Journal of the International Neuropsychological Society (2023), **29**, 283–289
doi:10.1017/S1355617722000157

Research Article

Slowing processing speed is associated with cognitive fatigue in newly diagnosed multiple sclerosis patients

Marco Pitteri[1], Caterina Dapor[1], John DeLuca[2,3,4], Nancy D. Chiaravalloti[3,5], Damiano Marastoni[1] and Massimiliano Calabrese[1]

[1]Neurology Section, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy, [2]Kessler Foundation, West Orange, NJ, USA, [3]Department of Physical Medicine and Rehabilitation, Rutgers, New Jersey Medical School, Newark, NJ, USA, [4]Department of Neurology, Rutgers, New Jersey Medical School, Newark, NJ, USA and [5]Neuropsychology and Neuroscience Lab, Kessler Foundation, East Hanover, NJ, USA

Abstract

Objective: To further investigate objective measures of cognitive fatigue (CF), defined as the inability to sustain performance over time, in newly diagnosed multiple sclerosis (MS) patients, by conducting a performance analysis on the Paced Auditory Serial Addition Test (PASAT) based on the type of errors (omissions *vs.* incorrect responses) committed. **Method:** Sixty-two newly diagnosed patients with MS (pwMS) and 41 healthy controls (HC) completed the PASAT. Analysis of the change in performance during the test was performed by comparing the number of correct responses, incorrect responses, and omissions in the 1st versus the 3rd tertile of the PASAT. **Results:** A significant decline in accuracy over time was observed to be related to an increment in the number of omissions, significantly more pronounced in pwMS than in HC. No change in the number of incorrect responses throughout the PASAT was observed for either group. **Conclusions:** CF can be detected even in newly diagnosed pwMS and might objectively manifest as a progressive increase in omissions during a sustained highly demanding task (i.e., PASAT). This pattern may reflect slowed processing speed and increased fatigue in pwMS. Focusing on omissions on the PASAT instead of correct responses only may improve its specificity as an objective measure of CF.

Keywords: multiple sclerosis; fatigue; cognition; processing speed; PASAT; SDMT

(Received 19 May 2021; final revision 26 January 2022; accepted 14 February 2022; First Published online 25 April 2022)

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system resulting in demyelination, neurodegeneration, and axonal injury (Lassmann, 2018). Among the heterogeneous symptoms that characterize MS, fatigue is one of the most frequently reported, affecting up to 90% of people with MS (pwMS; (Induruwa et al., 2012; Marchesi et al., 2020). Fatigue is among the main causes of reduced quality of life in pwMS, interfering with occupational status and participation in everyday life activities (Gullo et al., 2019; Strober & Arnett, 2005). Nonetheless, fatigue in MS remains poorly understood and often under-emphasized due to a lack of consensus over its exact definition, accurate quantification, and etiology (Calabrese & Pitteri, 2018).

Both structural and functional abnormalities of brain areas and networks have been evidenced as possible neural underpinnings of fatigue, and it has been consistently reported that MS-related fatigue is linked to a dysfunction of cortico-subcortical networks, mainly involving the basal ganglia and the fronto-parietal areas (Bakirtzis et al., 2020; Calabrese & Pitteri, 2018; Cercignani et al., 2021; Chen et al., 2020; Chen, Wylie, et al., 2020; Genova et al., 2013).

It has long been known that there are at least two main dimensions of fatigue: (1) subjective perception of fatigue; and (2) fatigability, that is, the dimension reflected in an objective change in performance over time (Kluger et al., 2013). Furthermore, fatigue affects both motor and mental activities, as such distinct physical and cognitive fatigue (CF) have been identified (Calabrese & Pitteri, 2018; Induruwa et al., 2012).

The assessment of CF has relied predominantly on self-report measures, which come with considerable limitations, including their subjective nature, the lack of an appropriate definition, and their susceptibility to recall biases (Cohen et al., 2000; DeLuca, 2005b). In an attempt to overcome such limitations, several objective measures of CF have been proposed (Calabrese & Pitteri, 2018; Linnhoff et al., 2019). One of the firstly proposed involved the repeated administration of neuropsychological tests batteries, with cognitively demanding tasks performed in between. The rationale behind this approach is that poorer performance observed on the repeated neuropsychological testing might be due to CF induced by

Corresponding authors: Marco Pitteri, email: marco.pitteri@nhs.net; Massimiliano Calabrese, email: massimiliano.calabrese@univr.it
Marco Pitteri and Caterina Dapor equally contributed to the present work

Cite this article: Pitteri M., Dapor C., DeLuca J., Chiaravalloti N.D., Marastoni D., & Calabrese M. (2023) Slowing processing speed is associated with cognitive fatigue in newly diagnosed multiple sclerosis patients. *Journal of the International Neuropsychological Society*, **29**: 283–289, https://doi.org/10.1017/S1355617722000157

mental exertion during the intervening cognitively demanding tasks (e.g., (DeLuca, 2005a; Krupp & Elkins, 2000)). Another approach was to objectively measure CF as a change in performance during sustained and highly demanding cognitive tasks (Bruce et al., 2010; Bryant et al., 2004; Morrow et al., 2015; Schwid et al., 2003). Accordingly, among other measures, the Paced Auditory Serial Addition Test (PASAT) has been used to objectively measure CF in pwMS (Berard et al., 2018; Bryant et al., 2004; Morrow et al., 2015; Schwid et al., 2003; Walker et al., 2012). In fact, the PASAT is a multicomponent task of information processing speed, working memory, short-term memory, calculation, and sustained attention, which makes it a useful, highly demanding task to capture CF.

The sensitivity of the PASAT in detecting CF may depend on the scoring methods applied (Walker et al., 2012). For instance, some authors have examined the number of correct responses comparing the first versus the last part of the test (Morrow et al., 2015; Schwid et al., 2003), while others have used a dyad system thought to be more sensitive to CF (Berard et al., 2018; Bryant et al., 2004). Both of these methods, however, consider only correct responses as the dependent variable, leaving question as to the nature of the errors committed. In fact, subjects can fail to give the correct response for two main reasons: (1) they give the wrong answer (incorrect response); or (2) they cannot provide an answer on time (omission). Disentangling the type of failure might offer valuable information regarding the nature of the underlying cognitive process involved. We hypothesize that an incorrect answer might be more related to an impairment in the calculation process and/or working memory; by contrast, the inability to provide an answer within a given timeframe (i.e., omission) may be more related to a core deficit in processing speed, which likely underlies CF itself (Bruce et al., 2010; Demaree et al., 1999).

The aim of the present study was to increase the sensitivity of an objective measure of CF in a group of newly diagnosed pwMS by examining omissions in performance. CF was operationalized as the inability to sustain performance throughout a continuous, highly demanding cognitive task (i.e., PASAT) as previously proposed by others (e.g., (Berard et al., 2018; Bryant et al., 2004; Morrow et al., 2015; Schwid et al., 2003; Walker et al., 2012). To address this aim, we analyzed PASAT performance focusing on the type of error committed, distinguishing between incorrect responses and omissions. We hypothesized that CF would result in an increment in the number of omissions, rather than incorrect responses, from the beginning to the end of the PASAT.

Methods

Study sample

Sixty-two newly diagnosed relapsing remitting (RR) pwMS were recruited at the MS Centre of the Verona University Hospital (Verona, Italy). Inclusion criteria for pwMS were diagnosis of RRMS (Polman et al., 2011), no concomitant neurological disorders (other than MS) or other pathological health conditions, nor substance abuse. Physical disability was measured with the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). At the time of neuropsychological testing, 35 pwMS were not treated with specific disease modifying therapy for MS, whereas 19 were treated with dimethyl fumarate, 2 with fingolimod, 2 with ocrelizumab, 1 with natalizumab, 1 with interferon beta1-a, 1 with peg-interferon beta1-a, and 1 with glatiramer acetate.

A group of 41 healthy controls (HC) was also recruited. Inclusion criteria for HC were absence of neurologic, psychiatric, or other pathologic health conditions, and substance abuse.

The study was completed in accordance with the Helsinki Declaration and was approved by the local Ethics Committee; all participants provided written informed consent.

Neuropsychological measures

As part of a more comprehensive neuropsychological examination consisting of the Brief Repeatable Battery (BRB) of neuropsychological tests (Amato et al., 2006), data derived from the PASAT and the Symbol Digit Modalities Test (SDMT) were available for both HC and pwMS.

The PASAT

While the BRB contains two versions of the PASAT (the PASAT-3 and the PASAT-2), in the present study only data derived from the PASAT-3 was utilized; the PASAT-2 was not examined because data was not available for several participants who refused to continue with PASAT testing due to the difficulty of the just-completed PASAT-3, reporting the test to be highly demanding and stressful.

Participants were given a single administration of the PASAT, according to standardized procedures. Sixty single digits were auditorily presented at a fixed rate of 3 seconds via audiotape. Participants were asked to add each newly presented digit to the one immediately before it, and to say the answer out loud before a new digit was presented. The final score was the total number of correct responses obtained in the 60 items.

For the purpose of the present study, we divided the PASAT into tertiles, each comprising 20 items. Each tertile was scored with the number of correct responses, the number of incorrect responses (i.e., wrong answer given), and the number of omissions (i.e., not answering within the 3-s interstimulus interval). To obtain a measure of the degree of change in performance during the task, we calculated the difference between the performance in the 1st tertile and the 3rd tertile for each dependent variable, thus computing three indices: (1) difference of correct responses (Δ-CR index); (2) difference of incorrect responses (Δ-IR index); and (3) difference of omissions (Δ-OM index). To calculate the Δ-CR index, we subtracted the number of correct responses given in the 1st tertile with that obtained in the 3rd tertile: the greater the number, the greater the decrement in performance over time. To be consistent with this measure, to calculate the Δ-IR and the Δ-OM indices, we subtracted the number of incorrect responses and omissions obtained in the 3rd tertile with that obtained in the 1st tertile, respectively.

The SDMT

The SDMT is a test of processing speed; patients were presented with a series of nine symbols, each of which paired with a single digit (1 to 9) according to a reference table placed at the top of the sheet. A pseudo-randomized sequence of the symbols was presented as a matrix table to the patient, who was instructed to verbally respond, as fast as possible, with the digit associated with each symbol. The final score was the total number of correct responses provided within 90 seconds.

The modified fatigue impact scale (MFIS)

PwMS were also administered the Modified Fatigue Impact Scale (MFIS), a modified form of the Fatigue Impact Scale

https://doi.org/10.1017/S1355617722000157 Published online by Cambridge University Press

Table 1. Demographic and clinical characteristics of pwMS and HC groups

	pwMS ($n = 62$)	HC ($n = 41$)	p value
Education (years)	14.4 ± 3.2	15.8 ± 3	p = 0.04
Age (years)	36.7 ± 10.6	33.8 ± 9.8	p = 0.17
Gender (M/F)	17/45	15/26	p = 0.32
EDSS	1.5 (0–3.5)	/	/
Disease duration (years)	0.6 ± 1.1	/	/

EDSS = expanded disability status scale; HC = healthy controls; *M* = mean; pwMS = people with multiple sclerosis; *SD* = standard deviation.
Means ± *SD* were provided for continuous variables.
Median (range) was provided for EDSS.

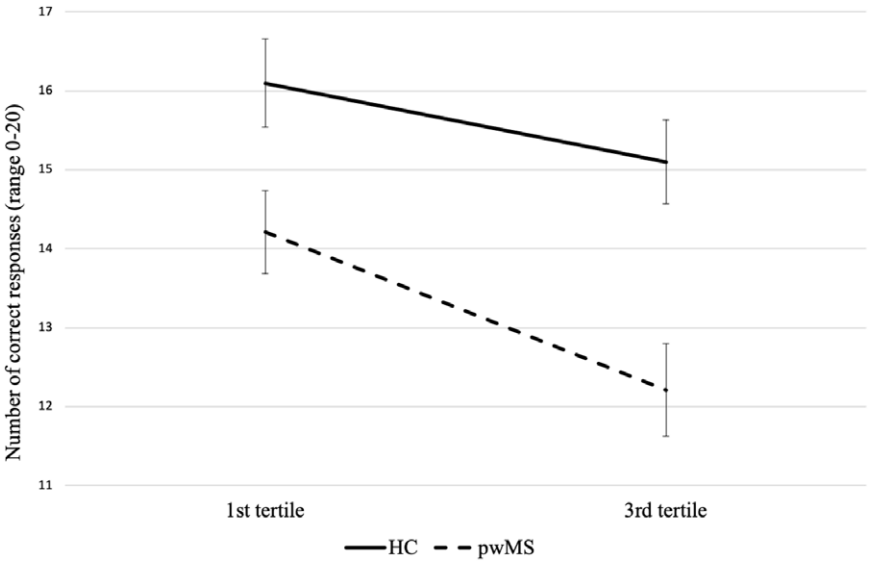

Figure 1. Change in the number of correct responses between the 1st and 3rd tertile of the PASAT. HC = healthy controls; pwMS = people with multiple sclerosis. The error bars indicate the standard error of the mean (SEM).

(Fisk et al., 1994) based on items derived from interviews with pwMS concerning how fatigue impact their lives. The instrument provides an assessment of the effect of fatigue in terms of physical, cognitive, and psychosocial functioning.

Statistical analyses

Demographic characteristics

Group differences on demographic characteristics were evaluated with independent sample *t*-tests (age and education) and the Chi-square test (gender).

Performance on the PASAT

To investigate the change in performance over time on the PASAT, three mixed-design repeated measures ANCOVAs, with age and education as covariates, were performed with *Group* (pwMS *vs.* HC) as the between-subjects variable, and *Tertile* (1st tertile *vs.* 3rd tertile) as the repeated measures variable; the total number of correct responses, incorrect responses, and omissions served as dependent variables. Post hoc analyses with Holm–Bonferroni correction were used to further investigate the significant interactions.

Correlation analyses

To examine the association between the CF indices (Δ-CR, Δ-IR, Δ-OM) and processing speed capacity as assessed with the SDMT, Pearson or Spearman correlation analyses were performed. Furthermore, in the pwMS group, Spearman correlation analyses between the MFIS scores (i.e., physical, cognitive, psychosocial subscales, and MFIS total score) and the CF indices (i.e., Δ-CR, Δ-IR, Δ-OM) derived from the PASAT were performed to examine the association between subjective and objective measures of CF.

All numerical values are reported as mean ± standard deviation ($M \pm SD$). Effect sizes were calculated with partial eta-square (small .01; medium .06; large .14). The statistical analyses were run with the JASP software (Version 0.9.0.1; JASP Team, 2019).

Results

Demographic and clinical characteristics

Demographic and clinical data of the studied populations are reported in Table 1. ANCOVAs were performed including education as covariate to control for this possible confounding factor. Despite the lack of difference between the groups on age, all analyses were also controlled for age due to the high variance observed.

Correct responses on the PASAT

The number of correct responses progressively decreased during the test in both HC (1st tertile: 16.1 ± 3.6; 3rd tertile: 15.1 ± 3.4; mean of -1 correct response) and pwMS (1st tertile: 14.2 ± 4.1; 3rd tertile: 12.2 ± 4.6; mean of -2 correct responses), $F(1,99) = 11.100$, $p = .001$, $\eta^2_p = .10$. Overall, the HC group emitted more correct responses than the MS group, $F(1,99) = 6.178$,

https://doi.org/10.1017/S1355617722000157 Published online by Cambridge University Press

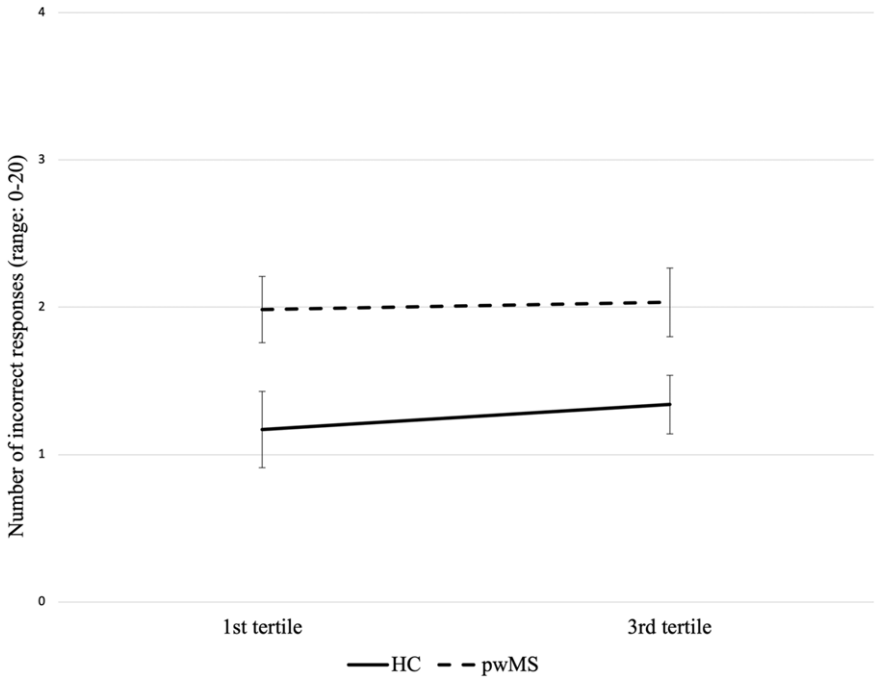

Figure 2. Change in the number of incorrect responses between the 1st and 3rd tertile of the PASAT. HC = healthy controls; pwMS = people with multiple sclerosis. The error bars indicate the standard error of the mean (SEM).

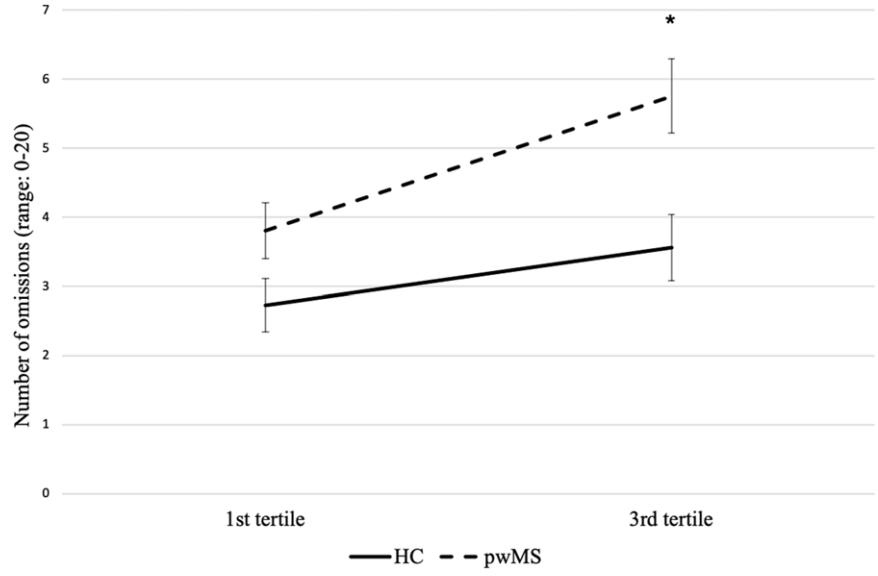

Figure 3. Change in the number of omissions between the 1st and 3rd tertile of the PASAT. HC = healthy controls; pwMS = people with multiple sclerosis. The error bars indicate the standard error of the mean (SEM). *$p < .05$.

$p = .015$, $\eta^2_p = .06$. The *Tertile* * *Group* interaction was not significant, $F(1, 99) = 3.205$, $p = .08$, $\eta^2_p = .03$ (Figure 1).

Incorrect responses on the PASAT

The mixed-design repeated measures ANCOVA on incorrect responses revealed that no significant change in the number of incorrect responses over time occurred in either pwMS (1st tertile: 2 ± 1.8; 3rd tertile: 2 ± 1.8; mean of $+ 0.05$ incorrect responses) or HC (1st tertile: 1.2 ± 1.7; 3rd tertile: 1.3 ± 1.3; mean of $+ 0.17$ incorrect responses), $F(1,99) = .094$, $p = 0.8$, $\eta^2_p < .001$. The mean number of incorrect responses overall was greater in the MS group than in the HC group ($F(1,99) = 4.618$, $p = 0.03$, $\eta^2_p = .05$). There was no significant change in the number of incorrect responses over time in either group, $F(1,99) = .182$, $p = .7$, $\eta^2_p = .002$ (Figure 2).

Omissions on the PASAT

The number of omissions increased over time in both the HC (1st tertile: 2.7 ± 2.5; 3rd tertile: 3.6 ± 3.0; mean of $+0.8$ omissions) and MS groups (1st tertile: 3.8 ± 3.2; 3rd tertile: 5.8 ± 4.3; mean of $+2$ omissions), $F(1,99) = 13.194$, $p < .001$, $\eta^2_p = .12$. On average, the MS group showed more omissions (9.6 ± 7) than the HC group (6.3 ± 5.1), $F(1,99) = 3.776$, $p = .05$, $\eta^2_p = .04$. Interestingly, the *Tertile* * *Group* interaction was significant: the increased omissions over time was significantly more pronounced in pwMS than in HC, $F(1,99) = 5.750$, $p = .02$, $\eta^2_p = 0.06$ (Figure 3). Post hoc analyses

https://doi.org/10.1017/S1355617722000157 Published online by Cambridge University Press

with Holm–Bonferroni correction showed that the two groups did not differ in the number of omissions at the beginning of the PASAT ($p = .76$), but they did differ in the number of omissions at the end of the test ($p = .03$).

CF indices, the SDMT, and the MFIS

The SDMT correlated with the Δ-OM index ($rho = -.24$; $p = .03$); by contrast, the SDMT did not significantly correlate with either the Δ-CR and the Δ-IR indices (all $p_s > .05$).

The MFIS cognitive subscale correlated with both the Δ-CR ($rho = .35$; $p = .05$) and the Δ-OM ($rho = .36$; $p = .05$) indices. No other significant correlations were found (all $p_s > .05$).

Discussion

The present study further investigated objective measures of CF in a group of newly diagnosed pwMS, by conducting an analysis of PASAT performance, focused on the type of error (incorrect response *vs.* omission) committed. As previously reported in works by others, objective CF was operationalized as the inability to sustain performance throughout a highly demanding cognitive task (i.e., PASAT) (Berard et al., 2018; Bryant et al., 2004; Morrow et al., 2015; Schwid et al., 2003; Walker et al., 2012). Accordingly, the present results offer further evidence that the PASAT is a reliable objective measure of CF, highlighting that a focus on omissions committed by pwMS may improve its specificity as objective measure of CF.

The present results showed an increase in the number of omissions over time in both HC and MS groups. However, the change in omissions was significantly more pronounced in the MS group (mean of +2 omissions) than in the HC group (mean of +0.8 omissions). By contrast, no change in the number of incorrect responses was observed for either group.

One potential explanation for the more pronounced increment in omissions (Δ-OM index) in the MS group compared to the HC group may be attributed to slowed processing speed in pwMS. Omissions, in contrast to incorrect responses, may reflect the failure to provide a response in the time allotted during the task, which may be a result of the slowed speed of processing in pwMS (Demaree et al., 1999). Alternatively, one might argue that increased omissions may be a result of cognitive processes other than processing speed, such as reduced working memory capacity. This is unlikely since it has been shown that working memory is relatively intact in RRMS, but significant processing speed impairments are evident (DeLuca et al, 2004). Support for the slowed processing speed hypothesis is provided by the significant negative correlation we found between the SDMT and Δ-OM index: the lower the processing speed capacity (SDMT), the higher the increment in the number of omissions over time (Δ-OM index). Interestingly, the SDMT significantly correlated with the Δ-OM index only, suggesting that a focus on the change in omissions, instead of correct and incorrect responses, allows one to capture the progressive slowing speed that might be related to CF in pwMS.

The results of the present study are consistent with other studies which have also shown a higher number of omissions on the PASAT in pwMS compared to HC. For instance, Solari et al. (2007) found differences between pwMS and HC in terms of correct responses and dyads, but not of wrong responses, thus concluding that differences between the two groups were due to more omissions in pwMS, which the authors interpreted as both reduced processing speed and "alternate-answer strategy" (Solari et al., 2007). Nevertheless, to the best of our knowledge, the current study is the first that focused on PASAT omissions specifically to infer CF in pwMS.

We were guided by the hypothesis that, on a behavioral level, the abnormal brain activity which underlies the feeling of CF may manifest itself as slowed processing speed. Indeed, in pwMS additional neural recruitment during complex cognitive tasks (e.g., the PASAT) has been observed and interpreted as a compensation mechanism to maintain adequate cognitive functioning despite brain damage (for a review see (Mollison et al., 2017)). The increased brain activation, acting within slowed myelin conduction, is likely one mechanism for the slower pace of processing and more rapid depletion of resources over time that might lead to the feeling of CF (Calabrese & Pitteri, 2018; Chen, Wylie, et al., 2020; Sandry et al., 2015).

The link between processing speed and CF has already been proposed by other authors (Andreasen et al., 2010; Bruce et al., 2010; DeLuca et al., 2004; Kluckow et al., 2016; Neumann et al., 2014; Penner et al., 2009; Tommasin et al., 2020; Wilting et al., 2016). Performance on the PASAT is indeed highly dependent on processing speed, considering that only a limited amount of time is given to process the information and answer before the next digit is presented (DeLuca et al., 2004; Demaree et al., 1999; Salthouse, 1996; Tombaugh, 2006). In the present study, we found a decrement in the number of correct responses from the beginning to the end of the PASAT in both HC and pwMS groups. Crucially, the change in correct responses did not significantly differ between the two groups, suggesting that a focus limited to correct responses would not have allowed detecting higher susceptibility to CF in pwMS compared to HC. Overall, the present results suggest that focusing on the nature of errors committed on the PASAT (incorrect responses *vs.* omissions) might be more sensitive to detect objective CF than looking at correct responses alone, as previously reported (e.g., Morrow et al., 2015; Schwid et al., 2003).

Additional support for the usefulness of our approach focused on change in omissions derives from the observation that the Δ-OM index allowed to capture objective CF in a group of newly diagnosed pwMS, with a mean disease duration of less than one year (0.6 ± 1.1 years). Indeed, even though other studies have found CF in the early stages of MS (e.g., Berard et al., 2018; Walker et al., 2012; Wilting et al., 2016), this is the first evidence of the presence of objective CF in pwMS with such a short disease duration. For instance, both Berard et al. (2018) and Walker et al. (2012) focused on pwMS with a mean disease duration of 4.35 ± 3.09 years, while the study of Wilting et al. (2016) was focused on pwMS with a disease duration up to ten years (median 2; range 0–10) (Wilting et al., 2016).

Finally, we found a moderate correlation between subjective and objective measures of fatigue, as the MFIS cognitive subscale correlated with the objective CF indices Δ-CR and Δ-OM ($p = .05$). While some studies have found mild correlations between subjective and objective fatigue (Bruce et al., 2010; Cehelyk et al., 2019; Loy et al., 2017; Morrow et al., 2015), to date the most accepted position highlights a dissociation between the two constructs, suggesting that objective and subjective fatigue might be actually independent (Bailey et al., 2007; Bakirtzis et al., 2020; DeLuca, 2005b; Paul et al., 1998; Sandry et al., 2015). Examining omissions rather than correct responses may lead to a more consistent relationship between objective and subjective measures of CF.

The current study is not free from limitations. First, we did not control for psychological factors, such as depression and anxiety,

https://doi.org/10.1017/S1355617722000157 Published online by Cambridge University Press

which may interact in the generation of CF in pwMS (e.g., see Strober & Arnett, 2005). Secondly, it has been argued that other disease-related issues (e.g., pharmacological treatment, disease stage, disease progression, level of physical disability) might exert a role on CF; as such, future studies should further investigate the contribution of these variables. Thirdly, the CF Δ-OM index should be validated in a larger and more representative sample of pwMS; due to the restricted size of our HC sample, we were not able to reliably calculate cut-off scores and clinical interpretation would benefit from the establishment of such scores in future studies. Importantly, future studies should better investigate the cognitive processes involved in the generation of omissions, for which the processing speed hypothesis may be just one. Lastly, important information might be derived from a more detailed analysis of the PASAT performance by differentiating between true omissions (i.e., not providing any answer at all) and late correct responses (i.e., correct sums provided after the 3-s time limit), which we argue might be better attributable to a *pure* processing speed deficit.

To conclude, CF can be detected even in newly diagnosed pwMS and might objectively manifest as an increasing number of omissions over time, resulting in progressive slowness in processing speed during a sustained, highly demanding cognitive task (i.e., the PASAT). When interpreting performance of pwMS on the PASAT, it would be important to take into account not only the number of correct responses but also the number of omissions, as these could be the core element suggestive of CF.

Author contributions. M.P. conceived the study. M.P. and C.D. contributed to the study design. M.P., C.D., D.M., and M.C. collected the data. C.D. performed data curation and data analysis. M.P. and C.D. worked on the original draft preparation. M.P., C.D., J.DL., and N.D.C. contributed to interpretation of results and to reviewing and editing the original draft. M.P. and M.C. supervised the study. All authors have read and agreed to the published version of the manuscript.

Funding statement. None.

Conflicts of interest. John DeLuca has served on advisory boards and/or as a consultant for Novartis, Biogen, Roche, and Celgene. He has received honoraria for speaking from Biogen. Nancy Chiaravalloti has served on advisory boards and/or as a consultant for Roche and Akili Interactive. Massimiliano Calabrese has served on scientific advisory boards and has received funding for travel or honoraria for speaking from Biogen, Merck-Serono, Roche, Novartis, and Sanofi Genzyme.

References

Amato, M. P., Portaccio, E., Goretti, B., Zipoli, V., Ricchiuti, L., De Caro, M. F., Patti, F., Vecchio, R., Sorbi, S., & Trojano, M. (2006). The Rao's brief repeatable battery and Stroop test: normative values with age, education and gender corrections in an Italian population. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *12*, 787–793. https://doi.org/10.1177/1352458506070933

Andreasen, A. K., Spliid, P. E., Andersen, H., & Jakobsen, J. (2010). Fatigue and processing speed are related in multiple sclerosis. *European Journal of Neurology*, *17*, 212–218. https://doi.org/10.1111/j.1468-1331.2009.02776.x

Bailey, A., Channon, S., & Beaumont, J. G. (2007). The relationship between subjective fatigue and cognitive fatigue in advanced multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *13*, 73–80. https://doi.org/10.1177/1352458506071162

Bakirtzis, C., Nikolaidis, I., Boziki, M. K., Artemiadis, A., Andravizou, A., Messinis, L., Ioannidis, P., & Grigoriadis, N. (2020). Cognitive fatigability is independent of subjective cognitive fatigue and mood in multiple sclerosis. *Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology*, *33*, 113–121. https://doi.org/10.1097/WNN.0000000000000228

Berard, J. A., Smith, A. M., & Walker, L. A. S. (2018). A longitudinal evaluation of cognitive fatigue on a task of sustained attention in early relapsing-remitting multiple sclerosis. *International Journal of MS Care*, *20*, 55–61. https://doi.org/10.7224/1537-2073.2016-106

Bruce, J. M., Bruce, A. S., & Arnett, P. A. (2010). Response variability is associated with self-reported cognitive fatigue in multiple sclerosis. *Neuropsychology*, *24*, 77–83. https://doi.org/10.1037/a0015046

Bryant, D., Chiaravalloti, N. D., & DeLuca, J. (2004). Objective measurement of cognitive fatigue in multiple sclerosis. *Rehabilitation Psychology*, *49*, 114–122. https://doi.org/10.1037/0090-5550.49.2.114

Calabrese, M., & Pitteri, M. (2018). Cognition and fatigue in multiple sclerosis. In J. DeLuca & B. M. Sandroff (Eds.), *Cognition and behavior in multiple sclerosis* (pp. 127–148). American Psychological Association.

Cehelyk, E. K., Harvey, D. Y., Grubb, M. L., Jalel, R., El-Sibai, M. S., Markowitz, C. E., Berger, J. R., Hamilton, R. H., & Chahin, S. (2019). Uncovering the association between fatigue and fatigability in multiple sclerosis using cognitive control. *Multiple Sclerosis and Related Disorders*, *27*, 269–275. https://doi.org/10.1016/j.msard.2018.10.112

Cercignani, M., Dipasquale, O., Bogdan, I., Carandini, T., Scott, J., Rashid, W., Sabri, O., Hesse, S., Rullmann, M., Lopiano, L., Veronese, M., Martins, D., & Bozzali, M. (2021). Cognitive fatigue in multiple sclerosis is associated with alterations in the functional connectivity of monoamine circuits. *Brain Communications*, *3*, fcab023. https://doi.org/10.1093/braincomms/fcab023

Chen, M. H., Deluca, J., Genova, H. M., Yao, B., & Wylie, G. R. (2020). Cognitive fatigue is associated with altered functional connectivity in interoceptive and reward pathways in multiple sclerosis. *Diagnostics*, *10*, 1–22. https://doi.org/10.3390/diagnostics10110930

Chen, M. H., Wylie, G. R., Sandroff, B. M., Dacosta-Aguayo, R., DeLuca, J., & Genova, H. M. (2020). Neural mechanisms underlying state mental fatigue in multiple sclerosis: a pilot study. *Journal of Neurology*, *267*, 2372–2382. https://doi.org/10.1007/s00415-020-09853-w

Cohen, J. A., Fischer, J. S., Bolibrush, D. M., Jak, A. J., Kniker, J. E., Mertz, L. A., Skaramagas, T. T., & Cutter, G. R. (2000). Intrarater and interrater reliability of the MS functional composite outcome measure. *Neurology*, *54*, 802–806. https://doi.org/10.1212/wnl.54.4.802

DeLuca, J. (2005a). Fatigue, cognition, and mental effort. In J. DeLuca (Ed.), *Fatigue as a window to the brain* (pp. 37–58). MIT Press.

DeLuca, J. (2005b). Fatigue: its definition, its study, and its future. In J. DeLuca (Ed.), *Fatigue as a window to the brain* (pp. 37–58). MIT Press.

DeLuca, J., Chelune, G. J., Tulsky, D. S., Lengenfelder, J., & Chiaravalloti, N. D. (2004). Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *Journal of Clinical and Experimental Neuropsychology*, *26*, 550–562. https://doi.org/10.1080/13803390490496641

Demaree, H. A., DeLuca, J., Gaudino, E. A., & Diamond, B. J. (1999). Speed of information processing as a key deficit in multiple sclerosis: implications for rehabilitation. *Journal of Neurology Neurosurgery and Psychiatry*, *67*, 661–663. https://doi.org/10.1136/jnnp.67.5.661

Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., & Schlech, W. F. (1994). Measuring the functional impact of fatigue: initial validation of the fatigue impact scale *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *18*, S79–S83. https://doi.org/10.1093/clinids/18.supplement_1.s79

Genova, H. M., Rajagopalan, V., Deluca, J., Das, A., Binder, A., Arjunan, A., Chiaravalloti, N., & Wylie, G. (2013). Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging. *PLoS ONE*, *8*, e78811. https://doi.org/10.1371/journal.pone.0078811

Gullo, H. L., Fleming, J., Bennett, S., & Shum, D. H. K. (2019). Cognitive and physical fatigue are associated with distinct problems in daily functioning, role fulfilment, and quality of life in multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *31*, 118–123. https://doi.org/10.1016/j.msard.2019.03.024

Induruwa, I., Constantinescu, C. S., & Gran, B. (2012). Fatigue in multiple sclerosis – a brief review. *Journal of the Neurological Sciences*, *323*, 9–15. https://doi.org/10.1016/j.jns.2012.08.007

JASP Team. (2019). JASP (Version 0.9.0.1) [Computer software]. https://jasp-stats.org

Kluckow, S. W., Rehbein, J. G., Schwab, M., Witte, O. W., & Bublak, P. (2016). What you get from what you see: parametric assessment of visual processing capacity in multiple sclerosis and its relation to cognitive fatigue. *Cortex*, *83*, 167–180. https://doi.org/10.1016/j.cortex.2016.07.018

Kluger, B. M., Krupp, L. B., & Enoka, R. M. (2013). Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology*, *80*, 409–416. https://doi.org/10.1212/WNL.0b013e31827f07be

Krupp, L. B., & Elkins, L. E. (2000). Fatigue and declines in cognitive functioning in multiple sclerosis. *Neurology*, *55*, 934–939. https://doi.org/10.1212/WNL.55.7.934

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis. *Neurology*, *33*, 1444. https://doi.org/10.1212/wnl.33.11.1444

Lassmann, H. (2018). Multiple sclerosis pathology. *Cold Spring Harbor Perspectives in Medicine*, *8*, 1–15. https://doi.org/10.1101/cshperspect.a028936

Linnhoff, S., Fiene, M., Heinze, H. J., & Zaehle, T. (2019). Cognitive fatigue in multiple sclerosis: an objective approach to diagnosis and treatment by transcranial electrical stimulation. *Brain Sciences*, *9*, 1–23. https://doi.org/10.3390/brainsci9050100

Loy, B. D., Taylor, R. L., Fling, B. W., & Horak, F. B. (2017). Relationship between perceived fatigue and performance fatigability in people with multiple sclerosis: a systematic review and meta-analysis. *Journal of Psychosomatic Research*, *100*, 1–7. https://doi.org/10.1016/j.jpsychores.2017.06.017

Marchesi, O., Vizzino, C., Meani, A., Conti, L., Riccitelli, G. C., Preziosa, P., Filippi, M., & Rocca, M. A. (2020). Fatigue in multiple sclerosis patients with different clinical phenotypes: a clinical and magnetic resonance imaging study. *European Journal of Neurology*, *27*, 2549–2560. https://doi.org/10.1111/ene.14471

Mollison, D., Sellar, R., Bastin, M., Mollison, D., Chandran, S., Wardlaw, J., & Connick, P. (2017). The clinico-radiological paradox of cognitive function and MRI burden of white matter lesions in people with multiple sclerosis: a systematic review and meta-analysis. *PLoS ONE*, *12*, 1–16. https://doi.org/10.1371/journal.pone.0177727

Morrow, S. A., Rosehart, H., & Johnson, A. M. (2015). Diagnosis and quantification of cognitive fatigue in multiple sclerosis. *Cognitive and Behavioral Neurology : Official Journal of the Society for Behavioral and Cognitive Neurology*, *28*, 27–32. https://doi.org/10.1097/WNN.0000000000000050

Neumann, M., Sterr, A., Claros-Salinas, D., Gütler, R., Ulrich, R., & Dettmers, C. (2014). Modulation of alertness by sustained cognitive demand in MS as surrogate measure of fatigue and fatigability. *Journal of the Neurological Sciences*, *340*, 178–182. https://doi.org/10.1016/j.jns.2014.03.024

Paul, R. H., Beatty, W. W., Schneider, R., Blanco, C. R., & Hames, K. A. (1998). Cognitive and physical fatigue in multiple sclerosis: relations between self-report and objective performance. *Applied Neuropsychology*, *5*, 143–148. https://doi.org/10.1207/s15324826an0503_5

Penner, I. K., Raselli, C., Stöcklin, M., Opwis, K., Kappos, L., & Calabrese, P. (2009). The Fatigue scale for motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *15*, 1509–1517. https://doi.org/10.1177/1352458509348519

Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., Fujihara, K., Havrdova, E., Hutchinson, M., Kappos, L., Lublin, F. D., Montalban, X., O'Connor, P., Sandberg-Wollheim, M., Thompson, A. J., Waubant, E., Weinshenker, B., & Wolinsky, J. S. (2011). Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology*, *69*, 292–302. https://doi.org/10.1002/ana.22366

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*, 403–428. https://doi.org/10.1037/0033-295X.103.3.403

Sandry, J., Dobryakova, E., & Deluca, J. (2015). New research on cognitive fatigue in multiple sclerosis. *National Academy of Neuropsychology Bulletin*, *29*, 25–27.

Schwid, S. R., Tyler, C. M., Weinstein, A., Scheid, E. A., & Mcdermott, M. P. (2003). Cognitive fatigue during a test requiring sustained attention: a pilot study. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *2003*, 503–508.

Solari, A., Motta, A., Radice, D., & Mendozzi, L. (2007). A shortened version of PASAT-3 is feasible. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *13*, 1020–1025. https://doi.org/10.1177/1352458507077619

Strober, L. B., & Arnett, P. A. (2005). An examination of four models predicting fatigue in multiple sclerosis. *Archives of Clinical Neuropsychology*, *20*, 631–646. https://doi.org/10.1016/j.acn.2005.04.002

Tombaugh, T. N. (2006). A comprehensive review of the paced auditory serial addition test (PASAT). *Archives of Clinical Neuropsychology*, *21*, 53–76. https://doi.org/10.1016/j.acn.2005.07.006

Tommasin, S., De Luca, F., Ferrante, I., Gurreri, F., Castelli, L., Ruggieri, S., Prosperini, L., Pantano, P., Pozzilli, C., & De Giglio, L. (2020). Cognitive fatigability is a quantifiable distinct phenomenon in multiple sclerosis. *Journal of Neuropsychology*, *14*, 370–383. https://doi.org/10.1111/jnp.12197

Walker, L. A. S., Berard, J. A., Berrigan, L. I., Rees, L. M., & Freedman, M. S. (2012). Detecting cognitive fatigue in multiple sclerosis: method matters. *Journal of the Neurological Sciences*, *316*, 86–92. https://doi.org/10.1016/j.jns.2012.01.021

Wilting, J., Rolfsnes, H. O., Zimmermann, H., Behrens, M., Fleischer, V., Zipp, F., & Gröger, A. (2016). Structural correlates for fatigue in early relapsing remitting multiple sclerosis. *European Radiology*, *26*, 515–523. https://doi.org/10.1007/s00330-015-3857-2