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A Pilot Study of Changes in Functional Brain Activity during a Working Memory Task after mSMT Treatment: the MEMREHAB Trial

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Abstract

Background—Working memory deficits are common in multiple sclerosis (MS). The modified Story Memory Technique (mSMT) has been shown to improve new learning and memory in MS, but its effects on working memory (WM) are currently unknown.

Objective—The present study presents a secondary analysis of data from a larger double-blind, placebo-controlled, randomized clinical trial and examines changes in cerebral activation on a WM task following mSMT treatment.

Methods—Sixteen participants with clinically definite MS were randomly assigned to treatment (n = 7) or placebo-control groups (n = 9) matched for gender, age and education. Baseline and immediate follow-up functional Magnetic Resonance Imaging (fMRI) was obtained for all subjects. During fMRI participants completed an N-back task, consisting of 0-, 1- and 2-back conditions.

Results—Significant increases in cerebral activation were noted in the dorsolateral prefrontal cortex, supplementary motor area and inferior parietal lobule at follow-up in the treatment group. No significant changes were noted in the placebo control group.

Conclusion—Due to the small sample size, results of the current study should be interpreted as preliminary. However, the observed pattern of activation of the frontoparietal network involved in

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WM found in the treatment group, suggests that mSMT training increases recruitment of attention- and WM-related neural networks. We conclude that mSMT treatment leads to changes in WM-related cerebral activation.

Keywords

mSMT; cognitive rehabilitation; working memory; fMRI; Multiple Sclerosis

1. Introduction

Multiple Sclerosis (MS) is an inflammatory, neurodegenerative disease of the central nervous system (CNS) marked by widespread white matter lesions and cortical atrophy¹. Cognitive deficits occur in 40-60% of persons diagnosed with MS². Cognitive deficits have been associated with significant negative consequences, with persons presenting with cognitive deficits experiencing a reduced quality of life, higher unemployment and less participation in social activities than cognitively preserved patients³. Thus, efforts to identify effective treatment for the cognitive impairments common in MS are needed.

The term working memory (WM) refers to the cognitive process by which information is temporarily maintained and manipulated in the brain. While processing speed has been shown to be the primary deficit in MS^{4,7}, a percentage of individuals with MS do show WM impairment⁷, with several studies showing beneficial effect of WM training programs (e.g.⁸⁻¹⁰). Further, patterns of cerebral activation underlying working memory have been shown to be altered in MS^{11,12,13,14}. Although WM tasks also activate frontoparietal regions in persons with MS, altered patterns of activation have been observed compared to healthy individuals¹⁵⁻¹⁹. In particular, a recent meta-analysis of fMRI studies on attention and WM in MS and healthy controls found that MS patients display higher neuronal activation in the left ventrolateral prefrontal cortex and the right premotor area as compared with healthy individuals²⁰.

Given the significant impact of cognitive deficits on multiple aspects of the lives of persons with MS²¹, the identification of effective treatment for these deficits is crucial.

Evidence attesting to the efficacy of many cognitive rehabilitation methods in persons with MS is building^{9,10,22}. The modified Story Memory Technique (mSMT) is a well-validated cognitive rehabilitation protocol designed to ameliorate deficits in new learning and memory abilities²³⁻²⁷. Through a 10-session standardized treatment protocol, the mSMT trains persons to use visualization and context to learn new information. We previously demonstrated that MS patients who completed treatment with the mSMT show significant improvement on neuropsychological tests of new learning and memory abilities and report improved functioning in everyday life post-treatment when compared to a placebo-control group^{23,25}. Additional work from our group demonstrated that mSMT training in MS patients results in increased cerebral activation in frontal, parietal and hippocampal regions²⁴ and that this activation pattern is maintained six months post-treatment²⁷. In addition, mSMT training leads to increased functional connectivity within memory networks as compared to placebo-controls²⁶. Therefore, the mSMT leads not only to improvements in learning and memory performance, but also to observable changes in brain activity.

Determining other cognitive domains that benefit from the mSMT can maximize the applicability and utility of this memory retraining technique. In the current study, we examined the effect of the mSMT on WM and associated brain activity, motivated by several factors. First, several fMRI studies showed considerable overlap between long-term memory and WM structures. For example, overlapping activation patterns have been observed during WM and episodic memory task performance, specifically in the prefrontal cortex^{28,31}, with the dorsolateral prefrontal cortex (DLPFC) activated during both WM and encoding tasks^{29,31}. Furthermore, it has been suggested that processes related to verbal encoding (a domain trained by the mSMT) and WM are interdependent³².

Further, both mental imagery, a crucial component of the mSMT training program, and WM consist of internal representations that can be attended to and both are mental capacities used to hold information online when the sensory information is no longer available. Indeed, a positive correlation between mental imagery and WM has been shown^{33,34}. Moreover, both functions partially share a neural network, as frontoparietal activation has been observed during both WM and mental imagery^{35,37}. Thus, mSMT training and WM appear to demonstrate a relationship at a neurofunctional level.

To achieve our goal, we examined functional brain activity of the treatment and control groups during WM task performance at baseline and immediately following mSMT treatment. Based on the literature, we expected that participants would show activation in frontal and parietal regions during WM task performance at baseline^{20,38,41}. In addition, as has been shown in earlier work²⁴, we expected to see a significant increase in cerebral activation in these areas at follow-up relative to baseline in the treatment group *only* due to the effect of the mSMT intervention. The current study was conducted as part of a larger randomized clinical trial (The MEMREHAB trial) in which the efficacy of the mSMT to improve learning and memory was investigated²⁵.

2. Methods

2.1 Participants

A total of 21 right-handed participants with clinically definite MS⁴² were enrolled in the study and completed baseline neuropsychological and fMRI evaluations. However, N-back data were not recorded consistently in 5 participants who were thus excluded from the current analyses. Sixteen participants were randomly assigned to the treatment (n = 7) or placebo-control group (n = 9, Figure 1). There were no significant differences between the groups in age ($t(14) = .17$, ns), education ($t(14) = .15$, ns), disease duration ($t(12) = .88$, ns), ambulation index ($t(13) = -1.14$, ns) or gender ($X^2(1) = .762$, ns; Table 1).

To qualify for study participation, potential participants were required to demonstrate a deficit in new learning ability, defined as a performance of at least 1.5 standard deviations below the mean of normative data on the Open-Trial Selective Reminding Test⁴³, in the presence of intact language comprehension. Participants were excluded if they reported a history of any neurological illness or injury, other than MS, alcohol or drug abuse (past or present), diagnosed learning disability, and major psychiatric disorder (e.g. bipolar disorder, schizophrenia or having been previously hospitalized for psychiatric reasons). Participants

with MS were at least 4 weeks post their most recent exacerbation and at least 4 weeks post use of corticosteroids. Participants were also required to complete standard imaging screening measures ensuring no presence of metal in the body (e.g. cochlear implants, pacemakers). Participants were recruited from the Kessler Foundation participant recruitment database, referrals from local MS clinics and from the community. Before beginning the study, participants signed an informed consent form approved by the Institutional Review Boards of Kessler Foundation and Rutgers, New Jersey Medical School (formerly UMDNJ).

2.2 Treatment Protocol

Participant randomization was achieved via a computerized random number generator. Researchers were blinded to group assignment (see²⁵ for blinding procedures). All participants engaged in 10 training sessions during a period of 5 weeks (2 sessions per week). The *treatment group* completed the mSMT, which trains imagery and context to facilitate learning. Sessions 1-4 focus on the application of visualization and sessions 5-8 train the participant to apply context to new information to facilitate learning. The final two sessions have been developed to facilitate transfer of the acquired memory skills to daily life. The *placebo-control group* received an equal number of sessions of similar duration, but did not learn imagery and context techniques. Instead, the placebo-control group saw the same stories the treatment group did and answered questions about these stories.

2.3 fMRI Paradigm

Participants requiring glasses in order to see the fMRI stimuli were provided with MRI-compatible glasses during the scan.

The N-back task was completed twice during scanning procedures: at baseline and immediately after completion of the treatment protocol. In the current N-back task, consecutive letters are visually presented to the participant every two seconds. The participant has to respond when the presented letter is identical to the one shown n letters previously. During the 0-back condition, which was used as a control condition for the 1-back and the 2-back conditions, participants were required to determine whether the presented letter was similar to a pre-specified letter ('K'). During the 1-back and 2-back conditions, participants had to identify letters similar to the ones presented 1 and 2 trials before, respectively. The N-back task was presented in a blocked design and consisted of three conditions (0-back, 1-back and 2-back). Each condition was conducted in a single run, and these runs were counterbalanced across subjects. Within each of these runs, there were 3 blocks of tasks (0-, 1-, 2- back), each of which was preceded by and followed by a block of rest. The blocks lasted 32 seconds (both the task blocks and the rest blocks).

2.4 Neuroimaging procedures

A 3-Tesla Siemens Allegra scanner was used to acquire all fMRI data. Behavioral data acquisition, randomization and stimulus presentation was administered using the "E-Prime" software⁴⁴. A T2*-weighted single-shot echo-planar imaging pulse sequence was used to collect functional images in 32 contiguous slices during three runs, with 115 acquisitions per run (echo time = 30 ms; repetition time = 2000 ms; field of view = 22 cm; flip angle = 80°;

slice thickness = 4 mm, matrix = 64×64, in-plane resolution = 3.438 mm²). A high-resolution magnetization prepared rapid gradient echo (MPRAGE) image was also acquired (TE = 4.38 ms; TR=2000 ms, FOV = 220 mm; flip angle = 8°; slice thickness = 1 mm, NEX = 1, matrix = 256×256, in-plane resolution = 0.859×0.859 mm), and was used to normalize the functional data into standard space.

2.5 Data analyses

2.5.1 Behavioral data analysis—Independent-samples t-tests and Chi-Square tests were used to compare baseline sample characteristics between groups. Behavioral data, consisting of the accuracy and reaction time (RT) on the N-back task, were analyzed with 3-way mixed ANOVAs in which task (0-, 1-, and 2-back) and time (pre- vs. post-intervention) were entered as within-subject variables and group (treatment vs. control) as between-subject factor. Because of the small sample size, normality tests were performed (Kolmogorov-Smirnov and Shapiro-Wilk tests) and non-parametric tests (Mann-Whitney and Wilcoxon signed-rank tests) were performed in the presence of non-normally distributed results.

2.5.2 fMRI data analysis—For each time series, the first five images were discarded to ensure steady-state magnetization. All images were preprocessed using AFNI⁴⁵. Each time series of images was realigned to the first remaining image of the first series. The images were smoothed using an 8-mm³ Gaussian smoothing kernel, and scaled to the mean intensity.

After preprocessing, the data was deconvolved with a boxcar function. Motion parameters were included as regressors of no interest. Group analysis was performed using mixed-effects ANOVA with group as a between subject variable and time and task as within subject variables. A region of interest (ROI) analysis was performed on the fMRI data. Our previous work investigated the effect of mSMT treatment on learning and memory in MS²⁴.

A cluster size of 25 contiguous voxels was adopted in that study leading to identification of the following areas of activation in the treatment group after mSMT treatment: frontal, parietal, temporal, precuneus and parahippocampal regions. This was not observed in the control group. The same threshold (of 25 contiguous voxels) was applied in the current study to identify clusters of activation. Therefore, cluster size was set at 25 voxels to correct the resultant statistical parametric maps to an alpha level of $p < 0.05$.

3. Results

3.1 Behavioral results

Mixed effects ANOVA revealed a significant effect of task on accuracy ($F(2, 24) = 84.95$, $p < .001$). Wilcoxon signed-rank tests revealed that, as expected, participants performed more accurately on the 0-back than on both the 1-back ($z = -3.41$, $p < .01$) and 2-back conditions ($z = 3.11$, $p < .01$). In addition, participants showed higher accuracy on the 2-back than on the 1-back ($z = 3.41$, $p < .01$). The time × group interaction was not significant. That is, there were no differences in performance accuracy between the treatment and placebo-control groups over time (Table 2).

A significant time $\times$ group interaction ($F(1, 11) = 5.07, p < .05$) was noted on reaction time (RT). The placebo-control group showed a significant decrease from baseline to immediate follow-up during the 2-back ($t(6) = 2.62, p < .05$), while the treatment group showed no change. During the 1-back, the treatment group showed a significant increase in RT at follow-up as compared to baseline, whereas no difference was found in the placebo-control group ($t(5) = -3.13, p < .05$, Table 2). However, there were no group differences in RT at baseline or at follow-up. Finally, we noted an increase in RT across tasks, irrespective of group. A significant increase in RT was noted from both the 0-back to 2-back ($t(14) = -4.42, p = .001$) and from 1-back to 2-back ($t(14) = -4.36, p = .001$).

3.2 fMRI results

Random-effects ANOVA revealed eight regions showing a three-way interaction (Table 3). The interaction effect was specifically driven by differences in activation of the inferior parietal lobule (IPL), dorsolateral prefrontal cortex (DLPFC), and supplementary motor area (SMA; Figure 2). Activation patterns within each of these regions were entered into ANOVAs for each task separately with time as within-subject variable and group as between-subject variable.

On the 0-back task, there were no significant main effects or interactions. The 1-back task, however, showed a significant group $\times$ time interaction ($F(1, 14) = 6.62, p < .05$).

A Wilcoxon signed-rank test revealed increased IPL activity at immediate follow-up in the treatment group ($z = 2.03, p < .05$), but not in the control group. Despite a baseline difference between the groups ($t(9.10) = 2.26, p = .05$), the SMA in the treatment group also showed significantly greater activation at follow-up compared to baseline ($t(6) = -3.42, p < .05$, Figure 3a and 3d), while there was no change in SMA activity in the placebo-control group.

On the 2-back, two-tailed paired sample t-tests revealed increased IPL and DLPFC activation at immediate follow up in the treatment group only ($t(6) = -2.61, p < .05$; $t(6) = -2.69, p < .05$, respectively). No significant differences in activation patterns were noted in the placebo-control group from baseline to follow-up (Figure 3b and 3c).

4. Discussion

The goal of the current study was to examine changes in functional brain activity associated with WM performance after mSMT treatment. As expected, we observed increased activation of the frontoparietal network usually involved in WM in the treatment group after mSMT training. Therefore, the mSMT appears to impact the cerebral processes underlying WM performance in persons with MS. We observed significant differences in the pattern of BOLD activity during the N-back task from before to after treatment with the mSMT. A frontoparietal activation pattern has been observed in previous WM studies^{40,41,46,48}, consisting of premotor, cingulate, lateral prefrontal and posterior parietal areas. Consistent with previous findings, we observed activation in the frontoparietal network in both groups. Importantly, only the mSMT treatment group showed increased activation within that network following the treatment period. Specifically, we observed increased activation in the

IPL, DLPFC and SMA in the treatment group at immediate follow-up, but not in the placebo-control group. We found increased IPL activity during both the 1- and 2-back tasks, while the SMA showed increased activity only in the 1-back and the DLPFC only in the 2-back task. These findings suggest that, although the mSMT seems to be most effective at improving new learning and memory^{24,27}, the effects on patterns of cerebral activation also generalize to WM.

The involvement of the IPL (BA 40) in WM tasks has been demonstrated in numerous studies^{40,49,51}. During WM tasks, the IPL is thought to be responsible for focusing attention on behaviorally relevant stimuli^{52,55}. The DLPFC (BA 9/46) has been demonstrated to be connected to the IPL⁵⁵ and to be involved in the active maintenance of information during delays^{56,58}. Therefore, both the IPL and DLPFC are regions crucial for N-back execution⁴¹. Since WM and attention are intimately related^{59,60} and all stimuli are behaviorally relevant in the N-back task, it is expected that IPL and DLPFC activity would be observed during N-back task performance. Greater activation of the IPL and DLPFC in the treatment group following treatment thus suggests that the mSMT increases recruitment of attention- and WM-related neural networks. While Figure 3c suggests that there may be a baseline difference in DLPFC, it is important to note that this difference did not reach significance. It is thus likely that the significant interaction observed post-treatment resulted from a difference in slopes. Specifically, only the treatment group showed significantly increased DLPFC activation from baseline to immediate follow-up treatment; the control group did not.

Kollndorfer and colleagues²⁰ showed that healthy controls and persons with MS demonstrate differences in patterns of cerebral activation when WM is engaged. The authors conducted an Activation Likelihood Estimation (ALE) meta-analysis on neuroimaging studies investigating attention and/or WM in MS and healthy controls. In healthy controls, higher likelihood of activation was found in the IPL, DLPFC and right ventrolateral prefrontal cortex. The activation pattern observed in MS patients that underwent mSMT treatment in the current study thus resembles that of healthy controls reported by Kollndorfer and colleagues²⁰.

Our finding that only participants in the treatment group displayed increased IPL and DLPFC activity in the present study, suggests that the mSMT training has the potential to restore the patterns of cerebral activation during the N-back task.

Finally, higher BOLD activity in the SMA (BA 6) was observed during the 1-back task. The primary role of the SMA is movement generation and SMA activity has been found in movements in which the motion suddenly must be withheld or its direction must be changed^{61,63}. Wendelken, Bunge and Carter⁶⁴ observe a network of IPL, DLPFC and SMA activity during WM tasks, proposing that this network is recruited when stimuli require organization according to a specific structure. This may indicate that participants who underwent mSMT treatment improved at organizing the stimuli during the N-back task. This interpretation is particularly promising when considering that sessions 5-8 of the mSMT train the participants specifically to organize information in a meaningful manner.

The mental imagery component of the mSMT may also have contributed to the patterns of cerebral activation observed in the treatment group following treatment. WM and imagery both consist of internal representations that can be attended to and remembered and have been demonstrated to be positively correlated^{34, 33}. Moreover, both functions partially share a neural network, as frontoparietal activation has been observed during both WM and mental imagery^{35, 37, 65}. Therefore, the mSMT may have led to an increased use of imagery during the N-back task performance and hence to more frontoparietal activation.

Limitations

There are some methodological limitations to this study that must be considered when interpreting the results. First, the sample size was small, resulting in limited power. Consequently, only large effect sizes could be identified which may explain why no group differences were detected in functional activation patterns. For example, the DLPFC activation at baseline during the 2-back task showed a marginally significant result ($p=.069$). Replication of the findings with a larger sample size and more comparable groups (e.g. for MS type) in future studies might reveal group differences that we were unable to detect in the present study. Second, behavioral results showed no significant improvements in accuracy or RT on the N-back task from before to after treatment with the mSMT. Moreover, a decrease in RT latency was observed in the placebo-control group, while an increase in RT latency was observed in the treatment group. While this might seem contradictory, the observed increase in RT of within the treatment group and a decrease in the control group might be due to variability that is present in the data due to the small sample size. It is also important to emphasize that we did not observe group differences, either at baseline or at follow-up. A replication of the findings with a larger sample size and more comparable groups is highly warranted.

Further, although it is difficult to interpret a null result, the mSMT does not specifically treat WM deficits, which might explain why no behavioral improvements were found. In addition, it is important to note that the current paper represents a secondary data analysis of a RCT designed to assess learning and memory outcome following treatment with the mSMT. Thus, participants were not required to demonstrate a pre-treatment impairment in WM abilities. These factors may have precluded our ability to document a behavioral effect of the treatment on WM functions that might be evident with longer treatment duration and a sample of WM impaired patients. It may be that the effect of mSMT on WM is simply too subtle to be observed at the level of behavioral performance, but strong enough to be seen on fMRI. This is a phenomenon that has been described in the fMRI literature⁶⁶ and therefore the fMRI results necessitate further investigation. Specifically, future research should compare WM-related cerebral activation patterns of people with MS who underwent mSMT treatment to those of healthy controls. By doing so, it can be determined to what extent the mSMT restores the patterns of cerebral activation to the levels observed in healthy controls.

Despite the study limitations, the observed changes in cerebral activation patterns in the treatment group suggest that there is some effect of mSMT treatment on WM-related neural networks. This may imply that the mSMT can be adapted to target WM deficits in the future. For example, Penner, Kobel & Opwis⁶⁷ developed a training tool that improves aspects of

WM, such as spatial orientation⁹. Participants are required to remember directions and navigate through a map of a virtual city. The final sessions of the mSMT also include remembering directions to a destination. Analogous to Penner and colleagues⁶⁷, the mSMT might be employed to train WM abilities with some adaptations.

Conclusion

In conclusion, regardless of the absence of WM performance improvements in the current study, mSMT treatment resulted in greater recruitment of the frontoparietal network during a WM task. The regions that showed increased activation in the treatment group are similar to those previously reported to be active in healthy controls²⁰ and might indicate an improvement in information structuring within the frontoparietal regions⁶⁴. Thus, the mSMT treatment protocol may be moving toward the restoration of neural activation patterns during a WM task in persons with MS.

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Highlights

- Working memory and brain activity after memory retraining (mSMT) was examined in MS
- No behavioral improvement in working memory was observed as a result of the mSMT
- Increased brain activation was observed in the treatment group after mSMT training
- No significant changes were noted in the placebo control group
- The mSMT may increase the recruitment of frontoparietal regions during WM tasks

Figure 1.

Participant Flow Diagram including the number of participants initially enrolled, how many were excluded and how many completed the trial.

Figure 2.
Activation patterns in the IPL (l), DLPFC (m) and SMA (r) showing an interaction effect of task, group and time.

Figure 3. Mean parameter estimates in the a) IPL 1-back, b) IPL 2-back, c) DLPFC 2-back and d) SMA 1-back. * Significant difference between baseline and follow-up in the treatment group. # Significant difference between treatment and control group at baseline.

Table 1

Demographic Data of Participants by Treatment Group.

Variable	Treatment (n = 7) M(SD)	Control (n = 9) M(SD)
Age, years	48.33 (10.17)	49.29 (7.80)
Gender, % female	86	67
Education, years	15.17 (2.71)	15.86 (2.04)
Ambulation index	2.00 (1.79)	3.22 (2.17)
Disease duration, months	186.7 (116.95)	134.0 (108.42)
MS subtype, frequency		
□ <i>Relapse Remitting</i>	6	3
□ <i>Primary Progressive</i>	0	2
□ <i>Secondary Progressive</i>	0	2
□ <i>Progressive Relapsing</i>	1	0
□ <i>Unknown</i>	0	2

Table 2

Accuracy (correct/incorrect response ratio) and reaction time (ms) on the N-back task. Values are shown as mean (SD).

	Placebo-control		Treatment	
	Pre	Post	Pre	Post
Accuracy				
0-back	.98 (.03)	1.00 (0.00)	1.00 (0.00)	.98 (.03)
1-back	.55 (.13)	.57 (.12)	.54 (.14)	.56 (.18)
2-back	.86 (.12)	.93 (.12)	.78 (.17)	.87 (.14)
Reaction time				
0-back	753 (222)	676 (110)	644 (101)	658 (74)
1-back	754 (194)	747 (127)	611 (93)	756 (174)
2-back	983 (220)	840 (220)	807 (165)	807 (187)

Table 3

Region of interest analysis comparing baseline to immediate follow-up.

Region	Brodmann Area	Hemisphere	Voxel size	Peak x	Peak y	Peak z	Peak F
SFG	6	L	47	14	-15	68	10.12
PCG	3	R	40	-22	33	52	8.87
DLPFC	9	R	40	-58	-11	24	8.77
PCL	5	L	41	22	37	48	8.33
Culmen	-	L	38	26	41	-24	7.76
IPL	40	R	33	-42	41	36	6.99
SMA	6	R	54	-34	-11	52	6.55
rACC	25/11	L	27	6	-19	-16	6.28

SFG = superior frontal gyrus, PCG = postcentral gyrus, DLPFC = dorsolateral prefrontal cortex, PCL = paracentral lobule, IPL = inferior parietal lobule, SMA = supplementary motor cortex, rACC = rostral anterior cingulate cortex.