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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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