Kessler Foundation Strategy-Based Training to Enhance Memory (KF-STEM™): Study protocol for a single site double-blind randomized, clinical trial in Multiple Sclerosis

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**ABSTRACT**

New learning and memory impairments are common in Multiple Sclerosis (MS) and negatively impact everyday life, including occupational and social functioning. Despite the demand for learning and memory treatments, few cognitive rehabilitation protocols are supported by Class I research evidence, limiting the degree to which effective treatments may be utilized with persons with MS. The present double-blind, placebo controlled randomized clinical trial (RCT) examines the efficacy of an 8-session cognitive rehabilitation protocol encompassing training in the application of three strategies with the strongest empirical evidence (self-generation, spaced learning and retrieval practice) to treat impaired learning and memory in persons with MS, Kessler Foundation Strategy-based Training to Enhance Memory (KF-STEM™).

A sample of 120 participants with clinically definite MS who have impairments in new learning and memory will be enrolled. Outcomes will be assessed via three mechanisms, an Assessment of Global Functioning, which examines everyday functioning and quality of life, a Neuropsychological Evaluation to examine objective cognitive performance, and functional Magnetic Resonance Imaging to examine the impact of treatment on patterns of cerebral activation. We will additionally evaluate the longer-term efficacy of KF-STEM™ on everyday functioning and neuropsychological assessment through a 6-month follow-up evaluation and evaluate the impact of booster sessions in maintaining the treatment effect over time. The methodologically rigorous design of the current study will provide Class I evidence for the KF-STEM™ treatment protocol for persons with MS.

1. Introduction

Multiple sclerosis (MS) is a progressive neurological disease marked by the development of lesions, throughout the brain and spinal cord, impacting white and grey matter [1–3]. A broad array of motor, psychiatric, and cognitive symptoms result [4]. Cognitive deficits are common across multiple aspects of cognition [5,6]. Long term memory is impaired in 40%–65% of patients [7], shown to result in impairment of new learning abilities specifically [8,9] (i.e., poor acquisition of material to be remembered, with intact retrieval).

Cognitive deficits in persons with MS have been shown to exert a substantial impact on everyday life and overall quality of life (QoL) [10], evident in participation in fewer social and vocational activities [11], higher rates of unemployment [12–14], and greater difficulties completing routine household tasks [15,16]. Deficits in new learning and memory in particular have been shown to result in a reduced ability to make decisions that could affect functioning in everyday life [17], negatively impacting daily living [18,19]. Not surprisingly, the effective treatment of memory deficits is accompanied by improvement on objective and subjective tests of everyday functional abilities [20–22]. Cognitive rehabilitation has also been shown to result in improved daily activities and QoL [21].

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1.1. The treatment of cognitive impairments

Cognitive rehabilitation is often used to treat cognitive impairment, with accumulating evidence supporting its efficacy across several domains of functioning in various neurological populations [23–26], including MS [27]. Improvements following cognitive rehabilitation have been noted in objective cognitive performance, everyday life activities [28–30], and brain function [31–34].

The application of learning strategies has been especially effective in the experimental literature. Kessler Foundation Strategy-Based Training to Enhance Memory (KF-STEM™), was developed to teach individuals three learning strategies to use in everyday life. Each of the three components of KF-STEM™ is well-grounded in the literature and has been demonstrated to be an effective means of improving NLM in healthy [35] and patient populations [36–42] (1) Self-generation [37,39,41,43], information that is self-generated is remembered better than information that is didactically provided for later memory [43–45], is a robust phenomenon in both healthy individuals and those with compromised neurological functioning [37–41,46–49]. (2) Spaced learning (SL) [38], the concept that new learning is significantly improved when trials are distributed over time (spaced presentation) compared to consecutive learning trials (massed presentation) [50], enhances learning in adults of different ages, across different memory paradigms and learning situations (for review see Ref. [51]). SL has been successfully applied to individuals with MS and TBI across lab-based and everyday life tasks [38,40]. (3) Retrieval practice (RP) [36,50,51] asserts that testing one’s memory for information results in greater subsequent information retrieval in the future [36] than simply providing information multiple times. The act of retrieving information has a mnemonic function, strengthening memories such that information becomes easier to recall [35,52–54]. RP leads to better memory than restudying information multiple times in adult [55–57] and pediatric [58] memory-impaired samples and the benefits of RP persist over time (i.e., one week) [55,56]. While SL, SG, and RP have been researched in laboratory-based designs for decades, KF-STEM™ is a manualized, interventionist-led protocol that teaches how to use these strategies in daily life situations.

Pilot work on KF-STEM™ in 20 persons with MS randomized to a treatment group or an active control group showed improvement in participant reports of General Contentment and prospective memory in the treatment group compared to the control group [59]. Although not significant, increased ratings of general health were also noted in the treatment group post-treatment on the Health Status Questionnaire [59]. Based on this pilot data, we propose that treatment with KF-STEM™ will result in improvements in memory abilities in everyday life in persons with MS. The current paper presents the methodology of a randomized clinical trial (RCT) testing the efficacy of KF-STEM™ in a large sample of individuals with clinically definite MS and a documented deficit in new learning and memory (NLM).

Our primary aim is to evaluate the impact of treatment with KF-STEM™ on everyday functioning through standardized measures of everyday memory as well as well-validated questionnaires examining multiple aspects of daily life functioning and overall quality of life (QOL) from the perspective of the patient. We will additionally test the efficacy of KF-STEM™ using standardized objective measures of NLM in an MS population via neuropsychological evaluation (NPE). Our third aim is to examine the neural correlates associated with the three strategy-based learning techniques utilized in KF-STEM™, as well as the neural correlates associated with new learning after KF-STEM™ treatment. We will also evaluate the longer-term efficacy of KF-STEM™ on everyday functioning and NPE through a 6-month follow-up evaluation and examine the impact of booster sessions in maintaining the treatment effect over time.

2. Design and methods

2.1. Overview of design

This double-blind, placebo-controlled randomized clinical trial (RCT) compares individuals with MS treated with KF-STEM™ to an active control group (aCTL; Fig. 1).

2.2. Overview of intervention

The KF-STEM™ protocol targets new learning ability, or the ability to acquire novel information for later recall and recognition. It consists of eight 45–60 min in-person sessions designed to teach the concepts of self-generation (SG), spaced learning (SL) and retrieval practice (RP) and their application to everyday life. Session 1 begins with a review of the memory process and the individual’s objective neuropsychological assessment results. Sessions 2–7 focus on the three techniques, with two sessions dedicated to the understanding and application of each. Session 2 focuses on what SG is, how it might work, examples and practice self-generating. Session 3 expands upon the teaching of SG including a review of concepts, the provision of more concrete examples and practice, applications in daily life and a discussion of restructuring one’s environment to use SG. Sessions 4 and 5 focus on SL and sessions 6 and 7 focus on RP, with the same emphasis as the 2 sessions focused on SG. Session 8 focuses on applying the techniques to daily life, reviewing all three techniques, and practicing their application in daily life. All sessions are one-on-one and follow a detailed manual. The KF-STEM™ protocol is an 8-week standardized protocol that is utilized in a standard, non-flexible manner for research purposes to ensure that all participants receive exactly the same treatment. However, clinically KF-STEM™ provides opportunities for clinicians to be flexible in examples and further direction that they may provide for patients.

 Booster Sessions have been shown to effectively maintain gains made during CR in previous studies [60]. Following KF-STEM™ training, participants in the treatment (TX) group only are randomly assigned to a booster session group (BST) or a no contact booster control group (NC-BST). The BST meet with the trainer once per month for a total of five booster sessions, each 1 h in duration. During that time, participants review the three techniques learned during KF-STEM™ training and practice their application to daily life tasks, similar to Session 8 of the treatment protocol. The staff member conducting the booster sessions will be the same individual who conducted the treatment sessions. As before, they will be blind as to pre- and post-treatment assessment results. The NC-BST group will have no contact with study staff consistent with previous studies utilizing the booster session design.

2.3. Overview of active control condition

The active control condition (aCTL) consists of 8 placebo sessions to match the KF-STEM™ group in training duration, frequency, and format. In Session 1, the participant is asked to read sentences and recall a target word. Subsequent sessions involve a word association task (2), learning and remembering names (3), recalling kitchen objects (4), learning recipes (5), managing finances (6) keeping a calendar (7) and reading sentences and recalling a target word (8). All sessions are one-on-one and highly manualized. Previous use of this aCTL condition in an RCT of SG [29] showed that 100% of aCTL participants thought they had completed the TX condition. This is thus a highly effective and active aCTL condition.

2.4. Participants

Participants will consist of 120 individuals with a diagnosis of clinically definite MS in accordance with the most recent diagnostic criteria [61]. Prior to enrollment, all potential participants undergo a 2-part screening: (1) an initial screening via telephone and (2) a detailed,
in-person screening completed only if the participant passes the initial screen (Table 1). Individuals with MS are included in the study if they meet full screening criteria.

2.5. Assessment schedule

Outcomes are assessed via three mechanisms, Neuropsychological Evaluation, functional Magnetic Resonance Imaging and an Assessment of Global Functioning. This combination of outcomes will allow examination of post-treatment changes in objective cognitive performance, brain activation during learning, and cognition in daily life, respectively.

Assessments take place at three time points: baseline, immediate follow-up, and long-term follow-up. The baseline assessment occurs soon after enrollment to document current cognitive performance. The immediate follow-up occurs within two weeks of completion of the treatment period to evaluate treatment effects. The long-term follow-up occurs six months following the completion of treatment to evaluate the maintenance of treatment effect over time and the impact of booster sessions to facilitate the maintenance of a treatment effect.

The assessment of global functioning and the neuropsychological evaluation are completed at all timepoints, administered in counterbalanced order, utilizing alternate forms where available. The influence of practice is evaluated via the aCTL, who completes the same measures. Half of the participants also complete neuroimaging procedures on a different day, following the standard assessments at baseline and immediate follow-up.

Following completion of the long-term follow-up, participants fill out a treatment survey to examine whether they believe they received the real versus placebo intervention, the self-assessed changes in everyday life, and willingness to undergo treatment again, if available.

2.6. Randomization

Participants are randomly assigned to one of two groups (TX or aCTL) following baseline utilizing a computerized random number generator. Group assignment is concealed. The same data collector conducts the treatment sessions for both groups and is blind to test performance. A second data collector administers the pre- and post-evaluations and is blind to group assignment as done in our prior RCT’s [21,62].

2.7. Outcome measures

2.7.1. Neuropsychological assessment measures

Summarized in Table 2, the neuropsychological assessment consist of core tests from the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) [12], including the California Learning Test-II (CVLT-II) [63], the Brief Visuospatial Memory Test—Revised (BVMT-R), and the Symbol Digit Modalities Test (SDMT). These measures are widely used, well-validated neuropsychological tasks that overlap with the Common Data Elements (CDE) Version 2, as recommended by the CDE committee convened by NIH/NINDS [64]. Additional CDEs were added to measure specific constructs of interest [64] (e.g., Delis-Kaplan Executive Function System; D-KEFS).

2.7.2. The assessment of global functioning

The assessment of global functioning has two main components (1)
Table 1
Screening criteria.

| Realm Assessed                  | Limit                                      | Rationale                                      |
|---------------------------------|--------------------------------------------|------------------------------------------------|
| Initial Screening via telephone | Age 18–65                                   | Control for age-related brain changes          |
| Neurological history            | Exclude persons with neuro history other than MS | Ensure sample with cognitive deficits from MS only |
| Most Recent Exacerbation        | Must be free from exacerbations for at least one month prior to testing | Control for major fluctuations in disease course that may confound data |
| Medications                     | Exclude participants on steroids, benzodiazepines | Potential cognitive effects of meds          |
| Detailed In-Person Screening    | Visual Acuity Snellen Eye Exam 20/60 minimum corrected acuity in worst eye |                                               |
|                                 | Language Comprehension/Basic Cognitive Capacity Token Test Low Average performance, minimum; assure understanding of directions/treatment |                                               |
|                                 | Montreal Cognitive Assessment – Blind Minimum total score of 18, with additional allowable missed points for memory items (lowest possible eligible score = 13); note, assessment includes language comprehension |                                               |
| New Learning & Memory Modified Selective Reminding Test (Open Trial-Selective Reminding Test; OT-SRT) | Sensitive to deficits in NLM that accompany MS. |                                               |
|                                 | Interview/review of medical records No treatment with steroids, benzodiazepines, or neuroleptics within past month; Free of exacerbations for 1+ month prior to training; verification of MS status, subtype, duration of disease |                                               |
| Neurological History Interview | No significant neurological history (i.e., stroke, TBI, epilepsy) |                                               |
| Psychiatric & Drug Abuse History Interview | No significant psychiatric (i.e., schizophrenia, bipolar) or drug abuse history |                                               |

Table 2
Neuropsychological assessment.

| Realm Assessed                  | Test                              | Description                                      |
|---------------------------------|-----------------------------------|-------------------------------------------------|
| Intelligence estimate           | WASI-II Wechsler Test of Adult Reading (WTAR) | Short, reliable measure of intelligence; Matrix Reasoning |
|                                 | WAIS-IV Digit Span                | 50-item assessment of irregularly pronounced words, thought to be indicative of premorbid IQ and resistant to cognitive decline |
| Attention/Concentration         | Symbol-Digit Modalities Test      | 3 segments: forward, backward & sequencing, each with 8 number pairs read aloud |
| Processing Speed                | WAIS-IV Letter-Number Sequencing  | Examinee substitutes a number for a figure, with the correct number shown in a key (1–9) |
| Working Memory                  | CVLT-II standard form (BL), alternate form (IF), CVLT-I (LTF) | Numbers and letters read aloud by examiner, participant orders numbers, then letters |
| Verbal New NLM                  | Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) | 16 words from 4 semantic categories presented over 5 trials with 20-min recall & recognition |
| Non-Verbal NLM                  | BVMT-R (6 versions)               | Main DV: total learning score (Trials 1–5) examiner reads a story, with free recall and 20-min delayed recall |
| Executive Control               | D-KEFS selected subtests          | Four alternate stories are now available |

Simulations (EMS) [65], in which the participant completes everyday memory tasks such as remembering medical instructions or object locations, and encourages the individual to utilize memory strategies as needed; this format allows the participant to learn real life information in whichever way he/she chooses, which will allow the participants an opportunity to apply the techniques learned in KF-STEM™ with daily life material and (2) self-report measures assessing the impact of chronic illness and cognitive deficits on daily life (Table 3). The Functional Behavior Profile is additionally administered as an informant report (if applicable) to obtain an external perspective on the participant’s daily functioning.

2.7.3. Neuroimaging

Half of the participants, both those randomized to TX and those randomized to aCTL, undergo an MRI scan of the brain, conducted at the Siemens Skyra 3T scanner at the KF Neuroimaging Center. Forty-three contiguous slices are obtained in an oblique orientation of 30° to the anterior commissure-posterior commissure line in order to reduce signal dropout in the inferior frontal and temporal areas [66,67]. Structural images (1x1x1 mm) are acquired using a standard T1-weighted pulse sequence and are used to localize functional activation. Functional images will be acquired with a standard 20-channel radio-frequency head coil with a T2*-weighted echo planar sequence (voxel size = 3 mm³, TR = 785 s, TE = 37.2 ms) with BOLD contrast. Simultaneous multi-slice technique with multiband factor of 8 will be used to allow us to double the amount of data without increasing the total scan time. Three fMRI tasks are performed in the scanner each at Baseline and Immediate Follow-up. Tasks are all completed in the same order within the same scanning session and include the presentation of words and word pairs.

All words used in the fMRI behavioral paradigms contain 4–8 letters and 1–2 syllables, have Kucera-Francis frequencies of 20–650 words per million, and have high imageability ratings (score of over 400 according to the MRC database) [68]. The words are matched for word length and frequency at the trial level for SG, SL and RP paradigms. Words presented on the same trial are not semantically related, with a score of less than 0.2 on the Latent Semantic Analysis similarity matrix [69], and do not rhyme or begin with the same letter.

1) SG paradigm. Participants perform a modification of a previously published paradigm [70] where paired associates are presented in a multiple-choice format. The paradigm consists of 2 phases: a study phase and a test phase. On each of the 80 trials of the Study Phase, participants are presented with three words: the top word as the target word and two-word options underneath. A total of 80 items are used, divided between 2 conditions (SG condition and read condition): 40 in the SG and 40 in the read conditions. During trials
Table 3
Assessment of global functioning (AGF).

| Domain | Test | Description |
|--------|------|-------------|
| Everyday Cognition (Objective Evaluation) | Ecological Memory Simulations | • Daily life-to-be-learned material including (a) address & phone number, (b) object locations, (c) medical instructions (d) news article, (e) biographical information, (f) routes, and (g) prospective memory tasks. Allowed to use memory strategies to assist performance. |
| Everyday Cognition (Subjective Evaluation) | Memory Functioning Questionnaire | • 64 items each rated on a 7-point scale, which refers to frequency, quality, or seriousness of the memory complaint; completed by participant and other |
| Quality of Life | Multiple Sclerosis Quality of Life Index (MSQLI) | • Compilation of generic and MS-specific measures of quality of life. |
| | The Functional Assessment of MS (FAMS) | • developed for use with MS, adequate reliability and validity |
| | Perceived Deficits Questionnaire | • 20 items; evaluates everyday situations in which cognition may play a role. |
| | The Functional Behavior Profile (Self and Family Form) | • Assesses the overall capacity for an individual to engage in tasks, social interactions and problem solving. |
| | | • 3 factors: task performance, social interaction, problem solving |
| Emotional Symptoms | Chicago Multidimensional Depression Inventory (CMID) | • Self-report depression measure |
| | State Trait Anxiety Inventory (STAI) | • Standardized measure of anxiety with demonstrated reliability and validity |

in the SG condition, words are presented with vowels omitted and replaced with an underline. Complete words are presented during the trials in the read condition. The correct match to the target word is highlighted in green. Participants are asked to press a button when they can identify the match for the target word. During the test phase, participants must select one of the word options as a match for the main word based on what they remember from the Study Phase.

2) **SL/RP paradigm.** To examine neural correlates of SL and RP, 90 verbal paired associates (e.g. Ground-Cold) equally divided across three learning conditions (massed learning (ML), SL, RP) are presented [73]. Each trial within the ML condition is presented for three consecutive trials (no intervening trials). Each trial within the SL or RP conditions is presented in a spaced fashion, with three intervening trials between the first presentation and first restudy (or test) trial, and six intervening trials between the first and second restudy (or test) trials. For RP trials, after the paired associate is presented initially in a complete form, the subsequent presentations will contain only one word of the paired associate for which the participant must retrieve the 2nd word.

3) **Strategy Assessment Paradigm.** To examine neural mechanisms associated with the utilization of strategies to learn new information, participants perform a word learning paradigm [72–74] that includes 2 phases: an acquisition phase and a recognition phase. In the acquisition phase, participants are instructed to learn the 24 words presented, applying techniques practiced during treatment. On each trial, they are presented with a word to encode for 2s, followed by a jittered fixation point (2–5s). These words are combined with 24 lure trials presented during the recognition phase. During each recognition trial, a word is presented for 2s, followed by a jittered fixation point screen (2–5s) during which participants have to press either a left or right button to indicate whether the presented word is old or new, respectively.

2.8. Treatment fidelity

2.8.1. Data collector training

All data collectors complete established, standardized training procedures. These include training by a research manager on neuropsychological assessment and the KF-STEM™ cognitive rehabilitation protocol. A minimum of 10 sessions of shadowing/observation of test administration and/or cognitive rehabilitation training is also required. Following the research manager’s approval to test or treat participants, approval is required by two additional study investigators. The first time a data collector tests a participant, he/she is observed by the research manager or a study investigator. Recommendations are made for any needed improvements or approval is granted for independent testing/treatment.

2.8.2. Fidelity assessment

Data collectors are required to score newly collected data within 2 workdays following data collection. The first 5 participant files are then checked for accuracy by the research manager. If any errors are noted, 5 additional files are checked. If no errors are noted, random checking is then implemented for every 5–6 participant files. Data entry is also monitored regularly. The data collector working on a given protocol is responsible for entering the data he/she collected with 5 workdays. Data entry is randomly checked for accuracy. In addition, the PI runs preliminary statistics after roughly every 20 subjects to aid in the identification of outliers or missing data, which can then be remedied immediately.

2.9. Power and sample size justification

Co-primary outcomes are pre to post changes in everyday memory, the Perceived Deficits Questionnaire (PDQ; self-report) and Ecologic Memory Simulations (EMS; objective performance on daily life tasks). Changes on the Perceived Deficits Questionnaire (PDQ; self-report), was the primary outcome in our pilot work. Based on the post-treatment data from our pilot study, a simulation was conducted with R software [75], assuming the post-treatment PDQ is associated with only the pre-treatment PDQ. Under this assumption, a total sample of 120 (60 TX, 60 aCTL) achieves a power of 100% with the reduction of 1.42 in PDQ (i.e., large effect) at $\alpha < 0.025$, as observed in the pilot study, using the planned analysis of covariance (ANCOVA) method. In the case of unexplained variance (i.e., covariates other than the pre-treatment PDQ) power will fall to approximately 87%. This is consistent with estimated power based on pilot data on our objective memory assessment (EMS), in which a sample of 120 is more than well-powered to detect the anticipated large effect change (1–$\beta = 0.96$) at $\alpha < 0.025$, even when considering additional covariates in the model (1–$\beta = 0.86$). Thus, a total sample of 120 (60 TX, 60 aCTL) will result in adequate power.

2.10. Statistical analysis plan

Descriptive statistics will be calculated for all variables, including
their mean and standard deviation, or median and interquartile range; categorical variables will be summarized as numbers and frequencies. Groups will be tested for significant differences on factors unrelated to the intervention that may influence cognition (e.g., age, education) and these factors will be included as covariates if necessary. Between-group comparisons of neuropsychological assessment and assessment of global functioning data will be performed via ANCOVA. Co-primary outcomes are pre to post changes in everyday memory, the Perceived Deficits Questionnaire (PDQ; self-report) and Ecologic Memory Simulations (EMS; objective performance on daily life tasks). The significance level will be adjusted to account for the inclusion of 2 primary outcomes, designated as < 0.025 and will be one-tailed to address the directional hypotheses. Longitudinal changes will be analyzed using repeated measures analysis of variance (ANOVA). Data will be analyzed according to the intention-to-treat principle, i.e., participants will be included within the group (KF-STEM, aCTL) to which they were assigned. No interim analysis is planned.

All MRI preprocessing and analysis will be performed using FSL software (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). The data will be co-registered to the T1 MPRAGE image for localization of activated areas and standardized to MNI space. To perform a single-subject fixed-effects analysis the regressors of interest from each paradigm will be convolved with a canonical hemodynamic response function. Between group analysis will involve comparisons at baseline and immediate follow-up using mixed effects ANOVA (2 × 2 × 2 analysis with group as between subject factor, time, and condition as within subject factor).

2.11. Ethics

This trial has been approved by the Kessler Foundation IRB. Prior to undergoing the detailed screening, all potential participants sign an IRB approved informed consent form. We have established protocols for managing any adverse events via IRB standard procedures. Participants have the right to withdraw from the study at any time. The trial was registered on clinicaltrials.gov prior to enrollment of the first participant (#NCT03983681).

2.12. Significance

Cognitive deficits in MS often lead to the inability to maintain employment, engage in social activities, participate in the community fully and experience a high QOL. Given the significant relationship between memory functioning, employment status and functional status in individuals with neurological compromise, the treatment of deficits in NLM should serve to significantly improve multiple aspects of the lives of such individuals, including everyday functioning, QOL, and emotional functioning. Therefore, efforts to improve NLM are vital to the overall QOL of individuals with MS. KF-STEM represents a unique clinical intervention developed through the conduct of lab-based research on techniques from cognitive psychology, encompassing the bench to bedside translation necessary to maximize real world benefit from scientific research.

Declaration of competing interest

STEM™ is a registered trademark owned by Kessler Foundation. All authors were Kessler Foundation employees at the time when the study was conducted.

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