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Original Article

Cognition and Cognitive Fatigability: Association with Employment Status in Multiple Sclerosis

Elise S. MacAdam[1], Jason A. Berard[2] and Lisa A.S. Walker[2,3]

[1]Queen's University, Kingston, Canada, [2]Ottawa Hospital Research Institute, Ottawa, Canada and [3]University of Ottawa Brain and Mind Research Institute, Ottawa, Canada

ABSTRACT: ***Background:*** Slowed processing speed impacts employment status in people with multiple sclerosis (PwMS). Studies on the Multiple Sclerosis Functional Composite (MSFC), which includes the Paced Auditory Serial Addition Test (PASAT), have demonstrated that the combined score predicts employment status. Whether PASAT performance alone is associated with employment status is less clear. In addition, no studies have yet evaluated whether cognitive fatigability (CF), as measured with the PASAT, is associated with employment status. The aim of the current study was to examine the association between PASAT performance, CF, and employment status in PwMS. ***Methods:*** Hundred and eighty-six PwMS completed the PASAT as part of a larger neuropsychological battery. ANOVAs and chi-squares analyzed group differences between employed and unemployed participants with respect to demographics, PASAT performance scores, and CF. Linear regression determined whether PASAT performance and/or CF scores were associated with employment status. ***Results:*** After controlling for demographic influences, group differences were noted between employed vs. unemployed individuals on PASAT performance scores only. Employment status was associated with PASAT performance scores but not CF. ***Conclusions:*** The current study confirmed that PASAT performance is associated with employment status in MS. Given that CF was not associated, it seems difficulties with information processing speed (IPS) and working memory have more impact on a PwMS's ability to remain employed rather than within-task performance decline.

RÉSUMÉ : Cognition et fatigabilité cognitive : association avec la situation professionnelle dans le cas d'individus atteints de sclérose en plaques. ***Contexte :*** Le ralentissement de la vitesse de traitement cognitif a un impact sur la situation professionnelle d'individus atteints de sclérose en plaques (SP). Des études portant sur l'outil d'évaluation *Studies on the Multiple Sclerosis Functional Composite* (MSFC), lequel inclut le *Paced Auditory Serial Addition Test* (PASAT), ont ainsi démontré que le score combiné obtenu dans le cadre de cette évaluation permet de prédire la situation professionnelle d'un individu. Il est toutefois loin d'être clair que les résultats obtenus au PASAT puissent être associés à la situation professionnelle. De plus, aucune étude n'a encore évalué si la fatigabilité cognitive (FC), telle que mesurée par le PASAT, peut être associée à cette même situation. L'objectif de la présente étude a donc consisté à examiner l'association entre les résultats obtenus au PASAT, la fatigabilité cognitive et la situation professionnelle d'individus atteints de SP. ***Méthodes :*** Au total, 186 d'entre eux ont complété un PASAT dans le cadre d'une batterie de tests neurologiques plus vaste. Des tests d'analyse de la variance et du khi carré nous ont ainsi permis de nous pencher sur les différences entre les participants employés et chômeurs en ce qui regarde leurs caractéristiques démographiques, leurs résultats au PASAT et leur FC. La méthode de régression linéaire nous a enfin permis de déterminer si les résultats obtenus au PASAT et/ou les scores en matière de FC étaient associés à la situation professionnelle d'un individu. ***Résultats :*** Après avoir contrôlé des facteurs d'ordre démographique, des différences entre groupes ont été notées en ce qui regarde uniquement leurs résultats au PASAT. La situation professionnelle d'un individu peut en cela être associée à des résultats au PASAT mais pas à la FC. ***Conclusions :*** La présente étude a confirmé que des résultats au PASAT pouvaient être associés à la situation professionnelle d'individus atteints de SP. Étant donné que la FC n'y était pas associée, il semble que des difficultés liées à la vitesse de traitement de l'information (VTI) et à la mémoire au travail aient plus d'impact sur la capacité d'individus atteints de SP à conserver leur emploi que le déclin des performances liées à des tâches particulières.

Keywords: Multiple sclerosis; Cognition; Neuropsychology; Cognitive fatigability; PASAT

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Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative demyelinating disease of the central nervous system, affecting both gray and white matter.[1–4] People with MS (PwMS) can experience a multitude of different neurological deficits, including cognitive impairment (CI).[1] CI impacts 40–70% of PwMS and correlates

Corresponding author: Dr. Jason Berard, Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, Ontario, K1H 8L6, Canada. Email: jberard@ohri.ca

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highly with gray matter lesions and atrophy, causing difficulties such as slowed information processing speed (IPS) and impaired working memory.[2,3]

Fatigue affects about 90% of PwMS.[5–7] There are varying definitions of fatigue throughout the literature including a state of reduced capacity for work following a period of mental or physical activity, and a feeling of physical tiredness and lack of energy that is distinct from sadness or weakness.[8,9] In most studies, fatigue is a subjectively measured concept and is largely evaluated using self-report tools.[10–12] In contrast, cognitive fatigability (CF) is less well understood and relies on objective quantification.[5,13] A unified taxonomy has been proposed to differentiate subjectively measured fatigue from objectively measured CF in clinical and research settings.[14] Although there are varying definitions of CF throughout the literature, it is presently defined as an inability to maintain optimal task performance throughout the duration of a sustained cognitive task.[5,8,15,16] PwMS demonstrate a greater susceptibility to CF compared to healthy controls during sustained cognitive tasks, often reflected by a breakdown or decline in performance throughout the task.[15] Those individuals who have a greater susceptibility to CF have greater difficulty maintaining the cognitive effort required to achieve desired task outcomes over a lengthy period of time.[17]

Although self-assessments are commonly used to evaluate CF in PwMS, they strictly assess subjective fatigue and are consequently subject to psychological error, thereby reducing their accuracy.[18] Objective tests are therefore used to compliment the subjective assessments in order to better quantify CF. Some studies have measured CF using reaction time tasks, such as the Psychomotor Vigilance Task.[13] CF indicators, such as cognitive processing speed and working memory changes, have been more commonly utilized to evaluate CF and can be measured using neuropsychological tests such as the Paced Auditory Serial Addition Test (PASAT).[19–21]

Physical and CIs associated with MS have a critical effect on daily functioning for PwMS. Approximately half of PwMS are unemployed, resulting in a significant burden on their quality of life.[22,23] A United Kingdom study found that unemployment rates of PwMS were approximately 75% within 10 years of diagnosis.[24,25] The correlation between physical disability in MS and employment status has been widely acknowledged in the literature, with studies showing that the rate of unemployment is proportional to the Expanded Disability Status Scale (EDSS) scores.[22,26,27] Although there is a strong correlation between a high EDSS score and unemployment, 54% of PwMS with an EDSS score ≤ 3 can be unemployed, suggesting that physical disability is perhaps not the sole factor contributing to the increased rates of unemployment.[23]

There is a growing body of literature demonstrating that CI can also negatively impact employment status and consequently quality of life for PwMS.[1] A systematic review of studies investigating the relationship between employment status and cognition found that PwMS who were unemployed scored lower on objective cognitive tests than PwMS who remained employed, although statistical significance varied throughout the studies. The most consistent finding was the difference in IPS between the groups.[22] Previous studies have found that the most robust predictor of employment status in PwMS was the Multiple Sclerosis Functional Composite (MSFC).[28] The MSFC is a measure of MS-related disability that includes measures of upper and lower extremity function and cognition (i.e., the sole cognitive measure is the PASAT). The combined measures in the MSFC explained 49.8% of the variance in employment status, surpassing the predictive value of the EDSS.[28] Progressive disease course, longer disease duration, and female sex were also associated with unemployment, as has poorer performance on the Symbol Digit Modalities Test (SDMT) and Word List Generation task.[28] Strober et al. also evaluated the utility of the MSFC in predicting employment status in PwMS, finding the SDMT, rather than the PASAT, to be the sole significant predictor of employment status.[29]

To date, no study has yet evaluated whether CF specifically influences employment status. It is this gap in the literature that the current study seeks to address. The current aim is to investigate whether PASAT performance and/or CF scores are associated with employment status in PwMS and, if so, to what degree (i.e., how much CF is associated with employment status).

Material and Methods

Participants

Participant data were aggregated from three separate, and now completed studies, all which had evaluated cognition in MS. All studies were approved by either the Ottawa Health Science Network Research Ethics Board (two studies), or by the Sunnybrook Health Sciences Centre Research Ethics Board (one study). A total of 186 individuals with a confirmed diagnosis of MS by their treating neurologist (McDonald criteria) were recruited from the Ottawa Hospital MS Clinic and Sunnybrook Health Sciences Centre. Inclusion criteria for all participants included being between 18 and 65 years of age, fluency in English, and a confirmed diagnosis of MS. Exclusion criteria included any neurological, medical, or psychiatric condition (besides MS and depression) that might impede cognition, use of legal or illegal drugs that might impact cognition, prior head trauma, learning disability, attention-deficit disorder, dementia, formally diagnosed mild CI, or substance abuse (alcohol, cannabis, tobacco, etc.). After all participants were given the opportunity to ask questions, informed consent was obtained.

Procedures and Measures

Participants completed the study protocol at the time of day that was most convenient for them. All participants completed a demographic interview with a research assistant on site that was trained by a licensed Clinical Neuropsychologist. As part of the interview, participants were asked about their employment status including whether they worked full-time or part-time, and how many hours they worked weekly.

In all three contributing studies, the PASAT was administered as part of a larger neuropsychological battery. In order to diminish the impact that the time of administration could have on participants performance on the task, the test was administered as either the third or fourth task in the battery. The PASAT measures IPS and working memory in the auditory modality by evaluating the participant's ability to add one number to a previously presented number at a 3-second interstimulus interval (i.e., 3" PASAT). Although there are drawbacks to the PASAT,[19] it is acknowledged as a reliable evaluator of IPS[17,19] and has been used extensively to evaluate CF in PwMS.[17,21] Participant responses were recorded, and the total number of correct responses, dyad score, and percent dyad scores were calculated. Traditionally, PASAT performance is assessed by counting the number of correct responses. However, the test's sensitivity may be affected if individuals use a "chunking method" which decreases the difficulty of the test. As such, the results achieved using this strategy are no longer a reflection of

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Table 1: Comparison of employed and unemployed groups on demographic and neurological variables

Demographic and neurological variables	Unemployed mean (SD)	Employed mean (SD)	*p*
Age	48.18 (10.15)	41.01 (8.73)	0.00
EDSS score	3.84 (1.93)	1.94 (1.46)	0.00
Disease duration in years	9.86 (6.66)	6.61 (6.31)	<0.01
Years of education	15.04 (2.34)	15.09 (2.18)	0.87

Table 2: Comparison of PASAT performance and cognitive fatigability score between employed and unemployed groups

		Employed mean (SD)	Unemployed mean (SD)	F	*p*
PASAT performance	Total correct	45.94 (10.77)	39.93 (14.92)	6.02	0.02
	Total dyad	38.03 (15.08)	30.93 (18.07)	5.96	0.02
	Total percent dyad	78.42 (19.86)	69.90 (23.4)	3.81	0.05
PASAT CF	Total correct	−2.25 (3.62)	−2.17 (3.13)	0.35	0.85
	Total dyad	−3.72 (5.19)	−3.65 (4.02)	0.126	0.72
	Total percent dyad	−9.60 (13.59)	−15.42 (21.73)	2.08	0.15

the participants true IPS and cognitive abilities.[17] Dyad scoring increases the sensitivity given that, when counting dyads, a response is considered correct only if the previous response was also correct. This ensures the working memory demands of the task are being met. Previous work has identified the percent dyad scoring method, a measure of the proportion of time a person is meeting the working memory demands of the task, as most sensitive to CF. Percent dyad scores were calculated using the following formula: (Dyad Score/Total Correct Score) × 100%. These three scores reflect various aspects of an individual's level of performance on the task (for further details about these scoring methodologies please, see Walker et al.[16]). In addition to these performance scores, CF scores can also be calculated using the PASAT by subtracting performance scores on the first half of the task from performance scores on the second half. This CF score was calculated for each of the three scoring methodologies. A negative CF score (total correct example: −2.25 indicates a decrease in the total number correct over time as the task progresses). This difference between the halves reflects how an individual's performance changes across the task (i.e., their susceptibility to CF).

Analyses

Analyses were first conducted to determine if there were any demographic differences between the employed and unemployed groups based on sex, age, and number of years of education. A chi-square test for independence was used to evaluate possible differences in the proportion of males and females present in the group. A one-way analysis of variance (ANOVA) compared the age and number of years of education between the groups. ANOVAs also examined whether differences in PASAT performance or CF measures existed between the two employment groups. Linear regressions, with employment status as the dependent variable, were performed to determine if PASAT performance scores or CF scores were associated with employment status.

Results

There were no significant differences in PASAT performance or CF measures between the three contributing studies. As such, the data were aggregated across all three studies for all analyses.

Demographics

The mean age of the sample was 43.1 years (SD 9.7, range 21–65). There were 145 (78%) women and 41 (22%) men. Average education of participants was 15.1 years (SD 2.2, range 11 years–21 years). Average disease duration was 7.6 years (SD 6.6, range 0 years–30 years). The breakdown in disease course was as follows: 84.4% relapsing–remitting MS, 11.8% secondary progressive MS, and 3.8% primary progressive MS. The mean EDSS score was 2.63 (SD = 1.88, range 0–7.0).

Group Differences

Comparison between the employed (either full or part-time) and unemployed groups on demographic and disease-related variables are found in Table 1.

Of the 186 participants, 54 (29%) were employed whereas 132 (71%) were unemployed. Unemployed participants tended to be older and have a longer disease duration and a higher EDSS score, indicating greater MS-related disability. Given these differences, age, EDSS, and disease duration were controlled for in subsequent analyses. Group differences were found on the 3-second PASAT for all three scoring methods (total correct, total dyad, and percent dyad), with the employed group scoring significantly higher than the unemployed group. There were no significant group differences for any of the CF measures (see Table 2).

Association with Employment Status

A binary logistic regression analysis, with employment status as the dependent variable, was conducted to identify potential associations with employment status. When controlling for age, EDSS score, and disease duration, 3-second PASAT performance scores for total correct ($\beta = 0.008$, $t(1,111) = 2.454$, $p = 0.02$), total dyad ($\beta = 0.006$, $t(1,111) = 2.440$, $p = 0.02$), and percent dyad scores ($\beta = 0.004$, $t(1,111) = 1.952$, $p = 0.05$) emerged as having significant associations with employment status. The amount of variance

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accounted for was 54.8% for both total correct and total dyad, and 53.5% for percent dyad scoring. Further analysis revealed that CF scores were not significantly associated with employment status when using the total correct raw score ($\beta = 0.002$, $t(1, 111) = 0.188$, $p = 0.85$), total dyad ($\beta = 0.003$, $t(1, 111) = 0.355$, $p = 0.72$), or percent dyad raw score ($\beta = 0.004$, $t(1, 111) = 1.441$, $p = 0.15$).

Discussion

General Information and Study Results

Unemployment rates in PwMS have been reported to be as high as 80%, a stark contrast to reports that rates of unemployment before diagnosis are approximately 4–10%.[30–32] The current investigation examined the associations between PASAT performance, CF scores, and employment status in PwMS. The 3" PASAT performance scores for the total correct, total dyad, and total percent dyad emerged as having significant associations with employment status. Contrarily, CF scores were not significantly associated with employment status. No other study has yet evaluated whether CF specifically, as defined by a decline in performance over the duration of a sustained cognitive task, influences employment status.

Demographic Results

Unemployed individuals were found to be significantly older, have longer disease duration, and higher EDSS scores; all of which are factors characteristic of greater MS-related disability. These findings are consistent with the literature. Work participation is reduced as a result of increasing age, functional changes, and disease severity. Notably, disease severity and associated impairments are reported as one of the most significant reasons for unemployment in PwMS.[33] Cadden & Arnett have also reported EDSS score as a measure that is significantly associated with unemployment status.[34] As well, a longer disease duration and higher EDSS score are indicative of a greater level of disability, which consequently make it harder for PwMS to manage work-related demands.

PASAT Performance Scoring

PASAT performance scores were revealed to have the only significant association with employment status in PwMS. The unemployed group scored significantly lower than the employed group, suggesting that those who are unemployed are more likely to have difficulty with tasks requiring quick thinking and mental manipulation of information (i.e., processing speed and working memory). Given the lack of association with CF, results suggest that the ability to maintain employment is related more to working memory and processing speed than it is to an objective decline in cognitive performance over the duration of a single cognitive task. Silvana et al. reviewed 157 articles that assessed IPS in PwMS and found that IPS deficits have negative impacts on aspects of cognition such as working memory. IPS deficits were also identified as predictors of employment status in PwMS.[35] IPS is said to be a primary cognitive function, important for higher cognitive processes with influences on learning, memory, word retrieval, and executive function. These are all factors that are important in job performance and maintenance.[36] Honarmand and colleagues evaluated the utility of the MSFC as a predictor of employment status in PwMS, and, in accordance with our findings, found that the PASAT was able to significantly differentiate employed and unemployed participants.[28] Nonetheless, there are discrepancies in the literature regarding the predictive ability of the PASAT, with other studies finding no difference in PASAT performance between employment groups.[29] This discrepancy may be due to differences in methodology or participant characteristics (i.e., a smaller proportion of RRMS, longer disease duration, etc.).

PASAT CF Scoring

As opposed to the 3" PASAT performance scores, CF scores were not associated with employment status. Studies evaluating the impact of fatigue on the employment status in other neurological conditions have demonstrated higher rates of unemployment in those subjectively reporting significant mental fatigue. Palm et al. evaluated the impact of mental fatigue on the employment status of people with traumatic brain injuries, and a correlation was found such that higher scores on the Mental Fatigue Scale resulted in less working time.[37] Similarly, Smith & Arnett evaluated factors that significantly contributed to a change in employment status in PwMS. The "no work" participants scored significantly higher on the Fatigue Impact Scale than the "work" group.[38] Just as the literature demonstrates no consistent correlation between subjective cognitive fatigue and objective CF, it seems that there are differences in the association of these concepts to employment status as well.

Limitations and Future Directions

One limitation of the current study is the lack of information about employment type. Whether there is a difference in PASAT performance, CF scores, and their association with employment status depending on the nature of the work being done is unclear. One can speculate that CF may have more of an influence on one's ability to perform jobs where there are greater cognitive demands than one's ability to perform jobs with fewer such demands (and perhaps more physically fatiguing components). In addition, the current study did not distinguish between those who worked full-time, part-time, or were retired/on disability (who were excluded in the current study). While data were collected on full- vs. part-time employment as part of the demographic interview, the small sample size of those that were employed overall (54/186 individuals) limited the potential to subdivide the sample further for more fine-grained comparisons. Furthermore, the generalizability of our findings may also be limited by the relatively early disease course in our sample (mean disease duration of 7.6 years). The current sample may not have exhibited the greater severity of CF that one would anticipate that a sample with a longer disease course would, and thus the restricted range of disease duration may have been a factor in why no association between CF and employment staus was observed. The current sample also had a relatively low mean EDSS score of 2.63. which may have also had a similar influence on outcomes. In addition to the above, given that recruitment into the studies were on a voluntary basis, there is the potential for a selection bias to occur, whereby only those who had an interest in participating in research, or those who were less likely to be impaired, would be more likely to have participated and have consented to being contacted to take part. One further confounding variable may be the time of day when the outcome measures were completed. Individuals were scheduled to take part in the study at a time of day of their choosing. As such, there is the potential that changes in daily fatigue levels may have impacted their cognitive performance (i.e., those who came in after working all day may have been more fatigued, resulting in poorer PASAT performance). Furthermore, whether individuals were taking

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medications that may have influenced their cognitive processing or levels of fatigue was also not considered at present. There is the potential that some medications, or some disease modifying therapies, may have resulted in improved processing speed on the PASAT for some individuals in each group, particularly those with relapsing–remitting MS.[39] A recent systematic review evaluating the cognitive efficacy of pharmacologic treatments for MS, however, suggests there is insufficient evidence for cognitive improvement at present given the contradictory findings in the literature.[40] Similarly, medications used to treat primary MS symptoms have the potential to also influence levels of fatigue. While some studies report no relationship between the use of immunosuppressive or immunomodulatory drugs and levels of fatigue,[41] others have reported an increase in fatigue levels, particularly with interferon – β, with improvements in fatigue being noted upon switching medications.[42,43] Given the potential influence of medications on both cognition and fatigue, and the inconsistent findings in the literature, a more thorough consideration of its impact on the present study's findings warrants future study, particularly given that little is known about the influence of medications on susceptibility to CF specifically.

Future studies should examine the associations between PASAT performance and CF scores in the context of a more inclusive statistical model accounting for other potential contributing factors to employment. For example, the current study did not exclude PwMS with depression, given the high rates of co-morbidity. Nonetheless, depression may have directly, or indirectly, impacted their cognition, their levels of CF, or their employment status. A more complex model could account for a greater proportion of the variance in employment status reported in the current investigation. Such a study could also allow for the examination of whether the relationship between cognition and employment status is bidirectional (i.e., does employment status also influence cognition?). In addition, future studies should also examine whether employment type has an impact on the association with employment status in PwMS given that certain jobs require a higher level IPS and working memory, factors that were found to be significantly associated with employment status. Accounting for employment type in future studies could help better understand the association between unemployment and PASAT performance scores. Future investigations should also evaluate if employment status is better associated with CF when CF is measured across time rather than within-task. Clinically, many individuals report that they do not necessarily experience the same level of CF when performing within-task CF tests, such as the PASAT, as they do following a full day of work. Having a more fined-grained analysis that takes into account different ways to measure and define CF may help to better our understanding of its association with employment status in PwMS.

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