An RCT to treat learning impairment in multiple sclerosis

The MEMREHAB trial

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ABSTRACT

Objective: To examine the efficacy of the modified Story Memory Technique (mSMT), a 10-session behavioral intervention teaching context and imagery to facilitate learning, to improve learning and memory abilities in persons with multiple sclerosis (MS).

Methods: This double-blind, placebo-controlled, randomized clinical trial included 86 participants with clinically definite MS, 41 in the treatment group and 45 in the placebo control group. Participants completed a baseline neuropsychological assessment, including questionnaires assessing everyday memory, a repeat assessment immediately posttreatment, and a long-term follow-up assessment 6 months after treatment. After completion of the treatment phase, persons in the treatment group were assigned to a booster session or a non-booster session group to examine the efficacy of monthly booster sessions in facilitating the treatment effect over time.

Results: The treatment group showed a significantly improved learning slope relative to the placebo group posttreatment. Similar results were noted on objective measures of everyday memory, general contentment, and family report of apathy and executive dysfunction. Long-term follow-up data showed that posttreatment improvement in the treatment group continued to be noted on the list learning and self-report measures. The provision of booster sessions demonstrated little benefit.

Conclusion: The mSMT is effective for improving learning and memory in MS.

Classification of evidence: This study provides Class I evidence that the mSMT behavioral intervention improves both objective memory and everyday memory in patients with MS over 5 weeks, with treatment effects lasting over a 6-month period. *Neurology*® 2013;81:2066-2072

GLOSSARY

CI = confidence interval; CVLT = California Verbal Learning Test; FAMS = Functional Assessment of Multiple Sclerosis; FrSBe = Frontal Systems Behavior Scale; MS = multiple sclerosis; mSMT = modified Story Memory Technique; RA = research assistant; RBMT = Rivermead Behavioural Memory Test; RCT = randomized clinical trial; RM-ANOVA = repeated-measures analysis of variance.

Multiple sclerosis (MS) is a progressive disease characterized by widespread lesions in the brain and spinal cord, as well as axonal and gray matter damage. Cognitive impairment is common, affecting social engagement and vocational activities.¹ Present in 40% to 65% of those with MS,² memory deficits represent the most disabling cognitive symptom associated with MS³ and profoundly affect employment⁴ and functional performance.⁵

Cognitive rehabilitation is frequently utilized to treat memory impairment,⁶ with few studies in MS. Despite some promising support,⁷ the most recent Cochrane review⁸ determined that there are limited data supporting the efficacy of memory rehabilitation in MS. The current study was designed to provide Class I evidence on one such treatment protocol. Rigorous studies based on sound methodology are limited, and adequately controlled randomized clinical trials (RCTs) have been called for by experts in the field.⁹

It is well established that memory impairment in MS is primarily attributable to inefficient new learning,² which is the most significant predictor of general functional disability.⁵ Given the prevalence and severity of learning and memory problems in MS because of inefficient

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acquisition, well-designed clinical trials examining effective treatments for improving learning in MS are needed.

We published a pilot, double-blind, placebo-controlled RCT examining the efficacy of the modified Story Memory Technique (mSMT), demonstrating that the imagery- and context-based memory retraining program significantly improved new learning and memory in MS.¹⁰ The current study examined the efficacy of the mSMT in a large MS sample. The primary hypotheses were that 1) subjects with MS who have learning deficits will demonstrate significant improvement on memory tasks after mSMT treatment, and 2) any changes in learning after mSMT treatment will be evident on objective measures of everyday memory. Our secondary hypothesis was that compared with the placebo control group, the treatment group will show improved self-reported functional abilities, and decreased apathy, executive dysfunction, depression, and anxiety. Maintenance of treatment effects was expected 6 months later, particularly in a subset receiving monthly booster sessions.

METHOD Participants. Eighty-eight individuals with clinically definite MS¹¹ were randomized to the treatment ($n = 46$) or placebo control group ($n = 42$). One participant was excluded before data analysis because of traumatic brain injury, and one participant withdrew before immediate follow-up. The final number of participants was 86 (treatment $n = 45$, control $n = 41$). Groups were similar in demographic and disease characteristics, disease-modifying therapy, pretreatment cognition, and emotional symptomatology (table 1).

Inclusion criteria were as follows: 1) new learning impairment (1.5 SD or more $<$ mean of healthy control group on the Open Trial Selective Reminding Test)¹²; 2) age 30–70 years; 3) free of exacerbations and steroid use for ≥ 1 month; 4) no neurologic history other than MS, including evidence of current dementia; 5) no history of major depressive disorder, schizophrenia, or bipolar disorder I or II; 6) no history of diagnosed substance use or dependence disorder; 7) intact vision (e.g., no scotomas); and 8) intact language comprehension.

Power. We expected a 0.13 difference in the California Verbal Learning Test (CVLT) slope between the treatment and placebo groups in our MS sample with moderately impaired new learning, based on our previous research on the mSMT in MS, which demonstrated a 10% increase posttreatment from a baseline CVLT slope of 1.3.¹⁰ With analysis of covariance as the primary method for examining group differences, a hypothesized 0.13 difference in CVLT slope at immediate follow-up and a criterion for significance set at 0.05 for a nondirectional test, 30 subjects per group were needed for a power of 0.80. The target number was increased because of the need to achieve sufficient samples in booster session groups, comprised of one-fourth of the total sample.

Study design. This RCT used a 5-week, double-blind, parallel groups design. Before enrollment, all potential participants were screened for inclusion criteria.

Using a computerized random number generator, a total of 200 participants were randomized to the treatment or placebo control group before beginning data collection. Data collection was discontinued at the end of the funding period, at which point 88 participants were randomized, thus randomization was not balanced at trial completion. Treatment allocation was concealed. The individual responsible for group assignment was not otherwise involved in data collection, and group assignment was verified by a second individual via duplicate copy of the randomization table generated before the initiation of data collection.

After randomization, participants completed baseline testing, consisting of a comprehensive neuropsychological assessment and questionnaires assessing everyday cognition, before treatment. Follow-up assessment was conducted within 1 week of completing treatment using the same procedures. All memory measures utilized alternate forms.

After immediate follow-up, the treatment group was randomized to a monthly booster session or placebo-booster session group to examine the efficacy of booster sessions in facilitating maintenance. All assessment measures were repeated 6 months after treatment for all participants. All memory measures utilized alternate forms.

The same research assistant (RA) conducted baseline, immediate, and long-term follow-up evaluations. All RAs conducting assessments were blinded to group membership. Masking was preserved via the following procedures: 1) the RAs conducting the treatment and assessments were different, and 2) the RAs did not communicate directly about participants. Study participants were also blinded to group assignment. Participants consented to participate in a study examining the impact of memory exercises in which they had a 50/50 chance of being in the treatment group. All participants completed a poststudy questionnaire; 41.4% of participants correctly identified group assignment (less than chance), while 58.6% of participants responded incorrectly. All data were collected in a research center in a quiet testing room with a one-way mirror.

Treatment protocol. The treatment group completed 10 sessions of the mSMT,¹⁰ 2 times per week for 5 weeks, with sessions lasting 45 to 60 minutes. The mSMT trains 2 related skills: imagery and context. Sessions 9 and 10 focused on applying the mSMT to real-world settings. The treatment is highly manualized, and the therapist follows a training manual with scripts. The treatment was administered by an RA who was blinded to assessment results and unaware of the study hypotheses.

The placebo control group met with the therapist at the same frequency as the treatment group, engaging in non–training-specific tasks to control for professional contact and disease alterations. The only difference between the groups was that only the treatment group was exposed to the active ingredients of the mSMT (imagery and context).

The booster session group received monthly sessions applying the mSMT to real-world situations, similar to training sessions 9 and 10. The placebo booster group completed nonbooster sessions in which they read a story and answered questions.

Outcome measures. There were 2 primary outcomes: 1) objective memory (CVLT-II¹³ learning slope), and 2) everyday memory (Rivermead Behavioural Memory Test [RBMT]¹⁴). These were identified before beginning data collection.

Secondary outcome measures included subjective report of overall functioning, behavioral symptoms associated with cognitive changes in neurologic injuries measured via the Functional Assessment of Multiple Sclerosis (FAMS),¹⁵ and significant others' report measured via the Frontal Systems Behavior Scale (FrSBe).¹⁶ Some FrSBe family forms were incomplete because the FrSBe was

Table 1 Sample demographic and disease characteristics

Variable	Treatment group (n = 45)	Control group (n = 41)
Age, y	48.13 (10.17)	49.32 (8.47)
Education, y	15.57 (2.55)	15.61 (2.42)
Sex, % female	76	76
Handedness, % right-handed	82	93
Months since diagnosis	170.87 (120.51)	173.37 (103.44)
Months since most recent exacerbation	32.46 (30.10)	27.64 (29.99)
Disease subtype, no.		
Relapsing-remitting	33	22
Primary progressive	1	4
Secondary progressive	6	11
Progressive relapsing	1	0
Unknown	4	4
Disease-modifying therapy, no.		
Avonex	9	4
Copaxone	13	11
Betaseron	4	5
Rebif	3	2
Tysabri	2	2
Methotrexate	1	1
Unknown	1	4
Ambulation Index score	2.68 (2.43)	3.13 (2.28)
Baseline CVLT slope	1.35 (0.53)	1.27 (0.58)
Baseline RBMT Story Memory	1.69 (0.60)	1.51 (0.71)

Abbreviations: CVLT = California Verbal Learning Test; RBMT = Rivermead Behavioural Memory Test.

Data are mean (SD) unless otherwise indicated. All comparisons nonsignificant.

sometimes taken home by participants and returned by mail. Not all forms were returned. Secondary outcome variables to examine changes in emotional functioning were the State Trait Anxiety Inventory¹⁷ and the Chicago Multiscale Depression Inventory.¹⁸

To characterize cognitive functioning, neuropsychological tests were administered assessing intelligence (Wechsler Abbreviated Scale of Intelligence),¹⁹ attention (Digit Span),²⁰ working memory (Letter Number Sequencing²⁰; Paced Auditory Serial Addition Test²¹), processing speed (Symbol Digit Modalities Test²²), executive functioning (Delis-Kaplan Executive Function System,²³ Trail Making, Color-Word, Tower, Fluency), and episodic memory (CVLT^{13,24}). All participants demonstrated impaired performance on the Open Trial Selective Reminding Test to ensure the need for memory rehabilitation. Many participants also demonstrated deficits in other cognitive domains such as working memory or processing speed, which frequently occur in MS.²

Statistical analyses. Statistical analyses were conducted on data of participants who had complete baseline to posttreatment information (treatment n = 41; control n = 45). Data were analyzed via analysis of covariance, with baseline performance as the covariate. All analyses utilized 1-tailed tests because our hypotheses were unidirectional; we hypothesized that the treatment group would improve on all measures as compared with the placebo control group. To examine the percentages of participants that benefited from treatment, a χ^2 was conducted. Long-term treatment effects were

analyzed via repeated-measures analysis of variance (RM-ANOVA). Analyses were performed with SPSS version 18 (SPSS Inc., Chicago, IL). No interim analyses were performed.

Standard protocol approvals, registrations, and patient consents. An institutional review board approved all study procedures. All participants provided written informed consent. The clinical trial is registered with clinicaltrials.gov (protocol ID: NCT00166283).

RESULTS The recruitment period was from December 1, 2004 to January 23, 2012. One person from the placebo control group did not complete the immediate follow-up, but did complete treatment. From immediate to long-term follow-up, attrition fell at 10%. Reasons for withdrawal included MS exacerbations (n = 1) and participant relocation. Analysis was based on intent-to-treat population. See figure 1 for a participant flow diagram. Neuropsychological performance of the 2 groups at each assessment can be found in tables e-1, e-2, and e-3 on the *Neurology*[®] Web site at www.neurology.org.

Treatment efficacy. Neuropsychological performance. The CVLT slope demonstrated a curvilinear relationship over 5 trials, consistent with the literature.^{25,26} Learning efficiency is not best captured by the final learning phase (trials 4 and 5), where the curve tends toward an asymptote. Rather, learning efficiency is related primarily to the slope of trials 1 to 4.²⁷ We therefore computed the slope from trials 1 to 4 as our primary outcome (CVLT slope T1–4).

After controlling for variance in the CVLT slope T1–4 at baseline, the treatment group demonstrated a greater learning slope at immediate follow-up (95% confidence interval [CI] 1.67–2.10) compared with the placebo control group (95% CI 1.26–1.72; $F_{1,83} = 6.145$, $p = 0.0075$; figure 2, table e-4), demonstrating a medium effect size (Cohen $d = 0.54$). The groups did not differ at baseline ($t_{84} = 0.48$, not significant); the treatment group performed better than the control group at immediate follow-up ($t_{84} = 2.52$, $p = 0.007$).

With benefit defined as a 10% or greater improvement on the CVLT slope T1–4 from baseline to immediate follow-up, consistent with studies of pharmacologic agents for cognition in MS,²⁸ 62% of patients in the treatment group showed improvement on their CVLT slope T1–4 from baseline to immediate follow-up, as compared with only 37% of the control group: $\chi^2 (1) = 5.64$, $p = 0.009$. The increase in performance in the control group is likely attributable to practice effects.

Objective everyday memory. After controlling for baseline RBMT performance, there was a difference between the treatment (95% CI 1.382–1.763) and placebo control (95% CI 1.050–1.450) groups on the RBMT Story Memory at the immediate follow-up ($F_{1,83} = 5.35$, $p < 0.0115$; table e-5), representing a small effect (Cohen

Figure 1 Participant flow diagram

mSMT = modified Story Memory Technique; OT-SRT = Open-Trial Selective Reminding Test; TBI = traumatic brain injury.

$d = 0.372$). There was no difference between the groups at baseline.

Paired t tests examining intragroup differences from baseline to immediate follow-up demonstrated a decrement in performance from baseline to follow-up in the placebo control group ($t_{40} = 2.58, p < 0.006$) not seen in the treatment group ($t_{44} = 0.73$, not significant).

Subjective everyday cognition and emotional functioning. After controlling for baseline (figure 3), the treatment group reported greater general contentment on the FAMS posttreatment (95% CI 16.400–23.361) as compared with the placebo control group (95% CI

11.953–18.914; $F_{1,67} = 3.17, p < 0.05$, 1-tailed), demonstrating a medium effect size (Cohen $d = 0.568$). Importantly, there was no significant difference between the groups at baseline (table e-1).

On the FrSBe, informants reported an improvement in apathy from before to after treatment in the treatment group (95% CI 30.559–37.729), but not in the control group (95% CI 27.013–33.237; $F_{1,29} = 2.86, p < 0.05$, 1-tailed, Cohen $d = 0.51$). Informant reports also indicated improvement in executive dysfunction posttreatment in the treatment group (95% CI 38.319–46.165), with no difference in the control

Figure 2 California Verbal Learning Test (CVLT) learning slope across the 5 learning trials of the CVLT immediately posttreatment, by treatment group ($p < 0.05$)

group (95% CI 334.690–41.528; $F_{1,29} = 2.59$, $p = 0.06$, 1-tailed, Cohen $d = 0.46$). Groups were similar at baseline. No significant differences were noted from pre- to posttreatment between the groups on the patient report forms.

There were no significant differences noted between the groups in level of awareness, depression, or anxiety from before to after treatment.

Long-term effects. To examine the long-term maintenance of the treatment effect, we conducted a 2 (group: treatment [$n = 38$] vs control [$n = 35$]) $\times$ 2 (follow-up interval: immediate vs 6 months) RM-ANOVA on each outcome.

The RM-ANOVA of the CVLT slope T1–4 showed a main effect of follow-up, such that all participants showed a decline in performance from the immediate to the 6-month follow-up ($F_{1,71} = 12.54$, $p < 0.001$; 95% CIs for treatment ($n = 38$) and control ($n = 35$)

groups: 1.579–1.940 and 1.193–1.582, respectively). The treatment effect was maintained over the 6-month follow-up period as demonstrated by no other main effects or interactions.

There were no significant main effects on the RBMT Story Memory, nor was the interaction significant.

The RM-ANOVA for the FAMS general contentment demonstrated a main effect of group ($F_{1,58} = 5.58$, $p < 0.05$) such that the treatment group ($n = 36$) reported higher general contentment in daily life (95% CI 15.990–20.462) than did the control group ($n = 29$) (95% CI 12.119–16.743) across both follow-up periods. This indicates that the treatment effect on general contentment observed at the immediate follow-up was maintained over the 6-month follow-up period.

An RM-ANOVA for the Awareness Questionnaire showed no significant main effects or interactions over the 3 assessments. The 6-month follow-up data for the FrSBe could not be analyzed because of the small number of participants who returned the FrSBe informant form.

Efficacy of booster sessions. To examine the ability of the monthly booster sessions to improve maintenance of the treatment effect over time, we conducted a 2 (treatment group: booster [$n = 18$] vs nonbooster [$n = 20$]) $\times$ 2 (follow-up: immediate vs 6 months) RM-ANOVA on each outcome variable.

The interaction between group and follow-up interval was not significant on the CVLT slope T1–4 or RBMT story, indicating that the impact of booster sessions was not significant. A similar pattern of results was noted on the FAMS. This analysis was not performed on the FrSBe because of the small sample size. No adverse or unintended effects of the treatment were noted in any participants.

Figure 3 Baseline and immediate follow-up Functional Assessment of Multiple Sclerosis general contentment scores for the treatment and control groups ($p < 0.05$)

DISCUSSION This study is the first to provide Class I evidence supporting the efficacy the mSMT in MS. Impaired memory in MS is a result of impaired initial learning.^{29,30} Thus, interventions must focus on improving learning in these individuals. The techniques used in the present study, context and imagery, have a long history showing that increasing the strength of encoding results in improved retention.^{31–37} In the present study, the treatment group showed significant improvements in learning compared with the placebo control group, confirming the pilot study, which found that the mSMT improved learning and memory in an independent sample of participants with MS.¹⁰ Taken together, these data provide strong evidence that a behavioral intervention, targeted to specifically strengthen the acquisition of information during learning, can significantly improve memory performance, which is maintained 6 months later.

In a subset of these participants, we demonstrated that the mSMT also exerted a positive influence on patterns of cerebral activation during a new learning task.³⁸ We conducted fMRI before and after treatment with the mSMT. After treatment, greater activation was evident in the treatment group within a widespread cortical network involving frontal, parietal, precuneus, and parahippocampal regions. No changes were noted in the control group. The observed increased activation likely reflects increased use of strategies taught during the mSMT and applied when learning new information. Together with the behavioral findings of the current study, training in context and imagery using the mSMT significantly improves memory performance and increases functional brain activity. Collectively, these data provide strong support for the mSMT as an effective intervention for learning and memory in MS.

Importantly, treatment with the mSMT significantly affected everyday functioning in only the treatment group, according to participants (FAMS) and informants (FrSBe). These findings indicate that the improvements in cognition resulting from treatment with the mSMT are associated with improvement in everyday functional activity, noted via subjective report and by significant others. On an objective test of everyday memory (RBMT), the control group showed a decline from pre- to posttreatment, while the treatment group did not.

It is notable that booster sessions did not aid in maintenance of the treatment effect over time in the current study. This is in contrast to previous work in normal aging that showed that booster sessions can help maintain a treatment effect over time.³⁹ There are several potential explanations for this discrepancy. First, the sample size for the booster session comparison in the current study was significantly less than the primary analyses, which could have affected our power. Second, the frequency of the booster sessions (monthly) was possibly inadequate. Perhaps a titrated decline in treatment frequency would be more effective. Finally, the content of the booster sessions was focused on generalization of the techniques to daily life. A more effective booster session might focus on the actual skills taught in treatment, with refreshers provided on the context and imagery itself. The one previous study to our knowledge that applied booster session methodology utilized booster session dosing similar to the current study.³⁹ The content of these sessions was unclear from the report. However, the treatment was focused on processing speed deficits, not teaching skills per se, but rather facilitating intense practice. The ideal content and frequency of booster sessions are important topics for future investigations.

The current study has some methodologic limitations. While the study was designed to examine the impact of treatment on everyday life, it relied primarily

on self-report and only to a limited extent on objective ecologically valid daily life tasks (i.e., RBMT). Future studies should focus more on actual everyday life activities⁴⁰ or utilize virtual reality to simulate everyday life. Additionally, the sample size for the booster session comparison was small. However, generalizability of findings to the population of persons with MS is excellent. Only inclusion criteria that were absolutely necessary to avoid confounds were applied, and the sample collected was very similar to the population of persons with MS.

The results provide Class I evidence supporting the efficacy of the mSMT to improve learning and memory in persons with MS with impaired learning. A treatment effect was documented on both standardized tests of memory and self and informant reports of everyday cognition. Future research should examine the optimal methodology for maintaining the treatment effect over time and the development of new treatment protocols that can be similarly successful in persons with MS.

AUTHOR CONTRIBUTIONS

Dr. Chiaravalloti developed the study protocol and oversaw the study execution. She led the data analysis, data interpretation, and manuscript preparation. Ms. Moore oversaw the day-to-day data collection for the entire study. She trained and supervised the research assistants. She supervised data entry and assured data accuracy and integrity. She assisted with data analysis and manuscript editing. Dr. Nikelshpur drafted the original introduction to the manuscript. She assisted with data analyses and interpretation, as well as manuscript preparation. Dr. DeLuca assisted heavily with study design and implementation. He assisted significantly with data analysis, interpretation, and manuscript preparation.

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DISCLOSURE

N. Chiaravalloti has served in the past as a consultant for Memen Pharmaceuticals. N. Moore and O. Nikelshpur report no disclosures. J. DeLuca has served as a consultant for Biogen and Memen Pharmaceuticals. Go to Neurology.org for full disclosures.

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