SciMedCentral

Journal of Neurological Disorders & Stroke

Short Communication

Feasibility and Findings from a Novel Working Memory fMRI Paradigm in Multiple Sclerosis

Nelson F[1]* and Steinberg J[2]

[1]University of Texas Health Science Center at Houston, Houston, TX, USA
[2]Virginia Commonwealth University Richmond, VA, USA

*Corresponding author
Flavia Nelson, Multiple Sclerosis Research Group, University of Texas Health Science Center at Houston, 6431 Fannin Street, MSB 7.220, Houston Texas, 77030, USA, Email: Flavia.m.nelson@uth.tmc.edu

Submitted: 23 July 2013

Accepted: 16 August 2013

Published: 19 August 2013

Keywords

- Functional MRI
- Multiple sclerosis
- Cognitive impairment
- Working memory

Abstract

Background: Functional MRI (fMRI) basic cognitive paradigms such as the n-back have been shown to detect cognitive impairment (CI) in Multiple Sclerosis (MS). The immediate memory task/delayed memory task (IMT/DMT) detects varying degrees of working memory (WM) by alternating three levels of complexity and two levels of WM delay. This paradigm has not been evaluated in MS nor validated against standard neuropsychological (NP) testing.

Objective: To evaluate the correlation between WM function and blood oxygen level dependent (BOLD) activation on fMRI in MS patients undergoing the IMT/DMT. To compare IMT/DMT behavioral scores to NP scores.

Methods: 10 MS patients with no history of CI underwent the Minimal Assessment of Cognitive Function in MS (MACFIMS) and an fMRI session where they performed the IMT/DMT. Working-memory ("wmem") activation was defined as the BOLD signal during DMT blocks for a particular condition (3, 5, or 7 digits per stimuli) minus the BOLD signal during IMT blocks for that condition. Areas of statistically significant Family Wise Error (FWE) -corrected cluster-level BOLD activation were identified using SPM8 Random Effects t-test. IMT/DMT behavioral data and MACFIMS scores were compared.

Results: The 3-digit as well as the 5-digit wmem showed significant fMRI BOLD activation. The 3-digit wmem, activation was found in portions of the bilateral superior and mid frontal cortex, supplementary motor area, pre and post central gyrus, bilateral superior and inferior parietal lobule, inferolateral pre-frontal cortex, cuneus, insula and cingulate regions. The 5 digit wmen activation was seen in the inferior medial frontal and medial orbitofrontal cortex. IMT/DMT behavioral scores were within normal range and consistent with MACFIMS.

Conclusion: IMT/DMT, a novel fMRI working memory paradigm, is associated with BOLD activation in areas of the brain related to cognitive function in patients with MS. Both MACFIMS and IMT/DMT scores were in agreement and supported intact cognitive function.

INTRODUCTION

Functional MRI (fMRI) has recently been used to assess cognitive impairment (CI) in MS. Sweet et al. using the 2-back, was among the first to evaluate verbal working memory (VWM). He concluded that high functioning patients showed a shift toward greater activity in regions associated with sensorimotor functions and anterior attention/executive components of the VWM system [1]. Chiaravalloti et al. using the modified Paced Auditory Serial Addition Test (PASAT) confirmed that working memory dysfunction in MS is associated with cerebral activation patterns in accordance with CI [2]. Filippi et al. in his review concluded that fMRI has great potential to provide insight into cortical reorganization following tissue damage in MS [3]. Although fMRI provides a better understanding of cognitive constructs determining pathology in CI, the most common paradigms used, do not evaluate varying degrees of working memory nor have they been validated by neuropsychological testing within the study reported.

The application of the immediate memory task/delayed memory task (IMT/DMT) fMRI paradigm in MS is a novel concept, since it has never been used to assess MS related CI. This paradigm has the potential to be more sensitive than fMRI

paradigms used for evaluation of working memory in MS like the N-back [1]. The IMT/DMT paradigm is similar to the N-back sequential letter memory test because there is a contrast between a longer working memory delay period (DMT) and a shorter delay period (IMT) analogous to 2-back vs. 1-back, respectively. In addition, the DMT/IMT is similar to N-back in that the rate of presentation of visual stimuli is constant throughout the task. However, IMT/DMT differs from N-back in that IMT/DMT allows the experimenter to manipulate task difficulty independently of the duration of the working memory delay. The IMT/ DMT create variation in working memory demands by changing the number of digits per stimulus to alter task difficulty in addition to changing the working memory delay. Thus, both the memory delay and the digit-load condition are varied parametrically in IMT/DMT but not in N-back. The parametric variation in task difficulty in IMT/DMT allows the researcher to compare several different levels of task difficulty within a single fMRI session, and thus determine the relation of task difficulty to BOLD activation, for example by using regression analysis. The IMT/ DMT also allows the behavioral performance-brain activation curves to be compared between patients and controls and among different patient severity subgroups, as opposed to comparing only one point on this curve between groups using other tasks such as N-back. These characteristics make the IMT/DMT an ideal candidate to potentially evaluate the presence of different degrees of MS related CI. Here we report the feasibility of using IMT/DMT in MS patients with intact cognition and validate the results with standard neuropsychological (NP) testing

MATERIALS AND METHODS

Patients

10 patients with the diagnosis of MS by the 2001 McDonald criteria [4] and no history of CI based on the MS Neuropsychological Screening Questionnaire (MSNQ) [5] or a normal NP evaluation within the previous year, underwent the Minimal Assessment of Cognitive Function in MS (MACFIMS) battery [6]. This was followed by one fMRI session within a period of no more than one week and no less than 2 days. Exclusion criteria included history of psychiatric disorders, history of drug or alcohol abuse, history of depression within 3 months of enrollment, history of pacemaker or metal implants, history of renal insufficiency (by creatinine and eGFR tests prior to MRI), history of allergy to gadolinium, history of other brain pathology, claustrophobia, or positive urine pregnancy test prior to the imaging session.

Behavioral laboratory measures

The MACFIMS is designed to quantify cognitive function with psychometric testing, it includes these component assessments: processing speed and working memory assessed by Paced Auditory Serial Addition Test (PASAT) and Single Digit Modality Test (SDMT), memory and learning evaluated by California Verbal Learning Test II (CVLT-II) and Brief Visuospatial Memory Test Revised (BVMT-R), executive function using the D-KEFS sorting test, visual perception/spatial processing using judgment of line orientation, and language by verbal fluency (COWAT).

IMT/DMT task

Patients underwent a 1 hour practice session in a mock scanner. Within the IMT/DMT fMRI protocol, the delayed memory test (DMT) condition was designed as a delayed matching to sample task to retain a visual stimulus in working memory in the presence of distracter stimuli [7,8]. In the DMT condition, each stimulus consists of numerals that are displayed simultaneously in a horizontal array for 0.5 s, followed by an inter-stimulus interval of blank screen for 0.5 s, at a rate of 1 stimulus per second. The target and probe stimuli are separated by distracter stimuli, consisting of a string of all zeros that is repeated three times. Thus the memory delay between the end of the target stimulus and beginning of the probe stimulus is 3.5 seconds. For example, one possible DMT trial would be: 24639, 00000, 00000, 00000, and 24639. Subjects are instructed to ignore the distracter stimuli and to remember only the target (e. g. , first occurrence of 24639) and to identify only the probe (e. g. , second occurrence of 24639). Subjects are instructed to press a button when a probe appears that matches the target. There is a 50% probability of a catch trial, in which the probe differs from the target by only 1 of the digits. Each trial consists of a completely new set of targets and probes. The “immediate memory test” (IMT) condition is a control condition that is similar to the DMT in rate and type of stimuli except there are no distracter stimuli, and thus the memory delay is 0.5 seconds. A stimulus consisting of all 1’s is presented once after each DMT trial and 4 times after each IMT trial. Thus the sum of nonsalient inter-trial and distracter stimuli is the same (four) during DMT and IMT conditions, and the number of trials is the same (seven) during IMT and DMT conditions. Runs with chance level of performance in the majority of the conditions are excluded from the fMRI analysis. The IMT/DMT fMRI protocol is a parametric block design. The number of digits in the stimulus string can be 3, 5, or 7 digits, and the number of digits per stimulus is held constant within each block. The type of memory delay condition (either IMT or DMT) is also held constant within each block. All 3 levels of the digit-load condition and 2 levels of the memory-delay condition are presented within each run. An IMT block is always followed by a DMT block with the same number of digits per stimulus. There are 6 IMT blocks and 6 DMT blocks within each run. The order of the digit conditions for the first 6 blocks is repeated during the last 6 blocks of each run and is counterbalanced between runs and subjects. The duration of each block is 42.5 seconds; there is 10 seconds rest between blocks and 20 seconds rest at the start of each run. The duration of each run is 10 min 47 s. An example run is shown here (abbreviations i3 = IMT 3-digit block; d5 = DMT 5-digit; etc. ; and r = rest) : r-i3-r-d3-r-i5-r-d5-r-i7-r-d7-r-i3-r-d3-r-i5-r-d5-r-i7-r-d7. Another example is shown in figure 2.

fMRI session

All MRI studies were performed on a 3T Philips Intera 8 channel receiver system scanner, equipped with Eloquence system (Invivo Corporation, Orlando, Florida) for displaying the IMT/DMT during the fMRI acquisition. The Eloquence System includes a keyboard-like button-press response device. The scanning session included a T1 weighted SE 3-plane localizer (scout), a SENSE localizer, and a high resolution T1 weighted 3D-magnetizaion prepared rapid acquisition gradient echo (MPRAGE) followed by 3 runs of the fMRI task. Image processing and analysis were done using AFNI and SPM8 software (Mathworks Inc. Sherborn MA, USA). All series were despiked

using AFNI 3dDespike with outliers defined as greater than 4 standard deviations from the mean of the time series. After slice-timing correction using SPM8, each fMRI time series was realigned to correct for head motion. Runs with head motion greater than 3.75 mm translation or rotation component greater than 3.75 degrees were eliminated from analysis. The high-resolution T1-weighted MPRAGE was co-registered with the mean realigned fMRI image then transformed into MNI space using the SPM8 Normalise module. The fMRI images were transformed to MNI space using the transformation parameters from the co-registerd MPRAGE, then re-sliced to (2 x 2 x 2) mm voxel dimensions. The fMRI images were then spatially smoothed with an 8 mm isotropic FWHM Gaussian filter.

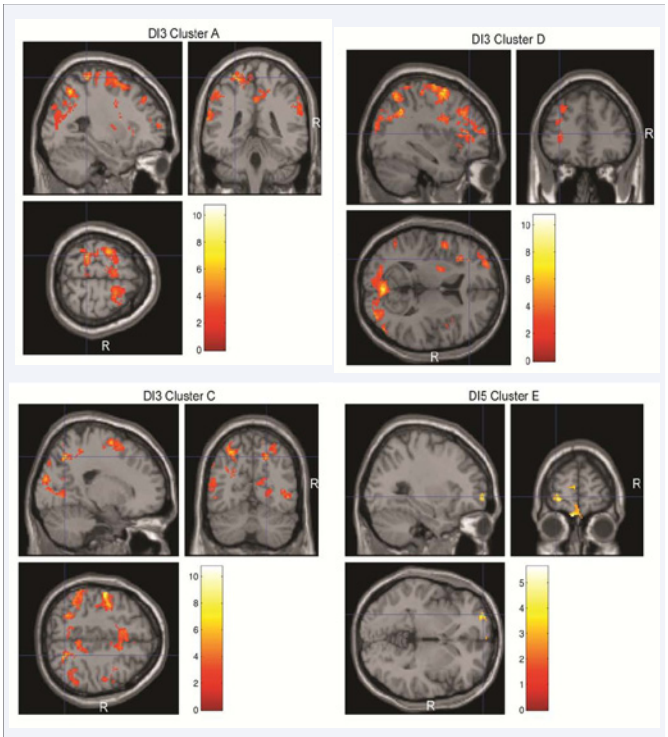

Figure 1 3-digit wmem, widespread FWE-corrected significant activation was found in portions of the bilateral superior and mid frontal cortex, supplementary motor area and pre and post central gyrus, bilateral superior and inferior parietal lobule, and inferolateral pre-frontal cortex, cuneus, insula and cingulate regions (see DI3 Clusters A, C, and D). 5 digit wmen, positive activation was seen in the inferior medial frontal and medial orbitofrontal cortex (DI5 Cluster E).

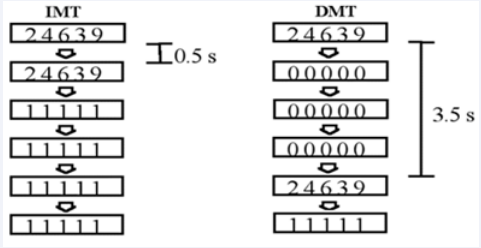

Figure 2 IMT/DMT creates variation in working memory demands by changing the number of digits per stimulus to alter task difficulty in addition to changing the working memory delay. Both memory delay and digit-load condition are varied parametrically unlike in N-back.

Statistical analysis

For the block design IMT/DMT protocol, the IMT and DMT conditions for each digit-load condition (3-, 5-, and 7-digit IMT, 3-, 5-, and 7-digit DMT) were modeled by boxcar functions convolved with the SPM8 canonical hemodynamic response function. The parameters for each condition were estimated using the General Linear Model at each voxel. The fMRI time series was high-pass filtered with a cut-off period of 330 s determined by Fourier transformation of each condition's time model. The working memory activation ("wmem") for each digit-load condition was defined as the DMT parameter estimate for that digit-load condition minus the IMT parameter estimate for that digit-load condition. Statistical significance was computed by SPM8, to correct for multiple comparisons over all the voxels in the brain. Areas of statistically significant differences in BOLD activation were identified using 2-tailed family wise error (FWE) -corrected cluster-level $p < 0.05$. Approximate anatomical labels for regions of activation were determined using the Anatomical Automatic Labeling toolbox (Tzourio-Mazoyer et al. , 2002).

The **A′** score (Donaldson, 1992) is used as an accuracy measure on the IMT/DMT, ranging from 0.5 (chance) to 1.0 (perfect discriminability). Recall failures or errors, as well as correct responses, are taken into account in the formula for calculating the **A′** accuracy score [9].

Based on MACFIMS testing CI was defined as patient scores being 1 or 2 standard deviations below the mean and impairment score of > 0.3 (based on 20 parameters).

RESULTS

fMRI

9 patients were included in the final analysis; one subject was eliminated prior to fMRI analysis due to scores within the borderline range for both the MACFIMS and the IMT/DMT behavioral results. The 3-digit wmem as well as 5-digit wmem showed significant BOLD activation on fMRI. For 3-digit wmem, widespread FWE-corrected significant activation (see figure 1; DI3 Clusters A, C, and D) was found in portions of the bilateral superior and mid frontal cortex, supplementary motor area and pre- and post- central gyrus, bilateral superior and inferior parietal lobules, and inferolateral pre-frontal cortex, cuneus, insula and cingulate regions. For 5 digit wmen, positive activation was seen in the inferior medial frontal and medial orbitofrontal cortex (DI5 Cluster E). For 7-digit wmem no significant positive or negative activation was found.

IMT/DMT

9 MS patients were found to have A' accuracy scores consistent with a previously evaluated normal control group [10], these results were also consistent with scores from the MACFIMS evaluation.

CONCLUSION

IMT/DMT, a recently developed fMRI working memory paradigm, is associated with BOLD activation in areas of the brain related to cognitive function MS in patients with no history of impairment. These results suggest that IMT/DMT may be

a feasible tool for evaluation of cognition in MS. An interesting observation was the lack of increased activation for the 7 digit wmen, supporting the notion that unlike what was seen during the 3 and 5 digit task where an increased degree of difficulty was overcome by an extension of the BOLD activation areas, the ability to increase BOLD activation in response to a task with higher degree of difficulty (7 digit) as a compensatory mechanism (brain plasticity) may be reduced in MS patients NP scores within the normal range. A limitation of this study is the lack of age and sex matched normal controls, further studies are being planned to include such group. Behavioral data from the fMRI task was consistent with scores from a previously evaluated normal control group [10] (data not shown) and with scores from a battery of NP tests recommended by the National MS Society for evaluation of CI, suggesting its potential validity. These findings are the foundation for a study which intends to use this technique for detection of MS related cognitive impairment.

ACKNOWLEDGMENTS

This research was supported by NIH/NINDS grant 5K23NS072134-02 awarded to Flavia Nelson MD and by donations from Clay Walker's "Band against MS". Special thanks to Vipulkumar "Vips" Patel MRI technician for excellent support.

REFERENCES

1. Sweet LH, Rao SM, Primeau M, Mayer AR, Cohen RA. Functional magnetic resonance imaging of working memory among multiple sclerosis patients. J Neuroimaging. 2004; 14: 150-157.

2. Chiaravalloti N, Hillary F, Ricker J, Christodoulou C, Kalnin A, Liu WC, et al. Cerebral activation patterns during working memory performance in multiple sclerosis using FMRI. J Clin Exp Neuropsychol. 2005; 27: 33-54.

3. Filippi M, Rocca MA. Disturbed function and plasticity in multiple sclerosis as gleaned from functional magnetic resonance imaging. Curr Opin Neurol. 2003; 16: 275-282.

4. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001; 50: 121-127.

5. Benedict RH, Munschauer F, Linn R, Miller C, Murphy E, Foley F, et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. Mult Scler. 2003; 9: 95-101.

6. Benedict RH, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. Clin Neuropsychol. 2002; 16: 381-397.

7. Dougherty DM, Marsh DM, Mathias CW. Immediate and delayed memory tasks: a computerized behavioral measure of memory, attention, and impulsivity. Behav Res Methods Instrum Comput. 2002; 343: 391–398.

8. Dougherty DM, Steinberg JL, Wassef AA, Medearis D, Cherek DR, Moeller FG. Immediate versus delayed visual memory task performance among schizophrenic patients and normal control subjects. Psychiatry Res. 1998; 79: 255-265.

9. Donaldson W. Measuring recognition memory. J Exp Psychol Gen. 1992; 121: 275-277.

10. Moeller FG, Steinberg JL, Schmitz JM, Ma L, Liu S, Kjome KL, et al. Working memory fMRI activation in cocaine-dependent subjects: association with treatment response. Psychiatry Res. 2010; 181: 174-182.

Cite this article

Nelson F, Steinberg J (2013) Feasibility and Findings from a Novel Working Memory fMRI Paradigm in Multiple Sclerosis. J Neurol Disord Stroke 1(2): 1011.