Research Protocol

Study title	Cognitive reserve-building activities in multiple sclerosis: A randomized controlled trial of the effect of cognitive leisure activities on objective and subjective measures of cognition
Study abbreviation	CRAMS
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Content

Background

Multiple sclerosis (MS) is a chronic, immune-mediated neurological disease caused by systemically activated immune cells crossing the blood-brain barrier, initiating a focal inflammatory response causing damage to nerve fibers and their protective myelin sheath[1].The prevalence of MS is high in Denmark, with almost 18.000 patients, and the disease is the primary cause of neurological disability in young people[2,3]. The cause of MS is not fully understood, but lifestyle and environmental factors play an important role in disease development in genetically predisposed individuals[4]. MS initially manifests as one of two types: relapsing-remitting MS (RRMS) or primary progressive MS (PPMS). While RRMS makes up around 85% of all cases, PPMS accounts for the remaining 15%. RRMS will, in many cases, progress to secondary progressive MS (SPMS)[5]. Age at onset typically ranges between 20 – 40 years, and symptoms include paresis, sensory problems, bowel and bladder dysfunction, fatigue, and cognitive impairment. The early age of onset and the broad spectrum of symptoms means that education, career, and family life are often affected. Thus, the disease has significant implications, affecting not only the level of independence in daily life activities but also financial stability. On a societal level, MS is associated with reduced work capacity resulting in lowered productivity and an increased need for social welfare services[6,7].

Cognitive impairment is a common symptom in all types of MS and can occur in the early stages of the disease[8]. Cognitive impairment occurs in more than 50% of people with MS (pwMS) and is often more pronounced in progressive MS[8,9]. The most commonly affected cognitive domains include information processing speed, memory, and executive functioning[8]. Furthermore, given that processing speed is a foundation for other cognitive processes, impairment may affect additional cognitive domains[10]. Cognitive impairment is associated with an increased risk of withdrawal from the labor market and greatly impacts the ability to engage in social activities. Specifically, cognitive impairment has been shown to be associated with lower income independent of the degree of physical disability[11–14]. Furthermore, cognitive impairment is associated with an increased risk of depression and a lower quality of life[12,15–17]. Additionally, pwMS with cognitive impairment have more difficulties performing daily life activities such as using the internet when compared to healthy individuals[18].

The International Multiple Sclerosis Cognition Society and The Consortium of Multiple Sclerosis have developed recommendations, that include early screening with a test of processing speed and yearly follow-up with testing[19]. However, neither the screening nor the follow-up is routinely performed in Denmark. There is also little consensus regarding best practice and no recommendations for rehabilitating cognitive functions for pwMS. Some systematic reviews,

including Cochrane reviews, have found effects of both pharmacological and neuropsychological treatments for cognitive impairment[20–22]. However, the level of evidence is generally low as previous studies have lacked methodological rigor[23]. Neurobiologically, functional magnetic resonance imaging (fMRI) studies have found changes in cortical activation and increased neural plasticity after different types of cognitive rehabilitative measures[24]. Regardless of the effectiveness of these methods, they are currently not systematically offered to Danish pwMS, who receive little treatment targeting cognition. There are currently only few computer-based training methods targeting MS-related deficits specifically, and those that exist are not necessarily meaningful to all pwMS who must prioritize daily activities due to fatigue. Computer-based training also often requires expensive licenses and professional guidance. Devoting and training staff for cognitive testing, instructing pwMS and performing follow-up is costly and time consuming.

An alternative approach to the computer-based methods is to focus on establishing preventative and even pre-clinical interventions targeting lifestyle modifications with the potential to enhance overall brain health. Examples of modifying lifestyle factors include physical exercise, stress management techniques, management of cardiovascular risk factors and other co-morbidities, and promoting a *cognitively active lifestyle*. The latter is related to the concept of *cognitive reserve* which can be thought of as an excess in cognitive capacity or strategies with the potential to buffer against brain damage caused by disease or brain trauma[25,26]. Building cognitive reserve via lifestyle modification could theoretically result in improved cognition or delayed disease progression, meaning delayed manifestation of cognitive symptoms. Given that MS is primarily diagnosed at a young age, delaying the onset and progression of cognitive impairment could have major impact on both a personal and a socioeconomic level.

The theory of cognitive reserve was introduced by Stern and colleagues and is based on studies of people with Alzheimer's disease in which persons with greater cognitive reserve were less likely to show signs of cognitive impairment as the disease progressed[26–28]. The theory of cognitive reserve is supported by studies showing that individuals with higher levels of education are less frequently – and to a lesser extent – affected by the disease, as well as the observation that cognitive symptoms tend to manifest at a later age in these individuals[26,27,29]. The theory is further supported by studies in animal models showing the effect of enriched environments on cognition in which cognitive stimulation is related to increased neuronal connectivity and brain plasticity[30]. Cognitive reserve can be measured indirectly via different proxy-variables reflecting intellectual enrichment throughout an individual's life. Examples include education, occupational attainment, and participation in cognitively stimulating activities before or after the onset of disease[31]. Examples of a cognitively active lifestyle include reading, writing and participation in different leisure activities,

etc.[32,33] Cognitive reserve has been studied in a variety of conditions in addition to Alzheimer's disease, including stroke, traumatic brain injury, Parkinson's disease, HIV-related dementia, and MS[25,27,29,34–37]. Most of these studies found that a higher level of cognitive reserve is associated with lower levels of cognitive impairment. Even in terms of normal aging, research has suggested that participation in socially and mentally stimulating activities can prevent cognitive impairment[38]. Although participation in cognitive reserve-building activities prior to MS diagnosis is associated with better cognitive status after diagnosis[32], it is currently unclear whether certain activities impart more on reserve than others. So far, research has indicated positive effects of reading and writing on memory as well as on hippocampal volume in MS[33].

According to Stern et al., reserve can be divided into passive and active models[26]. Passive reserve models assume a fixed cutoff or threshold at which cognitive impairment will occur for all individuals. In contrast, active models suggest that the brain tries to cope with neural injury by utilizing existing cognitive processes or by recruiting compensatory processes[26]. According to active models, reserve is furthermore influenced by enriching activities that contribute to keeping the brain healthy[26]. The hypothesis of cognitive reserve for neurological patient groups has so far mainly been supported by correlational studies, which cannot clarify potential causal relationships between intellectual enrichment and protection against cognitive decline. In dementia research, studies have shown an association between a cognitively active lifestyle and a reduced risk of developing dementia[39–41]. A recent study of 119 persons with mild cognitive impairment or subjective cognitive decline found that an intervention focused on positive changes in diet, exercise, and cognitive engagement over just eight weeks resulted in improved cognition and processing speed[42]. Research also shows that high cognitive reserve is associated with increases in perceived disability and cognitive impairment in addition to higher levels of subjective physical and mental well-being, specifically for pwMS[43].

The theory of cognitive reserve implies that disease-related cognitive impairment can be reduced or postponed by actively pursuing a cognitively active lifestyle. However, there is a need for studies exploring whether systematic engagement in activities aimed at improving cognition and increasing cognitive reserve can make up an active intervention in MS. A prerequisite for effective clinical interventions is that they are feasible and meaningful to the individual. Thus, factors such as motivation, understanding, and compliance are of utmost importance in addition to the personal goals, emotional and psychosocial situation.

A widely used method for training cognitive functions is the use of computer-based training programs, which have been tried in dementia and MS. A recent review of computer training in MS found a moderate effect on cognitive measures[44]. However, the effect waned without further

training. An alternative method of cognitive rehabilitation could be a more individualized approach aimed at modifying lifestyle factors based on the individual's pre-existing preferences for certain activities associated with cognitive reserve. These individualized cognitive training activities could be adjusted to match a person´s interests, priorities, motivations, and daily schedule to increase the likelihood that the person continues training independently post-intervention. Employing cognitive training methods based on individual desires and interests and grounding them in activities that fit into the person's daily life schedule may constitute a cost-effective alternative to computer training. Interventions based on individual skills and needs are easy to implement and thus clinically highly feasible.

Low cognitive reserve is associated with hazardous health behavior and a diminished ability to cope with chronic disease. For example, low cognitive reserve is associated with an increased risk of smoking[43]. In addition, hazardous health behaviors have been shown to predict symptom severity and disease progression in MS both physically and cognitively[45–48]. Identification of such risk factors and hazardous health behaviors can contribute to targeted intervention. This may reduce the risk of early retirement from the workforce, prevent depression, increase quality of life, and prevent or postpone the development of cognitive impairment in pwMS. In turn, this could potentially have great importance not only for the individual patient but also on a societal level. Unfortunately, there are currently no effective treatment options for cognitive impairment in MS, nor are there guidelines for prevention and follow-up. Thus, pwMS are currently not offered evidence-based advice or treatment focused on cognitive impairment or rehabilitation.

Purpose

The overall purpose of the study is to develop interventions and recommendations focused on prevention and potentially improvement of cognitive impairment in MS to help individuals maintain autonomy and quality of life. Furthermore, we wish to identify factors that can be employed clinically for the future development of supportive and preventative measures focused on the cognitive decline associated with MS.

The trial is a randomized, controlled trial investigating the effect of increased engagement in cognitive leisure activities with and additional qualitative investigation of adherence and acceptability of the intervention.

The primary purpose of the intervention study is to examine whether pwMS will improve on measures of subjective and objective cognition by increasing engagement in activities associated with cognitive reserve (active reserve) and secondly the following:

- To examine whether it is possible to develop a more individualized cognitive intervention to increase the active cognitive reserve.
- To examine the feasibility and acceptability of the intervention and thereby identify factors that may act as barriers or facilitators for the conduction of the study.
- To examine whether pwMS will continue to engage in the cognitively stimulating activities without continuous follow-up.

Method

The intervention

For a graphical overview of the study see appendix 1.

The intervention study will employ a randomized, controlled crossover design in which 60 participants with either RRMS or progressive MS (30 RRMS, 30 PPMS/SPMS) are allocated to either Group A (intervention) or Group B (passive control group) for 12 weeks. Using a computer-based random number generator, participants will be randomized to either Group A or B in blocks of 6 based on MS subtype (RRMS/progressive MS). Once participants have completed the first12 weeks, the groups are crossed over and followed up again after 24 weeks. This allows for investigation of the potential effect of the intervention and its sustainability. To allow for comparison of continued adherence to the intervention without rigorous follow-up, Group B will receive an additional follow up after 36 weeks. Total inclusion time from enrolment to last follow-up is thus 24 weeks for Group A and 36 weeks for Group B.

The relevance of investigating the effect of the intervention in different MS populations is to examine potential group differences in both the effect and feasibility in each group. For example, we expect that individuals with progressive MS will show poorer cognitive status at inclusion, and a hypothesis could be that increasing engagement in intellectually demanding tasks will be more difficult for persons with more severe cognitive impairment. Similarly, it could be hypothesized that there could be more potential for rehabilitation the greater the level of impairment. Thus, one might expect people with progressive MS to improve more than people with RRMS.

All suitable participants will initially be screened with three tests in the following order: The Trail Making A (TMA) test, the Major Depression Inventory (MDI), and a written Symbol Digit Modalities Test (SMDT) or Paced Auditory Serial Addition Test (PASAT) (depending on dexterity). To partake in the study, the participant must not have depression and must show impairment in processing speed. Processing speed will primarily be assessed with the written SDMT, and impairment is defined as a score of -1 standard deviation (SD) or below. However, if a participant tests below -1

SD on the TMA (indicating slowed motoric speed or reduced dexterity), this person will instead be tested with the PASAT. Impairment on the PASAT is defined as for the SDMT. A full description of inclusion and exclusion criteria is given below.

The primary outcome is the oral version of the SDMT (in a parallel version from the one applied for screening purposes) and the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ). The SDMT stems from the Brief International Assessment for MS (BICAMS) panel, which has previously been validated in a Danish sample[49]. Similarly, the MSNQ has previously been translated and employed in a Danish sample[50]. Secondary outcomes will include cognitive tests of memory and executive functions.

Once all tests and questionnaires are completed, participants are randomized to either the initial intervention group (Group A) or a passive control group (Group B; see appendix 1). Participants in Group A will then be exposed to educational material in a systematic, uniform manner and assisted in choosing cognitive training activities from a predefined list of activities (described below). Participants randomized to Group B will be informed that they will receive the intervention after a 12-week waiting period.

Group A will receive a brief follow-up phone call 3-6 days after the randomization to improve adherence to the protocol after which motivational phone calls are performed every 14 days (±3 days). This is done to maintain and increase engagement in the cognitively stimulating activities. Conversations will follow a semi-structured interview guide in Danish with reference to personal training goals identified before training commences (Appendix 2). Furthermore, participants will be asked to keep daily diaries via access to the electronic database (REDCap), thereby registering their daily performance in minutes. To ensure the best possible compliance, printed versions will be made available for all participants and the principal investigator will help fill in the missing electronical data in REDCap at the follow-up phone calls every 14 days.

At 12-weeks follow-up all participants will be evaluated with the same test battery and questionnaires as applied at baseline. A different version of BICAMS will be employed to avoid learning effects. As the test administrator at baseline will know group allocation and thus become unblinded, follow-up testing at week 12 and 24 will be administered by a different member of the research team to avoid bias. From Group A, 5-10 participants (half with RRMS, half progressive MS) will be selected to participate in semi-structured interviews following the initial 12 weeks or after potential drop put from the study. Focus will be on identifying factors that affected acceptance along with potential barriers to engaging in the intervention and reserve-building activities. Once 12-weeks follow-up is completed, groups will be crossed over. Participants from Group B will at this

point receive the same educational session as Group A did at baseline and be assisted in choosing cognitive training activities from the predefined list of activities (described below). This is done by the primary investigator to ensure uniformity. After this, Group B enters their intervention period.

At 24 weeks follow-up, all participants are reassessed with the same tests and questionnaires for a third time. As the BICAMS includes three versions of the SDMT and Brief Visuspatial Memory test-Revised (BVMT-R) but only two versions of the California Verbal Learning test 2 (CVLT-II), participants will complete the same version of the CVLT-II as at baseline. Once again, 5-10 participants from Group B (half RRMS, half progressive MS) having received the intervention from 12 – 24-weeks will be selected to participate in semi-structured interviews. Potential dropouts will also be selected to participate in the semi-structured interviews designed specifically for the study.

Primary endpoints

The primary endpoints will be analyzed as a change from baseline to 12 weeks follow-up and are co-primary endpoints:

1. SDMT (oral version from BICAMS)
2. MSNQ

Secondary endpoints

The following endpoints will be analyzed as a change from baseline to 12 and from 12 to 24 weeks follow-up and are listed in ranked order:

3. CVLT-II
4. BVMT-R
5. Phonological word fluency
6. Five-point test
7. Cognitive Leisure and Activity Scale (CLAS)

Tertiary endpoints

1. Multiple Sclerosis Impact Scale-29 (MSIS-29)
2. Fatigue Scale for Motor and Cognitive Functions (FSMC)
3. Cohen’s Perceived Stress Scale (PSS)

Cognitive tests

Brief International Cognitive Assessment for MS (BICAMS)

The BICAMS consists of three individual tests, each assessing some of the most frequently affected cognitive domains in MS[51]. One of these is processing speed which is reflected by the SDMT. The other tests included are the CVLT-II, a verbal episodic learning and memory test, and the BVMT-R, a test of visuospatial memory function. The BICAMS has been validated in Danish and takes approximately 15 minutes to complete[49]. To minimize learning effects, different versions of the tests will be employed at baseline, 12 weeks follow-up and 24 weeks follow-up when possible.

- SDMT is a fast, low-cost and highly sensitive test of cognitive impairment in multiple sclerosis[52]. The numbers 1 to 9 are each assigned an abstract symbol. The participant is asked to translate each symbol to its corresponding number. The number of points in the test is equivalent to the number of correct answers in 90 seconds[53]. The test is performed at screening in writing to compare with normative national material to confirm eligibility and orally from baseline and forward.
- CLVT-II is a verbal learning and memory test in which the test administrator reads a list of sixteen words out loud to the participant, who is then asked to repeat as many words from memory as possible. The test is repeated five times, and the total number of recalled words is the result[54].
- BVMT-R is a nonverbal, visuospatial memory test in which six abstract figures are presented on paper. The participant is then given 10 seconds to memorize the figures. The participant is then asked to draw the figures as detailed as possible. This is repeated three times, and points are given for each replicated figure[55].

Word fluency (phonological)

Word fluency test is a short and simple test of verbal and executive functions. During testing, the participant is asked to name as many words beginning with the letter “S” as possible within one minute. All words, apart from proper nouns, are accepted[56].

The five-point test

Originally developed by Regard et al. and later modified by Lee et al., the five-point test is a measure of nonverbal fluency thought to reflect executive functions such as planning and mental flexibility[57,58]. The participant is presented with a sheet of paper consisting of five-point matrices

and asked to produce as many different geometrical figures as possible within three minutes. This study will employ norms based on a Danish sample[59].

Paced Auditory Serial Addition Test (PASAT)

The PASAT is a test of cognitive processing which has been widely used in MS research[60,61]. Administration consists of the participant being presented with a series of single digit numbers of which the two latest presented digits must be added together. In the present study, a Danish version of the PASAT will be used solely as a screening tool of information processing speed for participants with poor hand functioning. In line with the inclusion criteria based on the SDMT, participants will be included if their score falls below -1 SD.

Patient reported outcomes (PROs)

The following PROs include one co-primary and one secondary endpoint (MSNQ and CLAS), the remaining are tertiary endpoints.

Multiple Sclerosis Neuropsychological Questionnaire (MSNQ)

The MSNQ is a brief 15-item questionnaire originally developed to measure self-perceived cognitive impairment specific to MS[62]. Each item is scored on a 5-point scale which ranges from 0 (never/does not occur) to 4 (very often/very disruptive). The MSNQ exists in both a self-report and informant version, of which this study will employ the former. A study employing the Danish MSNQ used in this study found that, while the test-retest reliability is acceptable, scores do not correlate with performance on neuropsychological tests. Instead they show a weak linear relationship with measures of anxiety/depression[50]. Employing the Evaluating the Measurement of Patient-Reported Outcomes (EMPRO) framework, a standardized tool for ranking strengths, weaknesses, and psychometric properties of questionnaires, Khurana et al. found the MSNQ score to rank above the minimum threshold, suggesting it to be an acceptable PRO[63].

Cognitive Leisure & Activity Scale (CLAS)

The CLAS is a short, recently developed questionnaire designed to estimate an individual's degree of participation in cognitive and leisure activities[64]. Informants are asked to rate the degree to which a study participant partakes in each of 16 activities on a 0–5-point scale, with 0 indicating never engaging in the activity and 5 indicating daily engagement. Total score ranges from 0–80. The CLAS has recently been found to have good psychometric properties in a sample of 318 elderly adults with and without cognitive impairment[64]. In this study, the CLAS is used to quantify the degree of participation in cognitive activities pre- and postintervention and to investigate whether participants in the intervention group stop performing the activities after the intervention

period. Importantly, this study will employ a slightly modified version of the CLAS in which the participants (rather than informants) will complete the questionnaire. This is in line with the original authors' suggestion that people with mild cognitive impairment can complete the measure[64]. Furthermore, this study will employ a modified version of the CLAS reflecting the participant's activity level within the past 12 weeks rather than one year (as the original).

Multiple Sclerosis Impact Scale-29 (MSIS-29)

MSIS-29 is a self-report questionnaire consisting of 29 questions. It is designed to assess the quality of life of MS patients. Two scores are generated, one physical and one psychological. The participant is asked to rate the degree to which MS has affected them during the previous 14 days [65]. In this study, the MSIS-29 is included to assess whether a more active cognitive lifestyle will affect self-assessed quality of life.

Fatigue Scale for Motor and Cognitive Functions (FSMC)

The FSMC is a MS-specific questionnaire constructed to measure MS-related fatigue. It generates three scores: Total, physical and cognitive fatigue. Participants are asked to answer the questionnaire to evaluate their general experience of how much the MS-related fatigue affects their everyday functioning[66]. In this study, the FSMC is included to explore whether fatigue mediates potential effects of the intervention.

Cohens Perceived Stress Scale (PSS)

The PSS is a short global self-report measure of stress designed to assess to which extent individuals rate their lives as being overloaded, uncontrollable and unpredictable[67,68]. The version employed in this study is the 10-item version which contains statements that are framed either positively or negatively and scored from 0 – 4, yielding a maximum score of 40. Higher scores are indicative of higher stress levels. The PSS has previously been translated into Danish and shown to have good psychometric properties in a Danish sample[68]. In this study, the PSS is included to investigate whether stress mediates potential effects of the intervention.

Major Depression Inventory (MDI)

The MDI is a self-report instrument designed to screen for depression based on symptoms in both the DSM-IV major depression diagnosis and the ICD-10 diagnosis of moderate to severe depression. The scale consists of 12 items, of which 10 are scored on a Likert scale. Using two different sets of algorithms, participants can be assessed for depression according to either the DSM-IV or the ICD-10 criteria[69]. The score can also be used as a rating scale in which the sum of each question results in a theoretical score ranging between 0–50. Here, research suggests that

the optimal cut-off score is 26, with scores between 21–26 categorized as mild depression and those above qualifying as moderate depression[70]. This study will employ the cut-off for moderate depression such that persons scoring ≥ 26 are excluded (the moderate depression cut-off). If a participant meets the criteria for depression, he or she will be referred for further evaluation. The MDI was developed and validated with Danish patients and has shown adequate psychometric properties[69,70].

The cognitive training activities

One secondary aim in the study is to investigate whether it is possible to increase a participant's level of engagement in cognitively stimulating activities. Given that the focus is not on the effect of any specific training activity, it is possible for a participant to switch from one activity to another. However, the requirements are: 1) the activity meets the general requirements for what counts as a *cognitive* leisure activity (described below) and 2) the activity chosen is approved beforehand by the research team. Furthermore, participants will be able to perform more than one activity should they so wish so long as the activities meet the general criteria. Although participants will be free to choose any activity from the predefined list, they will be told that activities should ideally be novel to them.

The cognitive leisure activities included in the intervention are listed below. The list is compiled with inspiration from the following measures of cognitive leisure activities: the Cognitive Leisure Scale, CLAS and the DeltaQuest Reserve-Building Activity Measure[32,64,71].

This list is based on previous studies that have found a correlation between increased engagement in these activities and 1) better preserved cognitive abilities after the MS diagnosis, 2) increased ability to withstand the effects of brain atrophy, 3) increased volume of the hippocampus after receiving the MS-diagnosis[32,72]. Studies have furthermore shown an association between the degree of engagement in these types of activities and a decreased risk of developing dementia[39–41].

The choice of cognitive leisure activity is not limited to this list and can include additional activities that the research team deems to be cognitively stimulating. Furthermore, assuming that novel activities for the participant will be more cognitively challenging and engaging, participants will be asked to try to choose an activity with which they are not already familiarized.

- Reading (e.g., books, magazines, newspapers)
- Writing (e.g., diary, blogs, articles, newsletters)
- Learning a new skill or studying a new subject (e.g., language, history, music theory, math)

- Producing art (e.g., painting, poetry, sculpture, songwriting)
- Learning/playing a musical instrument
- Participating in cognitively stimulating hobbies (e.g., model building, web design)
- Playing structured games (e.g., cards, board games, crossword puzzles)

Feasibility study

Feasibility and acceptability interview

A qualitative investigation will be carried out based on a semi-structured interview designed specifically for this trial to evaluate the feasibility of the intervention and assess factors related to acceptance in terms of completion of the activities. The semi-structured interview guide is inspired by the 14 theoretical domains described in the Theoretical Domains Framework and the Behavior Change Wheel[73–75]. These theories concerning implementation of interventions were developed to design and evaluate interventions targeting behavioral change such as those applied in this study.

The selection of participants for the interviews will be strategic and aimed at securing variation to collect rich data. The participants who are chosen will vary in diagnosis, age, sex, and years of education/educational level. We aim to include a total of 10-20 participants (5-10 from each group) for interviews, including participants who complete the intervention and some who may drop out before intervention completion.

The goal of the feasibility study is to identify factors influencing the degree of acceptance as well as potential barriers to completing the intervention. This is done with the aim of providing recommendations for increasing participant motivation and decreasing drop-out in future interventions, be they clinical or research based. To ensure a diverse and representative section of the study population, a total of 10 – 20 participants will be selected based on the following parameters:

- Age
- Sex
- EDSS
- MS type
- Participants who have completed the intervention
- Participants who dropped out before completing the full intervention

The interviews are transcribed verbatim, analyzed and thematized using content analysis[76]. The software NVivo® is used to structure the analysis[77].

Additional information

In addition to the cognitive tests and PRO's listed above, the following additional information will be collected:

Background information

- Age
- Sex
- Expanded disability status scale (EDSS)
- MS type
- Disease duration
- Type of MS treatment
- Additional use of medication
- Years of education/educational level
- Type of and occupational status

EDSS

The EDSS is the most widely used method for evaluating the degree of disability in MS, both clinically and for research purposes. The scale ranges from 0–10, with 0 indicating no disability and 10 being death caused by MS. EDSS is insensitive to cognitive impairment[78]. EDSS scores are attained by patient chart review and will be based on the latest reported score, except if the EDSS was assessed during a relapse.

Cognitive Reserve

Based on research practice, cognitive reserve will be estimated from three widely used proxy measures of cognitive reserve. The first of these includes the Danish version of the Vocabulary subtest from the Wechsler Adult Intelligence Scale 4th edition (WAIS-IV) – an often-used measure of premorbid IQ and one of the best predictors of general mental ability[56]. The second variable is a combined measure of educational and occupational achievement. In accordance with previous research, these will be coded as ordinal values and converted to a composite measure[79]. The third measure is the degree of engagement in leisure activities as measured by the CLAS. These three measures will then be combined into a composite cognitive reserve score for each participant using factorial analyzes described in previous research[79,80].

WAIS-IV, Vocabulary subtest

The WAIS-IV is an IQ test developed to measure intelligence and cognitive abilities[81]. The test consists of 10 individual subtests and five supplementary tests. From the 10 individual tests, it is possible to calculate index scores for different aspects of intelligence, including verbal comprehension, perceptual reasoning, working memory, and processing speed[82]: These can then be summarized to a full-scale IQ score. Of the 10 subtests, the vocabulary test has been identified as one of the single best predictors of general mental ability[56]. In accordance with previous research in the field, the test is taken as a measure of intellectual enrichment and included in the composite cognitive reserve score (see above).

Educational material and motivating interviews

At the initial meeting, all participants in the intervention group (Group A and later Group B) will participate in a preplanned, uniform educational session. The educational material will be covered in a systematic manner to minimize variation between participants while maintaining an openness to dialogue and questions. The presented material will be based on a premade slideshow which will be presented to all participants, ensuring that all participants have approximately the same level of knowledge about MS, MS symptoms, and cognition. Topics covered in the material will include the following:

- What is MS, and what is cognition
- Which cognitive difficulties can be associated with MS
- What influence does fatigue have on cognition and quality of life
- What is cognitive reserve
- Identification of current types of cognitive leisure activities and an approximate estimation of the number of minutes spent on these activities
- Setting goals to increase the extent of engagement in cognitive leisure activities
- Motivational interview aimed at identifying predictable barriers in training activities to minimize and avoid these

This educational session will be given immediately after the participants have completed the cognitive tests and questionnaires and after randomization to the intervention group.. During the educational session, participants will be asked to identify personal goals and assisted in formulating a plan for reaching those goals. This will be done with reference to the S.M.A.R.T goal framework (Appendix 2)[83]. As previously described, participants will receive one phone call 3-6 days after entry into the intervention phase and supportive phone calls from the research team every 2 weeks from then on. Focus will be on evaluating goals as well as on ways to handle fatigue and other obstacles, which could act as barriers to engagement in the activities. Similarly, the

phone calls will focus on increasing motivation and identifying potential obstacles that may negatively impact engagement in leisure activities. At week 12 the participants in Group B are switched to intervention and will undergo the same regimen.

Journals and registration of time spent on activities

Participants in the intervention arm are instructed to complete registration of their cognitive leisure activities in their respective intervention phase (baseline to 12 weeks or 12 weeks to 24 weeks). This should ideally be done every day. Diaries are written and stored in the electronic database (REDCap) and presuppose that the participant has internet access and enough technical skills to manage a computer or smartphone.

At the end of each day, participants are instructed to register the total amount of time they estimate having spent on leisure activities during the day. In addition, should they have engaged in several activities, they are asked to specify which, along with the approximate amount of time spent on each. This subjective measure of time spent on activities is included to assess if participants increase their efforts and to what extent.

Participants

Inclusion and exclusion criteria

Inclusion criteria

- RRMS, SPMS or PPMS
- Age 18-65
- EDSS score ≤ 6.5
- SDMT (or PASAT) score < -1 SD
- No depression based on an MDI < 26
- Able to use computer or smartphone and has internet access
- If in treatment with one or more of the following medications, the dosage must be stable:
    - Cannabinoids
    - Anticholinergic medications
    - Sedatives e.g., benzodiazepines
    - Opioids
    - Antispasmodics
    - Beta-blockers
    - Antidepressant medication
    - Fampridine

Exclusion criteria

- Planned start-up or discontinuation of one or more of the above-mentioned medications
- Structural brain changes following previous head trauma or neurological conditions other than which lead to structural changes or affect cognitive abilities
- Epilepsy
- Significant psychiatric co-morbidity
- Significant somatic co-morbidity including, but not limited to, severe cardiovascular disease as well as liver, kidney, and endocrine diseases
- Relapse 3 months prior to inclusion

Statistics

Power calculation

Power calculation for this study was based upon the potential to increase SDMT after having engaged in cognitive reserve building activities. The study aims to have 90% power to detect a 4-point difference in SDMT between the intervention group and the control group at a two-sided significance level of p=0.025. This requires 25 participants in each treatment arm. The power calculation was based on unpublished data from two populations (RRMS and progressive MS) collected in previous trials at our site. The power calculation assumes that the standard deviation of change in SDMT is approximately 4, and that there is no significant regression towards the mean. This cut-off was based on work published in 2010 which concluded that a worsening of at least 4 points was associated with decline in work status[84]. To account for a dropout rate of up to 20% (as observed in previous clinical trials in MS) we plan to include 60 participants in the study (RRMS n = 30 and progressive MS n = 30).

Primary outcome

The primary efficacy measure will be the difference in change of the co-primary endpoints SDMT and MSNQ between the intervention and the treatment group at 12 weeks follow-up. The aim of the statistical analyses is to test the null hypothesis that the observed difference in the change of SDMT or MSNQ score between the intervention group and the control group is caused by the random allocation of participants. Statistical analyzes will be performed using a general linear model with group allocation as factor and years of education and screening value of the given endpoint as covariate. The difference in change is reported with 95% confidence intervals and p-value. Change from screening will additionally be reported in absolute values in compliance with

the CONSORT statements[85]. In case of non-normally distributed data appropriate non-parametric analyzes will be performed.

Secondary outcome

Difference in change of the secondary outcome measures between the intervention and the control group will be assessed at the 12-week and 24-week follow-up. Plans for analyzes are pending.

Tertiary outcome

Tertiary outcome measures are exploratory and pending analyses plans.

Funding

The Danish Multiple Sclerosis Society has provided funding for the project Additional funding will be applied for with the Danish Multiple Sclerosis Society or other foundations.

Access to patient charts

Patient chart information may only be collected by the principal investigator or treating neurologist and only after the patient has provided written informed consent. A signed consent form gives the person or persons responsible for the study access to obtain information from the patient charts to review information regarding the participants' health conditions relevant to the research project and for control purposes. Control purposes include self-inspection, quality control, and monitoring.

Data and processing of personal information

All data is registered in REDCap. Permission for data collection was granted by *Center for Dataanmeldelse* (P-2021-882).

Recruitment of participants and obtainment of informed consent

Recruitment of participants will to a large extent be from the Danish Multiple Sclerosis Center and, if necessary, via advertisement through the Danish Multiple Sclerosis Society (Scleroseforeningen). Participants will receive written information about the study. An informed consent form must be signed before any study-related activities are performed.

Publication of results

The data and analyses described in this protocol will be published by the principal investigator, the sponsor of the project, and other collaborating authors as soon as possible and in accordance with

the Personal Data Protection Act (*Danish: Persondataloven*). The sponsor have the intellectual property rights to the data and results. Both negative, positive, and inconclusive findings will be published. All authors of papers related to this protocol will be given thorough opportunity to read every manuscript prior to publication. All data and analyzes which are not published are considered confidential. All publications will be sent to peer-reviewed, open-access journals. Co-authorships are determined in accordance with the Vancouver convention.

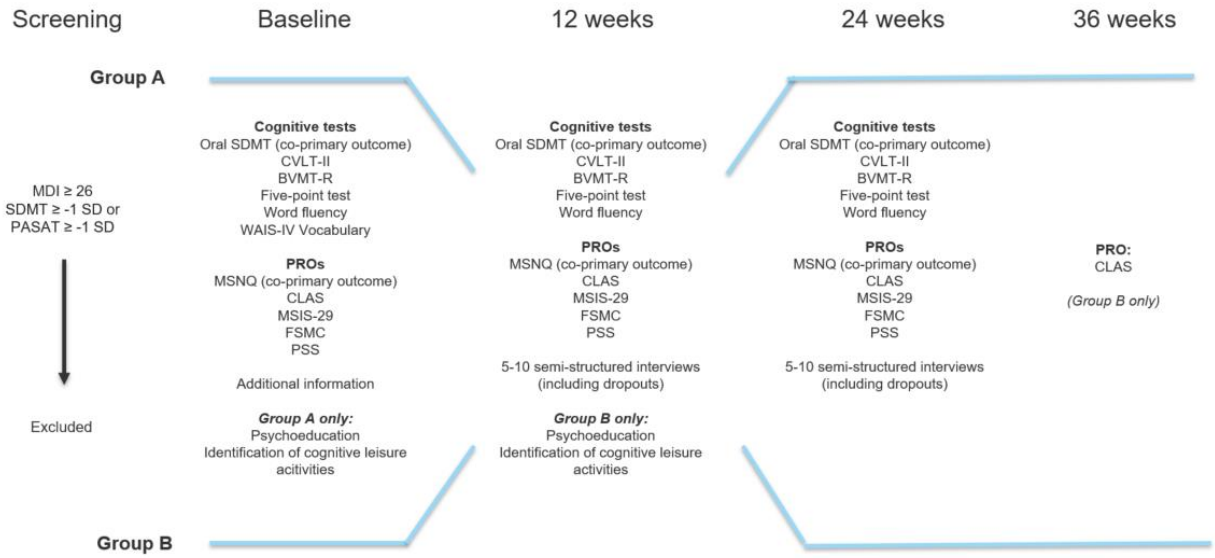
Ethics, risks, side effects and disadvantages

No ethical approval of this project is required. The National Committee on Health Research Ethics has been informed of the project and the project has been assigned the following file number: H-20075846. Participation in the study is not considered to involve any risks or side effects. However, the study is time-consuming and requires substantial involvement from the participants. Therefore, the amount of time required could be considered a potential disadvantage.

Compensation

All participants in health science research are covered by the Patient Insurance Act (Danish: *Patientforsikringsordningen*; see also "*lov om klage og erstatningsadgang inden for sundhedsvæsnet*", chapter 3).

Appendix 1. The intervention study



BVMT-R = Brief Visuospatial Memory Test Revised; CVLT-2 = California Verbal Learning Test 2; FSMC = Fatigue Scale for Motor and Cognitive functions; MDI = Major Depression Inventory; MSIS-29 = Multiple Sclerosis Impact Scale 29; MSNQ = Multiple Sclerosis Neuropsychological Questionnaire; PASAT = Paced Auditory Serial Addition Test; PSS = Cohen's Perceived Stress Scale; SDMT = Symbol Digit Modalities Test; WAIS-IV = Wechsler Adult Intelligence Scale;

Appendix 2. Semi-structured conversational guide for phone call follow-up every 14 days ±3 (performed in Danish)

Patient no.:

Chosen leisure activities:

S.M.A.R.T. Goal:

	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Goal:							

Interview guide

- Introduction and purpose (following up on training and supporting patient in reaching set goals)
- How is the training going? How are you finding the daily training sessions?
- Compare with personal weekly goals (e.g., I can see that your weekly goal was to train 30 minutes per day, how is that going?)
    - **If NOT reaching goal:**
        - Identify barriers (e.g., what is keeping you from attaining your goal?)
        - Identify facilitators (e.g., which factors have helped you in completing the training? Looking ahead, how can we use these factors?
            - If patient experiences difficulties due to fatigue:
                - Identification of factors which increase fatigue
                - Psychoeducation on fatigue (importance of planned rest periods, daily routines, structure and prioritizing daily activities)
            - If patient DISLIKES training activity or goal too ambitious
                - Support in choosing new activity and setting new goal
    - **If reaching goal:**
        - Identify if goal is appropriate or if should be more ambitious.
        - Recognize and encourage continued training effort.

Remind patient to log activities as often as possible.

Thank patient for participation and wish good day.

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