the

escape from everyday life, finding time to relax and to fully concentrate on one's health. Our results showed that this 'vacation from daily grind' can be regarded to be a reason for reduced fatigue by pwMS.

This has implications for future studies trying to evaluate the effect of an exercise intervention, or any other intervention regarding fatigue, during inpatient rehabilitation. Namely, the effect of an intervention might not be separable from that exerted of just being in the rehabilitation facility, as this seems to have an important effect, described and experienced by pwMS, as supported by the present results and the ones of Ghaidar *et al*.[41] Furthermore, in the present setting, participants might have complied with the exercise schedules and tolerated the high frequency of sessions per week, because they knew there were no competing activities (eg, housework, job, family), as otherwise, pwMS have described a need to avoid the experience of fatigue, to continue with their desired activities in daily life.[40] Appropriately, pwMS have also described inpatient rehabilitation with the image of being under a 'bell-jar'.[41] Two recent RCTs conducted in similar inpatient settings have not yet elaborated on this aspect, but it is noteworthy that in both studies, the control groups tended to also show reductions in fatigue experience, that is, potentially displaying 'vacation from daily grind'.[42 43] Moreover, it has to be noted that quantifying change in fatigue with established questionnaires, including the ones used in the two recent RCTs and the present feasibility study, proves to be difficult,[22 44 45] which is why qualitative investigations can be seen as a valuable methodology in these instances.

Limitations

The small sample size for this qualitative feasibility study, the lack of validating the results by the study participants, lack of cross-validation beyond investigator triangulation (eg, data triangulation), and that coders were non-independent must be considered when interpreting our findings. However, this is not uncommon for qualitative research conducted during the feasibility phase.[19] Overall, we only acquired a small glance at the diversity of fatigue experiences, while it is unclear whether saturation can be achieved at all for this complex phenomenon. Unfortunately, data from the SET group were less rich in content, and relatively short. Therefore, we did not analyse facilitators and barriers regarding SET. However, this was in line with one of our objectives being the exploration of the new MAT framework. Furthermore, we did not include patient representatives while constructing the interview guide, or in the analysis process, and no professional translation service for pwMS' quotes was used. It is possible that participants' responses at the time of the interview were influenced by other processes of their stay in the NRC (eg, overall satisfaction with their stay, perceived overall success, satisfaction with the recommendation regarding their future work situation), and by the fact that participants knew they were part of an intervention study.

Strengths of the study were its setting in a typical inpatient rehabilitation environment frequently encountered in Germany, evaluation of the new MAT approach, the inclusion of pwMS who were at least moderately fatigued, and the mixed-methods design.

CONCLUSION

MAT content was largely appreciated by pwMS and the fatigued patient collective was able to adhere to high-frequency exercise training, without an overall accumulation of fatigue during the intervention. However, social comparison and negative self-evaluation must be monitored closely and, if necessary, moderated by the group leader.

Future group-based exercise studies should include participants with similar levels of motor performance and include additional self-ratings of exercise demands, post-session. The present results, supplemented by our quantitative results,[22] further show that future studies conducted in an inpatient rehabilitation setting can involve fatigued pwMS in high-frequency exercise schedules if this includes adequate rest breaks. Furthermore, new forms of exercise interventions should be well described in the study information sheet to minimise participants favouring traditional exercise approaches. It will also be beneficial to include patient representatives in similar projects like this to construct the interview guide and aid in the analysis process. Finally, qualitative methods should be used alongside quantitative measures in the study of fatigue in the future, with one field of application being the investigation of the important factors of the inpatient rehabilitation environment contributing to fatigue reduction in pwMS.

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Contributors FW and JN developed the qualitative study design, qualitative research questions and the interview guide. JN conducted the interviews, while FW led the interview analysis. FW drafted the manuscript. JN, A-KF and PZ revised the manuscript. FW acts as guarantor.

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REFERENCES

1 Multiple sclerosis International Federation. In: *Atlas of MS*. 2020.
2 Dettmers C, Schmidt R, Jöbges M. Fatigue und Fatigability bei Multipler Sklerose – Leistungsbeurteilung. *Rehabilitation (Stuttg)* 2020;59:327–9.
3 Kobelt G, Langdon D, Jönsson L. The effect of self-assessed fatigue and subjective cognitive impairment on work capacity: The case of multiple sclerosis. *Mult Scler* 2019;25:740–9.
4 Nielsen J, Schnell R, Markett S, *et al*. Are “invisible MS symptoms” (fatigue, cognitive dysfunction, depression) significant in the professional performance assessment of multiple sclerosis patients two years after the inpatient primary evaluation? *Z Neuropsychol* 2020;31:11–25.
5 Sander C, Voelter H-U, Schlake H-P, *et al*. Assessment of Fatigue in Multiple Sclerosis. *Neurol Int Open* 2017;1:E79–85.
6 Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology* 2013;80:409–16.
7 Van Geel F, Moumdjian L, Lamers I, *et al*. Measuring walking-related performance fatigability in clinical practice: a systematic review. *Eur J Phys Rehabil Med* 2020;56:88–103.
8 Nourbakhsh B, Revirajan N, Morris B, *et al*. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. *Lancet Neurol* 2021;20:38–48.
9 Harrison AM, Safari R, Mercer T, *et al*. Which exercise and behavioural interventions show most promise for treating fatigue in multiple sclerosis? A network meta-analysis. *Mult Scler* 2021;27:1657–78.
10 Oken BS, Kishiyama S, Zajdel D, *et al*. Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology* 2004;62:2058–64.
11 Moss-Morris R, Harrison AM, Safari R, *et al*. Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis. *Behav Res Ther* 2021;137.
12 Dettmers C, Sulzmann M, Ruchay-Plössl A, *et al*. Endurance exercise improves walking distance in MS patients with fatigue. *Acta Neurol Scand* 2009;120:251–7.
13 Callesen J, Cattaneo D, Brincks J, *et al*. How do resistance training and balance and motor control training affect gait performance and fatigue impact in people with multiple sclerosis? A randomized controlled multi-center study. *Mult Scler* 2020;26:1420–32.
14 Hebert JR, Corboy JR, Manago MM, *et al*. Effects of Vestibular Rehabilitation on Multiple Sclerosis–Related Fatigue and Upright Postural Control: A Randomized Controlled Trial. *Phys Ther* 2011;91:1166–83.
15 Hebert JR, Corboy JR, Vollmer T, *et al*. Efficacy of Balance and Eye-Movement Exercises for Persons With Multiple Sclerosis (BEEMS). *Neurology* 2018;90:e797–807.
16 Wolf F, Eschweiler M, Rademacher A, *et al*. Multimodal Agility-Based Exercise Training for Persons With Multiple Sclerosis: A New Framework. *Neurorehabil Neural Repair* 2022;36:777–87.
17 Kalb R, Brown TR, Coote S, *et al*. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. *Mult Scler* 2020;26:1459–69.
18 Skivington K, Matthews L, Simpson SA, *et al*. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ* 2021;374.
19 O’Cathain A, Hoddinott P, Lewin S, *et al*. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. *Pilot Feasibility Stud* 2015;1.
20 Learmonth YC, Motl RW. Physical activity and exercise training in multiple sclerosis: a review and content analysis of qualitative research identifying perceived determinants and consequences. *Disabil Rehabil* 2016;38:1227–42.
21 Wolf F, Nielsen J, Saliger J, *et al*. Randomised controlled pilot and feasibility study of multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve multiple sclerosis-related fatigue and fatigability during inpatient rehabilitation (ReFEx): study protocol. *BMJ Open* 2022;12:e062160.
22 Wolf F, Nielsen J, Saliger J, *et al*. Multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve multiple sclerosis-related fatigue and fatigability during inpatient rehabilitation: a randomized controlled pilot and feasibility study [ReFEx][ReFEx]. *BMC Neurol* 2023;23:388.
23 Hersche R, Weise A, Michel G, *et al*. Three-week inpatient energy management education (IEME) for persons with multiple sclerosis-related fatigue: Feasibility of a randomized clinical trial. *Mult Scler Relat Disord* 2019;35:26–33.
24 Fortune J, Norris M, Stennett A, *et al*. 'I can do this': a qualitative exploration of acceptability and experiences of a physical activity behaviour change intervention in people with multiple sclerosis in the UK. *BMJ Open* 2020;10:e029831.
25 Penner IK, Raselli C, Stöcklin M, *et al*. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* 2009;15:1509–17.
26 Rädiker S, Kuckartz U. *Focused Analysis of Qualitative Interviews with MAXQDA: Step by*. Step: MAXQDA Press, 2020.
27 Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* 2007;19:349–57.
28 Pilarska J. The Constructivist paradigm and phenomenological qualitative research design. In: Anja P, Josephine P, Allison A, eds. *Research paradigm considerations for emerging scholars*. Bristol, Blue Ridge Summit: Channel View Publications 2021:64-83, 31 December 2021.
29 Mey G, Mruck K. Interviews. In: Mey G, Mruck K, eds. *Handbuch Qualitative Forschung in der Psychologie*. Wiesbaden: VS Verlag für Sozialwissenschaften 2010:423-35,
30 Learmonth YC, Marshall-McKenna R, Paul L, *et al*. A qualitative exploration of the impact of A 12-week group exercise class for those moderately affected with multiple sclerosis. *Disabil Rehabil* 2013;35:81–8.
31 Russell N, Gallagher S, Msetfi RM, *et al*. Experiences of people with multiple sclerosis participating in a social cognitive behavior change physical activity intervention. *Physiother Theory Pract* 2023;39:954–62.
32 Horton S, MacDonald DJ, Erickson K, *et al*. A qualitative investigation of exercising with MS and the impact on the spousal relationship. *Eur Rev Aging Phys Act* 2015;12:3.
33 Aubrey G, Demain S. Perceptions of group exercise in the management of multiple sclerosis. *Int J Ther Rehabil* 2012;19:557–65.
34 Akbar N, Hazlewood S, Clement M, *et al*. Experiences and perceived outcomes of persons with multiple sclerosis from participating in a randomized controlled trial testing implementation of the Canadian Physical Activity Guidelines for Adults with MS: an embedded qualitative study. *Disabil Rehabil* 2022;44:4663–71.
35 Mothes H, Leukel C, Jo H-G, *et al*. Expectations affect psychological and neurophysiological benefits even after a single bout of exercise. *J Behav Med* 2017;40:293–306.

36 Smith CM, M. Fitzgerald HJ, Whitehead L. How Fatigue Influences Exercise Participation in Men With Multiple Sclerosis. *Qual Health Res* 2015;25:179–88.
37 Copernicus Climate Change Service (C3S). European state of the climate 2022 full report; 2023.
38 Chen MH, DeLuca J, Sandroff BM, *et al*. Aquatic exercise for persons with MS: Patient-reported preferences, obstacles and recommendations. *Mult Scler Relat Disord* 2022;60.
39 Wallin A, Franzén E, Ekman U, *et al*. Struggling to Keep Up and Have A Good Life: A Qualitative Study of Living With Impaired Balance Control Due to Multiple Sclerosis. *Phys Ther* 2023;103.
40 Mezini S, Soundy A. A Thematic Synthesis Considering the Factors which Influence Multiple Sclerosis Related Fatigue during Physical Activity. *Behav Sci (Basel)* 2019;9:70.
41 Ghaidar D, Sippel A, Riemann-Lorenz K, *et al*. Experiences of persons with multiple sclerosis with rehabilitation-a qualitative interview study. *BMC Health Serv Res* 2022;22:770.
42 Patt N, Kupjetz M, Kool J, *et al*. Effects of inpatient energy management education and high-intensity interval training on health-related quality of life in persons with multiple sclerosis: A randomized controlled superiority trial with six-month follow-up. *Mult Scler Relat Disord* 2023;78.
43 Zrzavy T, Pfitzner A, Flachenecker P, *et al*. Effects of normobaric hypoxic endurance training on fatigue in patients with multiple sclerosis: a randomized prospective pilot study. *J Neurol* 2021;268:4809–15.
44 Close J, Vandercappellen J, King M, *et al*. Measuring Fatigue in Multiple Sclerosis: There may be Trouble Ahead. *Neurol Ther* 2023;12:1649–68.
45 Wolf F, Nielsen J. Factors contributing to change in fatigue as perceived by persons with multiple sclerosis attending inpatient rehabilitation: an exploratory qualitative analysis 9th Joint ECTRIMS-ACTRIMS Meeting, Milan. *Mult Scler* 2023;29(3_suppl):1109–34.

Experiences of fatigued persons with multiple sclerosis with multimodal agility-based exercise training and the ReFEx study protocol. A qualitative extension of a feasibility study.

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Supplement 1 - Interview guide and initial codes

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Fatigue concept* *Fatigue Konzept*		
No.	Questions	Initial Codes
1.	What does fatigue mean to you? *Was bedeutet Fatigue für Sie?#* Add-on: How do you experience your fatigue in your everyday life? *Zusatz: Wie erleben Sie die Fatigue in Ihrem Alltag?*	Fatigue concept
Experiences & demands (related to study therapies) ***Erleben & Beanspruchung (in den Therapieeinheiten der Studie)***		
2.	Only MAT: How did you feel about training in a group? *Nur MAT: Wie empfanden Sie das Training in der Gruppe?*	Facilitators & barriers
3.	How did you like the gym-based MAT/pool-based MAT/training on the cycle ergometer/strength training? *Wie fanden Sie die Gangschule/Bewegungsbad/Ergometertraining/Trainingstherapie?* Add-on: Was there something you particularly enjoyed? *Zusatz: Gab es etwas, was Ihnen besonders gut gefallen hat?* Add-on: Was there something that you particularly disliked? *Zusatz: Gab es etwas, was Ihnen gar nicht gefallen hat?*	Facilitators & barriers
4.	To what extent was participation in the respective therapies demanding or strenuous for you? *Inwiefern haben Sie die Therapien angestrengt oder gefordert?*	Exertion
5.	If you had the opportunity to change something about the respective therapies, what would it be? *Wenn Sie die Möglichkeit hätten, an den beiden Therapien etwas zu ändern, was wäre das?* Add-on: Why do you wish to change this? *Zusatz: Was sind die Gründe für Ihre Veränderungswünsche?*	Facilitators & barriers
6.	How did the therapies influence your fatigue? Could you please describe in detail, how you felt during and after the therapies? *Welche Wirkung hatte die Therapie auf Ihren Erschöpfungs-/Müdigkeitszustand? Können Sie bitte genau beschreiben, wie es Ihnen während und nach der Therapie ergangen ist?* Add-on: How long did it take for you to recover after the therapies? *Zusatz: Wie lange haben Sie nach der Therapie gebraucht, um sich zu erholen?* Add-on: How or where did your fatigue manifest itself? *Zusatz: Wie oder wo hat sich Ihre Erschöpfung geäußert?*	Fatigue
7.	Did you experience any discomfort during training? If yes, what kind of discomfort and where?	Facilitators & barriers

	Tauchten während des Trainings generell Beschwerden auf? Wenn ja, welche und wann?	
8.	To what extent were you able to recover in between the therapy sessions? *Inwiefern konnten Sie sich zwischen den einzelnen Therapien erholen?*	Fatigue
Personal relevance & goal achievement ***Persönliche Relevanz & Zielerreichung***		
9.	Do you feel like you were able to improve your balance? *Haben Sie das Gefühl, dass Sie Ihr Gleichgewicht verbessern konnten?*	Benefits
10.	Did you experience improvements in other areas? If yes, what do you think is the reason for this? *Haben Sie Verbesserungen in anderen Bereichen bemerkt? Falls ja, worauf führen Sie dies zurück?*	Benefits
11.	Are there any symptoms, that got worse, because of the therapies? If yes, what do you think is the reason for this? *Gab es Symptome, die sich durch die Therapien verschlechtert haben? Falls ja, worauf führen Sie dies zurück?*	Facilitators & barriers
12.	You were allocated to therapy program MAT/SET. There was also the program MAT/SET. How satisfied have you been with your allocation? *Sie wurden im Rahmen der Studie einem Therapieprogramm MAT/SET zugeteilt, es gab noch das Therapieprogramm MAT/SET. Wie zufrieden waren Sie mit der Zuteilung?*	Satisfaction with allocation
13.	How well did participating in the study fit into your overall rehabilitation schedule? *Wie fügte sich die Studienteilnahme zeitlich-organisatorisch insgesamt in Ihren Behandlungsplan ein?*	Organizational conditions
14.	How relevant was participating in the study for your personal rehab goals? *Welche Relevanz hatte die Teilnahme an dem Studienprojekt für Ihre persönlichen Rehaziele?*	Relevance for rehab-goals

MAT=multimodal agility-based exercise training; SET=strength and endurance training

*Block 1 (fatigue concept) was excluded from this analysis but will be analyzed and published elsewhere.

#The original German language questions are presented alongside the translations provided by the authors.

Supplement 2 – COREQ 32 checklist

No	Item	Guide questions/description	Response
Domain 1: Research team and reflexivity			
Personal Characteristics			
1.	Interviewer/facilitator	Which author/s conducted the interview or focus group?	JN (p.10)
2.	Credentials	What were the researcher's credentials	PhD
3.	Occupation	What was their occupation at the time of the study?	Clinical neuropsychologist at the NRC, researcher and lecturer at the University Hospital Cologne
4.	Gender	Was the researcher male or female	Male
5.	Experience and training	What experience or training did the researcher have?	Systemic therapist and counselor with many years of experience in clinical patient-centered communication. (p.11)
Relationship with participants			
6.	Relationship established	Was a relationship established prior to study commencement?	Most, but not all the participants met the interviewer in his role as a neuropsychologist prior to the interviews. (p.11)
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? *e.g., personal goals reasons for doing the research*	As part of the research team, the interviewer explained the ideas, design, and goals of the study to potential participants. Participants knew about the interviewer's clinical role. (p.11)
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? *e.g., bias, assumptions, reasons, and interests in the research topic*	Participants were informed that multiple sclerosis and the topic of the study was one of the researchers' preferred research areas. They were informed that the study was designed by the research team to gain a better understanding of fatigue and to find possible therapeutic ways to improve fatigue in the NRC. (p.11)
Domain 2: study design			
Theoretical framework			

9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e*.g., grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	Coding of the interviews was based on the approach of focused analysis for qualitative interviews, as described by Rädiker & Kuckartz (2020). (p.10)
Participant selection			
10.	Sampling	How were participants selected? *e.g., face-to-face, telephone, mail, email*	Face-to-face (p.8)
11.	Method of approach	How were participants approached? *e.g., face-to-face, telephone, mail, email*	Face-to-face (p.8)
12.	Sample size	How many participants were in the study?	12 (p.8)
13.	Non-participation	How many people refused to participate or dropped out? Reasons?	Zero (p.8)
Setting			
14.	Setting of data collection	Where was the data collected? *e.g., home, clinic, workplace*	Office in a rehab clinic. (p.10)
15.	Presence of non-participants	Was anyone else present besides the participants and researchers?	No
16.	Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	Important characteristics are sex, age, working capacity, functional disability, multiple sclerosis type, time since diagnosis, and fatigue, as reported in Table 2. (p.12)
Data collection			
17.	Interview guide	Were questions, prompts, guides provided by the	A guide was provided by the authors. It was pilot tested with

		authors? Was it pilot tested?	two persons with multiple sclerosis prior to the start of the study. (p.9)
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?	No repeat interviews were carried out.
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?	We used audio recordings. (p.10)
20.	Duration	What was the duration of the interviews or focus group?	Interviews had a median length of 11:55min, median length per group was 15:42min for MAT and 09:31min for SET. (p.12)
22.	Data saturation	Was data saturation discussed?	Data saturation was discussed briefly in the limitations section. (p.26)
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction	No (p.26)
Domain 3: analysis and findings			
Data analysis			
24.	Number of data coders	How many data coders coded the data?	FW coded all interviews, while one Interview was coded together by FW and JN. (p.10)
25.	Description of the coding tree	Did authors provide a description of the coding tree?	The coding tree is provided in table 1. (p.13)
26.	Derivation of themes	Were themes identified in advance or derived from the data?	Initial codes were derived in advance from the interview guide. These were then adapted and expanded by data derived from the interviews. (p.10-11)
27.	Software	What software, if applicable, was used to manage the data?	MAXQDA2022 (p.10)
28.	Participant checking	Did participants provide feedback on the findings?	No (p.26)
Reporting			
29.	Quotations presented	Were participant quotations presented to illustrate the themes/findings?	Yes (Results section)

		Was each quotation identified? *e.g., participant number*	
30.	Data and findings consistent	Was there consistency between the data presented and the findings?	Yes
31.	Clarity of major themes	Were major themes clearly presented in the findings?	Yes
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes

Eidesstattliche Versicherung

Hiermit versichere ich an Eides statt, dass ich die Dissertation selbständig verfasst habe und alle in Anspruch genommenen Quellen und Hilfen in der Dissertation vermerkt wurden. Die Dissertation ist in der gegenwärtigen oder in einer anderen Fassung oder in Teilen noch nicht an der Technischen Universität Dortmund oder an einer anderen Hochschule im Zusammenhang mit einer staatlichen oder akademischen Prüfung vorgelegt worden.

Köln, 15.05.2024

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