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# Cognitive fatigue in individuals with multiple sclerosis undergoing immunoablative therapy and hematopoietic stem cell transplantation

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ABSTRACT

*Background:* Fatigue presents as a significant problem in multiple sclerosis (MS). Cognitive fatigue (CF) can be defined as a decrease in, or inability to maintain task performance throughout the duration of a continuous cognitive task. CF was evaluated using the Paced Auditory Serial Addition Test (PASAT) both pre- and post-immunoablation and hematopoietic stem cell transplantation (IA-HSCT) over a 3-year follow-up period. The magnitude of CF was examined and the impact of scoring methodology was evaluated.
*Methods:* Twenty-three individuals with rapidly progressive MS and poor prognosis underwent high dose immunosuppression and subsequent HSCT. Individuals completed the 3″ and 2″ PASAT at baseline and every 6 months thereafter over a period of 36 months. As scoring methodology can impact its sensitivity to CF, the PASAT was scored according to three scoring methods.
*Results:* CF was noted across all three scoring methods at baseline and at the majority of time points post-IA-HSCT on both the 3″ and 2″ PASAT. The magnitude of CF remained consistent both pre-and post-IA-HSCT.
*Conclusions:* While results suggest that the procedure itself does not ameliorate an individual's susceptibility to CF; neither does it seem to negatively impact levels of CF. As such, results support the notion that the IA-HSCT procedure, despite its aggressive nature, does not exacerbate CF in this particular sample.


## 1. Introduction

Fatigue presents as a significant problem in multiple sclerosis (MS), occurring in up to 90% of those diagnosed [1]. Individuals with MS frequently report higher levels of fatigue when compared to healthy controls with the severity of fatigue being found to independently predict quality of life [2]. Despite the large body of literature examining MS-related fatigue, the concept of fatigue remains a poorly understood concept likely due to its multifaceted nature. In the past, research has focused predominantly on the study of physical fatigue; however, cognitive fatigue can often be equally as debilitating for those individuals affected.

Cognitive fatigue (CF) can be defined as a decrease in, or inability to sustain, task performance throughout the duration of a continuous information processing speed (IPS) task [3,4]. During IPS tasks, individuals with MS show more susceptibility to the effects of CF when compared to healthy controls [4]. Individuals susceptible to CF are less able to maintain the required cognitive effort necessary to continuously meet task demands on an IPS task over time. This is often reflected by a breakdown in task performance as the task progresses. Previous work by our group examining IPS tasks as potential measures of CF has shown that, despite its limitations [5], the Paced Auditory Serial Addition Test (PASAT) can serve as a reliable and sensitive measure of CF in MS [6].

### 1.1. PASAT scoring methods

The PASAT is a measure of IPS and working memory (WM) in which participants are presented with a series of single digit numbers (60 trials) where the two most recent digits heard must be summed out loud. The speed at which information must be processed can be manipulated by altering the interstimulus intervals (ISI). CF can be measured using the PASAT by comparing performance on the first half of the task (i.e. the first 30 trials) versus the second half of the task (i.e. the last 30 trials). Despite the challenges associated with the use of the PASAT [5–10], it remains one of the most sensitive measures of IPS and WM deficits in MS [10,11]; and as such has been continuously used in studies examining CF in MS where sustained cognitive effort is required [4,6,12].

Traditionally, PASAT performance is scored by counting the overall number of correct responses. Individuals may, however, adopt a "chunking method" strategy such that the first two numbers are added, the next number is skipped, the following two numbers are

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added, and so forth [10]. This strategy reduces the overall difficulty of the task by decreasing the need to perform multiple cognitive processes simultaneously (i.e. diminishes the working memory demands). While these individuals may still achieve a score within normal limits, their performance no longer reflects the ability to meet the task demands as intended.

The number of correct dyad responses better reflects an individual's ability to successfully meet task demands [6,10]. In this case, a correct score is only assigned when one correct response immediately precedes another; thus, dyad scoring provides an indication of *performance when executing the task as intended*. As such, the number of correct responses and the number of correct dyads both provide a measure of *performance level*. One may further calculate a percent dyad score; an indication of the *proportion of time* an individual is performing the task as intended. While not a measure of performance accuracy per se, higher percent dyad scores reflect a greater ability to produce correct responses in accordance with the task demands [10]. The percent dyad scoring method thus provides a reflection of an individual's *performance strategy*.

### 1.2. IA-HSCT procedure

Presently, no curative treatment exists for MS. While current treatment therapies aim to slow the progression of the disease, results have been limited in their success. In an attempt to eradicate the autoimmune processes which give rise to MS, the Ottawa Hospital MS Clinic (as well as other groups worldwide) has adopted a Bone Marrow Transplant approach to treatment in hopes of establishing long-lasting periods during which progression of the disease is halted [13]. Given the intensive nature of the procedure, only a select group of individuals with rapidly-progressing MS and poor prognosis was chosen to undergo immunoablative therapy and hematopoietic stem cell transplantation (IA-HSCT). Of the 23 individuals to undergo the procedure, no new attacks or MRI lesions have been reported [14, Freedman & Atkins, 2013 personal communication]. Neuroimaging has revealed, however, that the procedure itself results in a rate of brain atrophy significantly greater than is expected on the basis of natural disease progression. Individuals experienced a 3.2% (median) decrease in total brain volume over 2.4 (median) months [15]. Preliminary results suggest that atrophy may not have any lasting negative impact on cognition [16], but to date, the potential impact on cognitive fatigue has not been addressed.

Given the aggressive nature of the treatment alongside the increased rate of atrophy noted, the current study aims to evaluate levels of CF in the 23 individuals before and after undergoing the IA-HSCT procedure. To the best of our knowledge, no research to date has evaluated the impact of such a procedure on levels of CF in an MS population.

### 1.3. Hypotheses

The primary objective was to examine performance across the task on the 3″ and 2″ PASAT in the 23 individuals both pre- and post-IA-HSCT in order to determine whether the procedure influenced levels of CF. Furthermore, we determined whether PASAT scoring method influenced its sensitivity in detecting CF in this particular sample. It was hypothesized that CF would be evident both pre-and post IA-HSCT as evidenced by lower performance on the 2nd half of the PASAT when compared to the 1st half of the PASAT at all time points. Furthermore, given the aggressive nature of the procedure, we hypothesized that the magnitude of CF (i.e. the degree of change between 1st and 2nd half performance) would be greater for those time points immediately following the IA-HSCT procedure when compared to the magnitude of CF at baseline; with the degree of change returning to baseline levels with temporal distance from the procedure.

## 2. Methods

### 2.1. Participants

This study was approved by the Ottawa Hospital Research Ethics Board and informed consent was obtained. A total of thirty-four individuals were screened as potential candidates for the study. Eleven individuals did not meet specific inclusion criteria; as such, twenty-three individuals (14 females; 9 males) with rapidly progressing MS who failed to respond to routine therapy were enrolled. High risk of progression was defined as ≥5 relapses in the first two years of the disease or attainment of a Functional System (FS) Score of at least 3 affecting pyramidal/cerebellar subscores within 5 years of disease onset. If a patient had previously received a cytotoxic agent (Mitoxantrone or Cyclophosphamide) they must have had normal bone marrow morphology and cytogenetics before being considered eligible. Age ranged from 23 to 44 years (mean = 32.65 (5.82) years) and education ranged from completion of high school to completion of graduate degrees. Expanded Disability Status Scale (EDSS) scores pre-IA-HSCT ranged from 1.5 to 6.5 (mean = 4.87 (1.40)). Twelve individuals were diagnosed with relapsing–remitting MS (RRMS) with the remaining 11 diagnosed with secondary progressive MS (SPMS). Those with primary progressive MS were excluded.

### 2.2. Procedure

The study was a tri-center phase II efficacy study of the role of IA-HSCT on the natural history of MS. Participants underwent stem cell mobilization with IV cyclophosphamide (4.5 g/m$^2$) and 10 days of granulocyte colony-stimulating factor (10 μg/kg/day) followed by stem cell collection using peripheral vein leukapheresis. All stem cell grafts were CD34 selected and cryopreserved until transplantation. Immunoablation was accomplished in the first six individuals using cyclophosphamide (200 mg/kg), oral bulsufan (16 mg/kg), and IV rabbit antithymocyte globulin (5 mg/kg). A similar regimen was used for the remaining 17 individuals although these individuals received dose-adjusted IV busulfan (9.6 mg/kg) in place of the oral bulsufan. Steroids were administered concurrently with chemotherapy. Patients did not receive further MS-disease modifying drugs or experimental therapy after HSCT.

The PASAT was administered by a trained research assistant. Participants completed the 3″ and 2″ PASAT at baseline (pre-IA-HSCT) and serially every 6 months post-IA-HSCT for a period of 3 years (i.e. 36 months). PASAT performance was compared between the first and second half of the task at all time points for both the 3″ and 2″ ISIs. Responses were recorded and the following scores were obtained: total number of correct responses, total correct dyad score, and percent dyad score. According to convention, in order to have an equal number of dyad responses in each half (i.e. 30 possible dyads in both halves), a dyad score was given for a correct response to the first pair of numbers presented; despite there being no possible preceding response. Percent dyad scores were obtained using the following formula: (1 − ((total correct score-dyad score)/total correct score)) × 100% [6,10]. Two participants did not complete follow-up evaluations past 18 months as they did not comply with the study demands and inclusion of their data would have made it more difficult to interpret findings in the context of the treatment of interest.

### 2.3. Data analysis

In order to examine performance differences between the first and second half of the PASAT, data was analysed for both the 3″ and 2″ ISIs using paired-samples *t*-tests. This was repeated for all three scoring methods and across all time points. In order to determine the magnitude of CF at each time, difference scores were calculated such that scores from the first half of the task were subtracted from scores