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Poor Encoding and Weak Early Consolidation Underlie Memory Acquisition Deficits in Multiple Sclerosis: Retroactive Interference, Processing Speed, or Working Memory?

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Abstract

Objective: Learning and memory impairments are common in multiple sclerosis (MS) and may be related to difficulty acquiring (encoding or consolidating) new information. We evaluate the role of retroactive interference and investigate whether minimizing interference immediately following encoding (early during consolidation) will improve MS participants' ability to remember new verbal information. Additionally, we investigate processing speed differences between memory-impaired and unimpaired participants and present an exploratory analysis of how the dual-components of working memory (capacity vs. processing) relate to memory impairment.

Method: MS memory-unimpaired ($N = 12$) and MS memory-impaired participants ($N = 12$) were compared to healthy controls ($N = 15$). Interference onset following encoding (early, mid, late, no interference) was manipulated over the retention interval of a verbal learning and memory task. Response times (RT) were recorded during interference trials.

Results: MS memory-impaired participants encoded less information and lost proportionally more information over the retention interval (weak consolidation). Lengthening the onset of interference did not benefit memory performance in this sample. Memory performance was unrelated to RT but was related to performance on the Symbol Digit Modalities Test. Primary capacity of working memory did not differ across groups; however, secondary memory processing was reduced for MS memory-impaired participants.

Conclusion: Minimizing interference following encoding did not improve memory in this sample. Both initial encoding and early consolidation were reduced for memory-impaired MS participants. Evidence for a relationship between processing speed and memory was mixed and depended on the processing speed assessment used. Memory impairment in MS may be partially due to inefficient processing within working memory.

Keywords: Multiple sclerosis; Memory disorders; Memory consolidation; Learning; Processing speed; Working memory

Neural damage associated with multiple sclerosis (MS) often manifests in symptoms of neurocognitive impairment with some prevalence estimates of cognitive disability as high as 70% (Chiaravalloti & DeLuca, 2008). Learning and memory problems are a main concern among MS patients and one of the more commonly impaired cognitive domains (Benedict et al., 2006; Thornton & Raz, 1997). There has been some progress in developing effective memory rehabilitation treatments, however, the outcomes are largely mixed and there remains a strong need to continue to develop and test novel treatment approaches (das Nair, Marin, & Lincoln, 2016; Sandry, Akbar, Zuppichini, & DeLuca, 2016). One potentially effective strategy for developing new treatments is to target the specific impaired cognitive and neural processes that underlie memory impairment (Sandry, 2015). Given the demand for new treatment approaches, our primary aim for the present study was to better understand what underlies memory acquisition deficits in MS. Specifically, we sought to (1) evaluate whether retroactive interference negatively impacts memory acquisition and (2) determine whether minimizing retroactive interference will improve retention. Our secondary aim was to investigate whether slowed information processing speed is related to memory

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acquisition deficits in MS. Additionally, we present an exploratory analysis investigating how working memory is related to long-term memory impairment by quantifying and comparing the dual-components of working memory across groups. While both visual and verbal memory ability can be negatively impacted by MS (Benedict et al., 2006), the present study is restricted to verbal memory.

Memory Acquisition: Encoding & Consolidation

Early research identified poor free recall performance among MS patients while recognition memory remained intact and this was interpreted as a deficit in the ability to retrieve information (Rao, 1986; Rao, Leo, & Aubin-Faubert, 1989). More recent accounts characterize memory impairment in MS as difficulty acquiring (encoding or consolidating) new information. When MS participants were given multiple opportunities to learn new information, through selective reminding, their delayed recall performances improved and did not differ from that of a healthy control group (DeLuca, Barbieri-Berger, & Johnson, 1994) and this and similar findings have been replicated many times (DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998; DeLuca, Leavitt, Chiaravalloti, & Wylie, 2013; Demaree, Gaudino, DeLuca, & Ricker, 2000; Lafosse, Mitchell, Corboy, & Filley, 2013; Olivares et al., 2005). Importantly, heterogeneity in MS can lead to differing memory ability across disease subtypes (Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001). A recent meta-analysis across 47 studies reported lower overall global cognitive functioning and worse memory performance in progressive MS compared to relapsing remitting subtypes of the disease (Johnen et al., 2017). That same meta-analysis also concluded that the core memory impairment in MS was difficulty acquiring new information.

While these studies aimed at differentiating retrieval deficits from acquisition have established an important role for acquisition deficits in MS, they have not taken the next step and specified what about acquisition is impaired. That is, these investigations have not parsed *encoding* from *consolidation*. This may partially be a result of vague operational definitions of acquisition in the MS literature. Memory acquisition has been discussed as encoding, as well as encoding *plus* consolidation (Chiaravalloti, Balzano, Moore, & DeLuca, 2009; Markowitsch, 2000). While this confusion is not entirely specific to MS, our view of acquisition is congruent with the latter definition. Acquisition is a more general term that we use to describe the processes of *encoding* and *consolidation* [see also, Ricker (2015)]. There has not been much systematic research to begin to disentangle these mnemonic processes in MS.

The encoding process can be operationalized as information from the outside environment being effectively perceived by our senses and entering working memory. Encoding is followed by consolidation, which is a complex temporal process that involves the strengthening and stabilization of encoded information into a durable memory representation (Ricker, 2015). Neurobiological models of consolidation assume that consolidation can be broken down into two closely related neural subprocesses, cellular consolidation and systems consolidation.

Cellular consolidation is best understood in the context of cellular neuroscience and long-term potentiation at the molecular level of the synapse (Bliss & Lømo, 1973). Cellular consolidation is a stabilization process that occurs immediately after encoding, is thought to have a strong link to the hippocampus, and only lasts a few hours (Dewar, Cowan, & Della Sala, 2010; Genzel & Wixted, 2017; McGaugh, 2000; Wixted & Cai, 2013). Cellular consolidation is the intermediate step between initial encoding and systems consolidation. Neurobiological evidence suggests that cellular consolidation can be further reduced into early and late stages of long-term potentiation. Protein synthesis and postsynaptic changes might only occur during the late stage that requires an appropriate level of stimulation from the presynaptic neuron (Genzel & Wixted, 2017). Recent evidence for widely occurring synaptopathy in MS (Jürgens et al., 2016; Mandolesi et al., 2015) may imply these processes are impacted by the disease. Systems consolidation on the other hand is a longer process that follows and partially overlaps cellular consolidation and involves memory representations becoming independent of the hippocampus by further stabilizing into higher neocortical networks of the cortex (Dewar, Cowan, et al., 2010; Frankland & Bontempi, 2005; Genzel & Wixted, 2017; McGaugh, 2000; Wang & Morris, 2010; Wixted & Cai, 2013), more closely paralleling a long-term storage process. Given the current MS literature (described next), it may be that the hippocampally-dependent process of early cellular consolidation is partially responsible for memory acquisition deficits observed in this population and this may be a result of increased susceptibility to interference.

Hippocampal damage (Geurts et al., 2007; Papadopoulos et al., 2009; Roosendaal et al., 2008), including reductions in hippocampal synaptic density and changes in the glutamatergic system (Dutta et al., 2011), is common in MS. MS related hippocampal dysfunction (Hulst et al., 2015) as well as hippocampal damage is correlated with worse memory performance (Muhlert et al., 2014; Paulesu et al., 1996; Sicotte et al., 2008; Sumowski et al., 2016), including greater information loss during early consolidation (Kiy et al., 2011). Corroboratory evidence from experimental autoimmune encephalomyelitis animal models of MS revealed synaptic plasticity and long-term potentiation is impaired with early inflammation (Di Filippo et al.,

2013; Di Filippo et al., 2015) and also is related to impairments in learning and memory (Kim et al., 2012). Hippocampal sensitivity to MS disease processes may imply that the early process of cellular consolidation is disrupted in MS patients. Behaviorally, this may be because the hippocampus is sensitive to retroactive interference (Dewar, Cowan, et al., 2010; Kuhl, Shah, DuBrow, & Wagner, 2010). Thus, information loss during early consolidation, a memory process that largely depends on hippocampal functioning, may be a result of increased susceptibility to interference in MS.

Susceptibility to Retroactive Interference in MS

The process of memory consolidation is sensitive to retroactive interference (Postman & Underwood, 1973), which occurs when interfering information is introduced during the retention interval between initial encoding (immediate recall on a traditional clinical assessment of memory) and delayed test, that is, the early consolidation period. Retroactive interference can be compared with proactive interference that occurs when previously learned material impedes learning of new information. Traditional views of retroactive interference assume that disruptions to early consolidation result mainly from interference due to competition from similar information when learning new information, however this is not a requirement. Introducing new information, either *related* or *unrelated* to the to-be-learned material, immediately following encoding can negatively impact memory consolidation (Dewar, Cowan, & Della Sala, 2007; McGaugh, 2000; Wixted & Cai, 2013).

When evaluating interference effects in MS and using traditional neuropsychological verbal assessments, an interfering verbal list that follows learning trials more negatively affects MS participants memory compared to healthy controls (Rao, Hammeke, McQuillen, Khatri, & Lloyd, 1984) and accounts for 37% of the variance in delayed recall ability (long-term memory) (Griffiths et al., 2005). In some cases, MS participants show comparable retroactive interference effects to that of a healthy control group (Minden, Moes, Orav, Kaplan, & Reich, 1990). Other studies investigating interference effects in MS have used the Brown–Peterson paradigm (Brown, 1958; Peterson & Peterson, 1959), where learning a short list of words is followed by counting backwards by three's. Originally used to prevent rehearsal, counting introduces unrelated retroactive interference that can disrupt early consolidation. When comparing an unfilled delay interval (no interference) against a filled delay interval (interference; counting backwards) MS participants outperformed the healthy controls in the no interference condition (albeit by a small margin), however, they performed substantially worse than healthy controls in the interference condition (Grant, McDonald, Trimble, Smith & Reed, 1984; see also, Beatty et al. 1995; Johnson, DeLuca, Diamond & Natelson, 1998). In contrast, one study did not report a difference between MS participants and healthy controls on the Brown–Peterson paradigm (Rao et al., 1989).

Although there is mixed evidence, a considerable number of studies outlined above have reported that persons with MS exhibit increased susceptibility to retroactive interference compared to healthy controls (Beatty et al., 1995; Grant et al., 1984; Griffiths et al., 2005; Johnson et al., 1998; Rao et al., 1984) even when interference is semantically unrelated. The discrepancy between studies reporting a negative impact of interference and those that do not (Minden et al., 1990; Rao et al., 1989) may be partially due to heterogeneous memory performance across the MS samples tested. The reviewed MS studies were mainly designed to evaluate memory differences between MS participants and healthy controls and they did not selectively recruit participants with and without documented memory impairment. Susceptibility to retroactive interference early during the retention interval (during early consolidation) may be partially responsible for the observed memory deficit in MS patients.

In sum, the role of the hippocampus in early consolidation processes (Dewar, Cowan, et al., 2010; Frankland & Bontempi, 2005; McGaugh, 2000; Wang & Morris, 2010; Wixted & Cai, 2013) and hippocampal sensitivity to retroactive interference (Dewar, Cowan, et al., 2010; Kuhl et al., 2010), combined with evidence that MS disease pathology is related to both hippocampal damage (Dutta et al., 2011; Geurts et al., 2007; Kiy et al., 2011; Muhlert et al., 2014; Papadopoulos et al., 2009; Paulesu et al., 1996; Roosendaal et al., 2008; Sicotte et al., 2008; Sumowski et al., 2016) and MS patients exhibit increased susceptibility to retroactive interference (Beatty et al., 1995; Grant et al., 1984; Griffiths et al., 2005; Johnson et al., 1998; Rao et al., 1984) may identify a novel target for memory remediation. Specifically, strategies aimed at reducing susceptibility to retroactive interference during the early stages of memory consolidation may be one way to alleviate some memory difficulties in MS patients.

Minimizing Interference

One way to improve early consolidation and/or mitigate the degradation of newly formed memory representations is to follow initial encoding with a period of minimal interference, that is, a rest-filled delay (McGeoch & McDonald, 1931). Minimizing interference is an effective memory rehabilitation approach, with improved memory performance after a period of post-encoding rest, when retroactive interference is reduced (Dewar, Cowan, et al., 2010). Moreover, longer durations of

minimal interference result in better memory, similar to a dose-dependent effect (Dewar, Garcia, Cowan, & Della Sala, 2009). Minimal interference paradigms have been successfully applied to memory-impaired populations including patients with anterograde amnesia and mild cognitive impairment (Alber, Della Sala, & Dewar, 2014; Cowan, Beschin, & Della Sala, 2004; Della Sala, Cowan, Beschin, & Perini, 2005; Alber et al., 2014; Cowan et al., 2004; Della Sala et al., 2005; Dewar, Della Sala, Beschin, & Cowan, 2010; Dewar et al., 2009), patients with mild to moderate Alzheimer's Disease (Dewar, Pesallaccia, Cowan, Provinciali, & Della Sala, 2012) and healthy older adults (Dewar, Alber, Butler, Cowan, & Della Sala, 2012). The application of minimizing interference as a rehabilitation strategy has not been evaluated in MS. The primary aim of the present research is to evaluate how retroactive interference affects memory acquisition in MS and determine whether strategies designed to minimize retroactive interference will lead to improved memory acquisition.

Working Memory, Processing Speed, and Memory Impairment in MS

Learning and memory impairment is often co-morbid with other types of cognitive dysfunction and it is necessary to understand how other cognitive processes may contribute to acquisition deficits in this population. Two cognitive processes that are impaired (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004) and may contribute to memory impairment in MS are working memory and processing speed. Working memory is a cognitive system involved in the storage and processing (Baddeley, 2012; Baddeley & Hitch, 1974) of a limited amount of information (Cowan, 2005) while processing speed is the amount of time it takes to complete a mental operation (Costa, DeLuca, Sandroff, Goverover, & Chiaravalloti, 2017; Kail & Salthouse, 1994). (Information processing speed is sometimes used abstractly to refer to "mental capacity" or "cognitive efficiency/inefficiency" and this can result in confusion because these definitions are aspecific. That is, poor definitions may stifle research and clinical progress because abstract definitions cannot be used operationally to generate predictions or test hypotheses. In the present research, rather than use an amorphous definition, we appeal to the principle of parsimony by assuming and operationalizing slowing of information processing speed as slowing in the rate at which cognitive operations can be performed.) Slowing of information processing speed is common in MS (Archibald & Fisk, 2000; Costa, Genova, DeLuca, & Chiaravalloti, 2017; Litvan, Grafman, Vendrell, & Martinez, 1988) and observable in the both relapsing remitting and secondary progressive stages of the disease (DeLuca et al., 2004). Working memory impairments are more common in the secondary progressive stage (DeLuca et al., 2004), especially evident at high but not low cognitive loads (Lengenfelder, Chiaravalloti, Ricker, & DeLuca, 2003) and correlated with long-term memory impairment (delayed recall) (Sandry & Sumowski, 2014). There are conflicting findings in the literature when evaluating whether processing speed or working memory is the main cognitive deficit and how these cognitive processes relate to memory impairment in MS. Some evidence suggests that slowed information processing speed may underlie memory acquisition deficits (Chiaravalloti, Stojanovic-Radic, & DeLuca, 2013) while other evidence implicates working memory as the underlying cognitive factor (Berrigan et al., 2013).

Performance on the Paced Auditory Serial Addition Test (PASAT) was correlated with the amount of information recalled (Litvan et al., 1988) and with the total number of trials to reach criterion (an index of memory *acquisition*) (DeLuca et al., 1994). Other studies have reported a relationship between processing speed measured using the symbol digit modalities tests (SDMT) and immediate memory performance in MS (Olivares et al., 2005). The SDMT is often interpreted as a measure of processing speed and quite sensitive to cognitive change in MS (Benedict et al., 2017; Costa et al., 2017). A conceptual replication using alternate measures of processing speed rendered a similar relationship between processing speed and memory acquisition (Chiaravalloti et al., 2013). There is also a relationship between processing speed and the efficacy of memory rehabilitation in MS. Specifically, patients who exhibited slower processing speed (measured with the SDMT) exhibited less benefit from treatment (Chiaravalloti & DeLuca, 2015). While the authors of these studies interpret this as evidence for a relationship between processing speed and memory it is important to keep in mind that the PASAT is a non-specific assessment (Diehr, Heaton, Miller, & Grant, 1998; Lockwood, Linn, Szymanski, Coad, & Wack, 2004) that largely depends on executive attention and other cognitive resources and it should be considered at minimum a measure of working memory and processing speed (Tombaugh, 2006). Like the PASAT, the SDMT and similar coding tests tap into other cognitive resources beyond "processing speed", including visual scanning and memory (Joy, Fein, & Kaplan, 2003) and they may serve as a more general measures of cognition. The choice of measurement has clear interpretive implications for understanding the complex relationships between working memory, processing speed, and memory impairment in MS.

Not all processing speed tasks exhibit a relationship with memory. In other clinical populations, complex information processing speed (measured with a complex response time [RT] task) correlated with verbal and visuospatial memory but simple processing speed (measured with a perceptual RT task) did not correlate with memory performance (Chiaravalloti, Christodoulou, Demaree, & DeLuca, 2003). There is some corroboratory evidence for this dissociation in relapsing remitting MS. Specifically, complex processing speed correlated with some tests of immediate verbal and visual memory while simple

processing speed measures did not (Berrigan et al., 2013). If valid, the relationship between complex information processing speed and memory may be because both complex processing speed tasks and memory acquisition place a high demand on overlapping cognitive (e.g., working memory) and neural resources and this manifests as an indirect relationship between complex processing speed and memory. The secondary aim of the present research is to further investigate the relationship between processing speed and memory acquisition in MS.

Present Experiment

In the present quasi-experimental study, we investigated a number of related research questions. Primarily we are interested in how retroactive interference differs between MS participants with and without a priori defined memory impairment. On the basis of past research, we hypothesized that memory-impaired MS participants will be more susceptible to interference than memory-unimpaired MS participants and more susceptible to interference than healthy controls. Directly related to this research question, we are also interested in whether minimizing retroactive interference immediately following encoding will improve early consolidation in these participants. We hypothesized that the more time spent after encoding without interference will cause memory-impaired MS participants to better retain new information (a dose-dependent effect of interference onset whereby more time after encoding without interference will lead to stronger early consolidation into long-term memory). Additionally, because evidence suggests that cognitive slowing may be related to difficulty with memory, we evaluated the relationship between simple and complex processing speed and memory performance in these participants. Given there is some evidence supporting this relationship, if present, we expect to observe this relationship for complex processing speed but not for simple processing speed. We also present an exploratory analysis investigating how different components of working memory may relate to long-term memory impairment in MS.

Method

Participants

Twenty-four community dwelling MS participants without an exacerbation or current corticosteroid use within the previous 4 weeks, no learning disabilities, no history of serious psychiatric illness and no other neurologic conditions were identified and recruited from our research participant database. An additional 15 self-reported healthy control participants were recruited from the local community, through an online advertisement. All participants were fluent in English. Recent neuropsychological test scores were available for the MS participants ($M = 8.2$ months old) and used to calibrate recruitment to achieve balanced groups of memory-impaired ($N = 12$) and memory-unimpaired ($N = 12$) MS participants. Memory-impairment was operationalized a priori as delayed recall T-scores at or below the seventh percentile (1.5 standard deviations below the mean) on the Hopkins Verbal Learning Test – Revised (see Table 1 for disease characteristics).

Materials & Procedure

The materials and procedure closely followed Dewar and colleagues (2009). The experiment was run using e-prime 2.0 on a computer with a 21-in monitor positioned approximately 22 inches away from participants. Participants completed a total of four blocks, three experimental and one control. In each block participants were sequentially presented with a list of 15 standardized words (5 s each) (Snodgrass & Vanderwart, 1980) and asked to pay close attention, read each word aloud, and try and memorize each word (study phase). Verbal word stimuli were selected to be congruent with the design and stimulus parameters of Dewar and colleagues (2009) and used the most common name of each visual image. Presentation across semantic category was randomly intermixed for each participant. This was followed by an immediate recall task, then a 9-min retention interval and finally a delayed recall task. The main experimental manipulation occurred during the retention interval. Interference Onset (the amount of time before interference was introduced following initial encoding) was manipulated to begin either immediately, 3 min, or 6 min after the immediate recall task along with an unfilled retention interval (no interference control see Table 2). The four Interference Onset experimental blocks and four word lists were manipulated within participants using a 4×4 graeco-latin square design. Assignment to counterbalanced condition utilized pseudorandom assignment. Presentation order of the words within each list was randomized for each participant. Word stimuli consisted of monosyllabic nouns between four and five letters.

Table 1. Demographic (all participants) disease and neuropsychological performance (MS participants only)

	Healthy Control	Unimpaired	Impaired	Statistic (df)	*d*
		Demographic characteristics			
Age	45.94 (10.96)	53.5 (10.33)	50.92 (8.12)	$F(2, 36) = 2.04$	
Years Education	15.60 (2.80)	16.75 (2.31)	14.84 (2.37)	$F(2, 36) = 1.76$	
Percent Female	67%	83%	83%	$X^2(2) = 1.44$	
		MS disease characteristics			
RRMS/SPMS		10/2	11/1	$X^2(1)=.38$	
Years since diagnosis					
Disease duration		18.92 (7.85)	13.79 (6.01)	$t(22) = 1.81$	
		MS neuropsychological performance			
SDMT total		56.00 (6.93)	44.59 (10.14)	$t(22) = 3.23$**	1.34
PASAT 3 Second Version		47.89 (11.28)	38.40 (11.54)	$t(17) = 1.81$	
WTAR		40.82 (7.50)	38.37 (11.23)	$t(20) = 0.61$	
[WTAR Standard Score]		111.91 (11.09)	107.91 (17.07)	$t(20) = 0.66$	
HVLT-R Trial 1[a]		7.75 (2.06)	4.75 (1.14)	$t(17.2) = 4.44$***	1.89
[HVLT-R Trial 1 T-Score][a]		51.84 (11.14)	34.09 (6.60)	$t(17.9) = 4.76$***	2.01
HVLT-R Total Recall		28.59 (4.04)	19.75 (3.87)	$t(22) = 5.48$***	2.24
[HVLT-R Total Recall T-score]		52.42 (9.26)	30.25 (9.53)	$t(22) = 5.79$***	2.37
HVLT-R Delayed Recall		10.75 (1.36)	5.34 (2.02)	$t(22) = 7.73$***	3.22
[HVLT-R Delayed Recall T-score]		53.67 (6.87)	27.75 (5.74)	$t(22) = 10.04$***	4.12
BVMT-R Trial 1		6.82 (2.14)	4.00 (2.70)	$t(21) = 2.76$*	1.17
[BVMT-R Trial 1 T-Score]		55.10 (11.73)	40.59 (13.71)	$t(21) = 2.72$*	1.15
BVMT-R Total Recall		26.28 (5.45)	16.84 (8.66)	$t(21) = 3.10$**	1.34
[BVMT-R Total Recall T-score]		54.28 (12.05)	37.42 (14.62)	$t(21) = 3.01$**	1.27
BVMT-R Delayed Recall		9.91 (2.03)	6.09 (3.63)	$t(21) = 3.09$**	1.36
[BVMT-R Delayed Recall T-score]		55.64 (12.98)	37.50 (14.30)	$t(21) = 3.18$**	1.33
Digit Span Forward		11.00 (2.70)	9.75 (2.27)	$t(22) = 1.24$	
[Digit Span Forward Scaled Score]		11.09 (3.43)	9.42 (2.85)	$t(22) = 1.30$	
Digit Span Backwards		9.00 (2.70)	8.67 (3.18)	$t(22) = 0.28$	
[Digit Span Backwards Scaled Score]		10.42 (3.03)	9.92 (3.53)	$t(22) = 0.38$	
Digit Span Sequencing		9.17 (2.45)	7.59 (2.11)	$t(22) = 1.70$	
[Digit Span Sequencing Scaled Score]		11.09 (3.27)	9.00 (2.93)	$t(22) = 1.65$	
Digit Span Total		29.17 (6.05)	26.09 (5.70)	$t(22) = 1.29$	
[Digit Span Total Scaled Score]		11.09 (3.37)	9.50 (3.12)	$t(22) = 1.20$	

Data presented as mean (standard deviation). Phenotype: *RRMS* = Relapsing Remitting MS, *SPMS* = Secondary Progressive MS; *SDMT*=Symbol Digit Modalities Test total score; *PASAT*=Paced Auditory Serial Addition Test; *WTAR*= Wechsler Test of Adult Reading; *HVLT*-R=Hopkins Verbal Learning Test-Revised; BVMT-R=Brief Visuospatial Memory Test-Revised. Age/Education adjusted scores presented in brackets below corresponding test. $N = 3$ MS-Unimpaired & $N = 1$ MS-Impaired PASAT scores unavailable; $N = 1$ MS-Impaired & $N = 1$ MS-Unimpaired WTAR scores unavailable; $N = 1$ MS-Unimpaired BVMT-R score unavailable.

[a]Homogeneity of variance assumption violated & degrees of freedom adjusted.

<.01, *<.001. *d*=Cohen's *d* estimate of effect size presented only for significant effects.

Table 2. Example of experimental conditions and temporal location of interference onset manipulated within participants

Early	Mid	Late	Unfilled	seconds
Study Word List	Study Word List	Study Word List	Study Word List	82.5
Immediate Recall	Immediate Recall	Immediate Recall	Immediate Recall	120
Interference	Unfilled	Unfilled	Unfilled	180
Unfilled	*Interference*	Unfilled	Unfilled	180
Unfilled	Unfilled	*Interference*	Unfilled	180
Delayed Recall	Delayed Recall	Delayed Recall	Delayed Recall	120

Administration of conditions was counterbalanced across participants and across groups. The total length of the experiment was approximately 60 min including instructions. Early, Mid, and Late conditions all had 3 min of interference while the Unfilled condition did not have any interference.
Adapted from Dewar and colleagues (2009).

Interference task. The interference task lasted for 3 min and was a same or different choice discrimination Stroop-like task that used 45 gray scale line drawings taken from the same normed database that the words were drawn from Snodgrass and Vanderwart (1980). Study words were never used as interference stimuli. The interference task was manipulated to begin at one

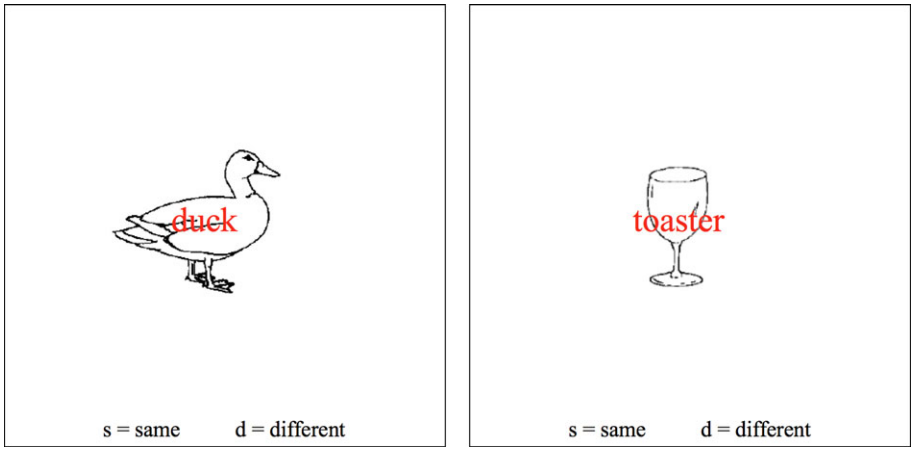

Fig. 1. Example of the same (left)/different (right) Interference Task (choice response time). Each picture–name pair was presented on the screen and participants were instructed to decide whether the picture and text were the same or different and respond by keypress and overt vocal response. Picture was presented as a black line drawing and text was presented in red Times New Roman font.

of the three different intervals (immediate, 3 min, 6 min) but not during the unfilled control condition. A gray scale line drawing appeared on the screen with a superimposed word in red font for 4 s each (Fig. 1). On one-third of trials, the superimposed word did not match the gray scale drawing (different/incongruent/complex trials) and on the other two-thirds of trials, the superimposed word matched the gray scale drawing (same/congruent/simple trials). The superimposed word and drawing were randomized differently for each participant. Participants were instructed to make a same or different judgment about whether the superimposed word matched or did not match the gray scale drawing by pressing the "s" or "d" keys, respectively and concurrently vocalizing "same" or "different". Participants were asked to respond as fast and accurately as possible. Vocalizing reduced the chances that any memory benefit from the minimal interference condition could be attributed to participants overtly or covertly using rehearsal strategies (Baddeley, Lewis, & Vallar, 1984). The superimposed word and picture remained on the screen for 4 s and did not terminate with a response, feedback followed each trial. This procedure was intentionally slightly different from prior research (Dewar et al., 2009) in that we also required the button press and recorded accuracy and RT on the interference task in order to directly evaluate the processing speed hypotheses. Measuring RT to infer processing speed is advantageous because it is less susceptible to practice effects and feasible for clinical practice (Reicker, Tombaugh, Walker, & Freedman, 2007). Prior to beginning the experimental blocks, participants completed three practice interference trials to familiarize them with the procedure.

Rest phase. The remaining time during the retention interval outside of the interference task consisted of a rest phase. Participants were instructed to rest quietly with their eyes closed and informed that they would know when it was the rest phase because the computer screen was completely black. When the rest phase ended, the screen was no longer black and a tone sounded to alert participants that the next phase was about to begin. Aside from a small nightlight, all of the lights in the testing room remained off over the course of the entire experiment in an effort to maintain an environment that minimized interference. The experimenter remained in the room and monitored the participant throughout the experiment.

Test phase. During the test periods, participants recalled the words aloud and the experimenter wrote down responses for later scoring.

Processing speed measurement. Two different measurement procedures are used as proxies of information processing speed. Average RT for accurate same or different trials on the interference task was computed as the first indices of simple and complex information processing speed, respectively. Archival SDMT (Smith, 1982) scores served as the second index of information processing speed. On the SDMT, participants are shown a key with nine symbol–digit pairings located at the top of the page with a larger grid positioned underneath. The grid contains only symbols and participants are asked to use the key to complete the pairings. SDMT total score is computed as the total number of correct pairings made in a 90 s timeframe.

Sample Size

Sample size was estimated on the basis of past research (Dewar et al., 2009) that used a highly similar design and reported a large effect for the two Group × four Interference Onset interaction ($\eta_p^2 = .21$; effect size derived from reanalysis of data included in Table 2 of Dewar and colleagues, 2009) with $N = 12$ healthy control and $N = 12$ amnesiac participants. Using estimates from this prior research and alpha set at .05 for a non-directional test and three groups (MS memory-impaired, MS-memory-unimpaired, and Healthy Control) rendered an estimated total sample size of nine per group to achieve Power of .80 (Faul, Erdfelder, Buchner, & Lang, 2009). Given the degree of memory impairment in the MS participants in the present study would not be as severe as Dewar et al.'s participants, we set out to recruit a minimum of $N = 12$ participants for each of the three groups, matching the group sample sizes of Dewar et al.'s original report.

Ethics and Registration

The study was approved by an institutional review board and participants provided written informed consent. The design was preregistered on clinicaltrials.gov (NCT02081508). Recruitment took place between March 2014 and May 2015.

Statistical Analysis

Differences between groups on demographic, disease, and neuropsychological variables were evaluated using one-way Analysis of Variance (ANOVA), independent samples *t*-tests and Chi-square. Data analysis for the primary aim followed the procedure described in Dewar and colleagues (2009). All memory scores were first converted to proportions by dividing the number of words recalled by the total number of words presented for each condition (/15). Proportion retention scores were then computed by dividing delayed recall by immediate recall (to better control variability and individual differences in initial encoding across participants, see also, Sandry, Chiou, DeLuca & Chiaravaloti, 2016). Statistical differences were evaluated using mixed model ANOVAs on proportion retained (main outcome variable) as well as immediate and delayed raw scores (total number correctly recalled). Data analysis for the secondary aim investigating the relationship between memory and processing speed was evaluated using mixed model ANOVAs on simple and complex RTs for the interference task. These analyses were followed by correlations and linear regression between memory and processing speed variables, including SDMT scores. Finally, we present a follow-up exploratory analysis evaluating how the dual-components of working memory differ as a function of memory status by recoding immediate recall as retrieval from either the primary or secondary memory component of working memory (Tulving & Colotla, 1970) and evaluate differences with a mixed ANOVA.

Results

Group Characteristics

The MS memory-impaired, MS memory-unimpaired and healthy control groups did not differ on any demographic characteristics (Table 1). The MS groups did not differ in disease severity with mild to moderate levels of disability (Ambulation Index Scores = 2.71, $SD = 2.66$, see Table 1 for disease characteristics and MS phenotypes). Ambulation Index assesses mobility and level of assistance over a 25-foot distance using a 10-point (0 to 9) ordinal scale; higher scores indicate greater disability (Hauser et al., 1983). Neuropsychological status was only available for the MS group. MS memory-impaired participants performed worse than the MS memory-unimpaired participants on the SDMT, subscales of the Hopkins Verbal Learning Tests- Revised and Brief Visuospatial Memory Test-Revised (Table 1). Differences on these specific neuropsychological variables verify differences between groups in memory ability.

Primary Analysis: Memory

One MS memory-impaired participant did not complete the last block of their testing session due to time constraints (Late Condition because of assigned counterbalancing order). Recall proportion for that cell was imputed by entering the mean recall score from the MS memory-impaired group in that condition.

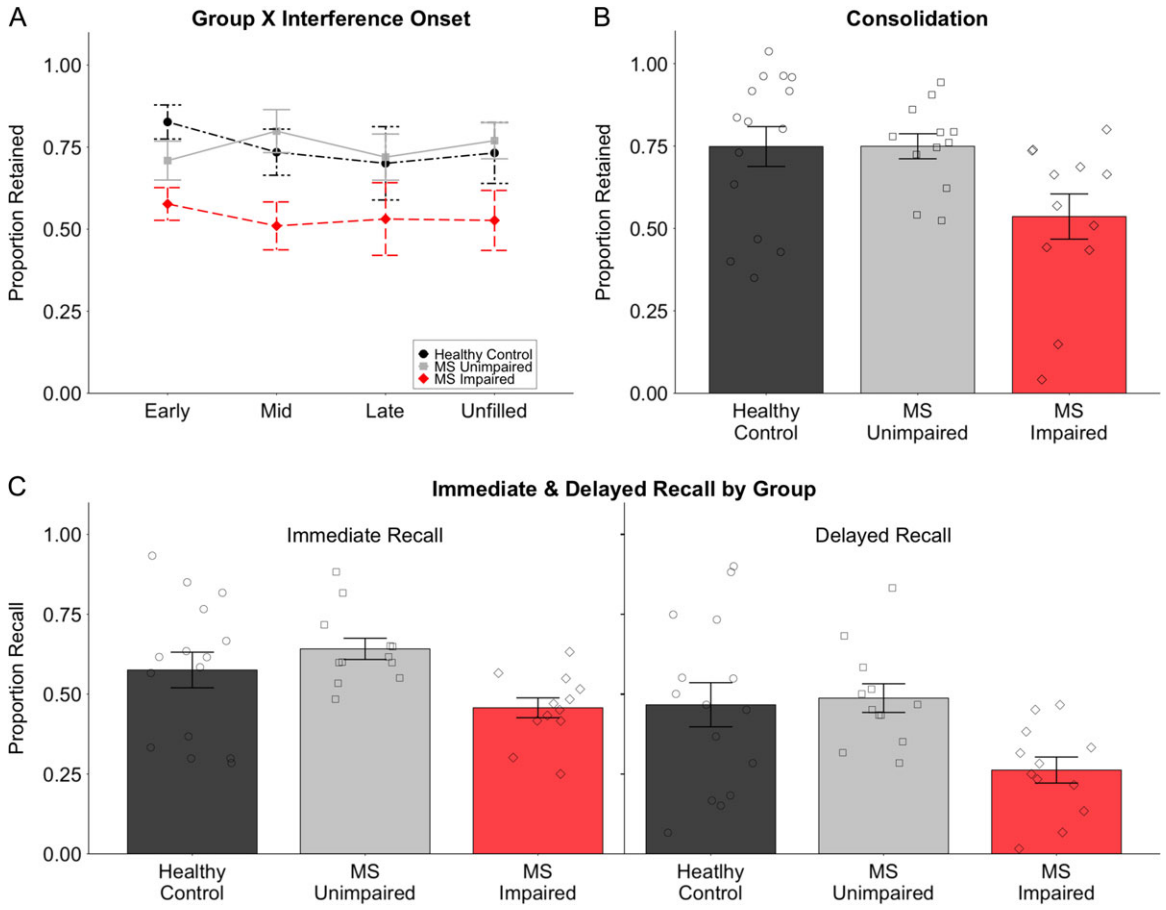

Fig. 2. (A) Proportion *retained* (delayed/immediate) as a function of Group and Interference Onset (B) Proportion *retained* as a function of Group (collapsed across Interference Conditions and showing main effect). (C) Proportion of words recalled during immediate and delayed recall as a function of Group.
Note. Error bars represent ±1 standard error. Points represent scores for each participant, plotted for each of the three Groups. Healthy control (black); multiple sclerosis memory-unimpaired (gray); multiple sclerosis memory-impaired (red).

Proportion retained. The proportion retained scores were analyzed using a mixed model ANOVA with Interference Onset (Early, Mid, Late, Unfilled) as the within participant factor and Group (Healthy Control vs. MS memory-unimpaired vs. MS memory-impaired) as the between participant factor. The main effect of Interference Onset, $F(2.84,102.05)=.32$, $p=.80$ and the interaction between Group and Interference Onset, $F(5.67, 102.05)=.45$, $p=.84$ were not significant (sphericity assumption violated & degrees of freedom adjusted). There was a significant main effect of Group, $F(2,36) = 4.29$, $p = .02$. $\eta_p^2 = .19$. MS memory-impaired participants ($M = .54$, $SD = .24$) performed worse than MS memory-unimpaired participants ($M = .75$, $SD = .13$), $t(22) = 2.72$, $p = .01$, $d = 1.08$, who were not different from controls ($M = .75$, $SD = .23$), ($p = .99$). As presented in Fig. 2A and B, the MS memory-impaired participants lost proportionally more information during consolidation (over the retention interval) as evidenced by lower proportion retained scores. However, the manipulation of minimizing interference (and complimentarily, introducing interference) did not serve to differentially improve (or impair) memory for any of the groups in this study. We also evaluated ordering effects by including Counterbalanced Order as a between participant factor in the analysis; Counterbalanced Order was not significant, $F(3,27) = .29$, $p = .83$. The results did not change when restricting the analysis to only MS participants (2 × 2 mixed ANOVA).

Raw scores. In order to fully evaluate the memory data, we completed a second analysis and included both immediate and delayed recall proportions as a within participant factor in a three Group × four Interference Onset × two Time (Immediate or Delayed) mixed analysis of variance (ANOVA). The main effect of Group was significant, $F(2,36) = 4.42$, $p = .02$, $\eta_p^2 = .20$, overall MS memory-impaired participants performed worse than the MS memory-unimpaired and Healthy Control Groups. The main effect of Time was significant, $F(1,36) = 155.97$, $p < .001$, $\eta_p^2 = .81$, with higher performance for Immediate ($M = .56$, $SD = .17$) compared to Delayed recall trials ($M = .41$, $SD = .22$). The interaction between Group and Time was also significant,

$F(2,36) = 4.31$, $p = .02$, $\eta_p^2 = .19$, corroborating the proportion retained analysis reported above (Fig. 2C). No other main or interactive effects were significant (all *p*s>.31). To be thorough, we also computed a final analysis with average immediate recall scores included as a covariate in a three Group × four Interference Onset mixed ANOVA with delayed recall as the dependent measure. The findings remained unchanged when adjusting for immediate recall. The analysis of raw scores suggests that MS memory-impaired participants are also impaired on initial encoding. We further investigate this finding in the Exploratory Analysis section, below, but first turn to the secondary aim by evaluating the relationship between memory and processing speed.

Secondary Analysis: Memory & Processing Speed

Interference task. The design of the interference task was similar to a choice RT task whereby individuals were presented with a choice and had to differentiate between alternative options as quickly as possible, by button press. We first present the analysis on accuracy to evaluate whether there was a difference in task difficulty between Same versus Different trials and provide justification for interpreting Same versus Different trial type as differing indices of processing speed. This was followed by the analysis on RT for accurate trials. We interpret RTs on the interference task as an index of individual differences in processing speed where Same trials reflect simple RT and Different trials reflect complex RT. If RTs differ as a function of memory status it would corroborate the assumption that processing speed is related to memory impairment in MS. Additionally, we investigate the relationship between measures of processing speed (RTs and SDMT) and memory acquisition scores for the MS participants.

Accuracy. The interference task occurred on three out of four blocks during the 3 min filled intervals (there was no interference during the unfilled interval). The interference task accuracy data were analyzed using a two Trial Type (Same vs. Different) × three Group (Healthy Control vs. MS memory-unimpaired vs. MS memory-impaired) mixed ANOVA. There was a main effect of Trial Type, $F(1,36) = 13.32$, $p < .001$. $\eta_p^2 = .27$ with higher accuracy for Same Trials ($M = .97$, $SD = .03$) compared to Different Trials ($M = .95$, $SD = .06$). The main effect of Group and interaction between Group and Trial Type were not significant (*p*s > .25). This suggests that error rates were higher when the picture and word were different (incongruent) corroborating the simple versus complex nature of the RT task. The results did not change when restricting the analysis to only MS participants (2 × 2 mixed ANOVA).

Response time. RTs for accurate trials in the interference task were analyzed using the same 2 × 3 mixed ANOVA that was applied to the accuracy data and revealed a similar pattern. RTs were inspected for outliers (operationalized as responses shorter than 200 ms), however, none were present. There was a main effect of Trial Type, $F(1,36) = 99.80$, $p < .001$. $\eta_p^2 = .74$ with shorter RTs for Same Trials ($M = 1139$, $SD = 222$) compared to Different Trials ($M = 1301$, $SD = 249$). The main effect of Group and Group × Trial Type interaction were not significant (*p*s>.43) (see Table 3). Additionally, given RT distributions are positively skewed, we computed the same mixed model ANOVA on median values and the outcome remained the same. The results did not change when restricting the analysis to only MS participants (2 × 2 mixed ANOVA). This analysis does not support the hypothesis that differences in processing speed, measured with RT, are related to memory impairment in MS.

Response time and memory. We investigated correlations between processing speed (RTs on the interference task) and memory performance (collapsed across the four Interference Conditions): immediate recall, delayed recall and consolidation (proportion retained) for MS participants. Because Same and Different RTs were strongly correlated (Table 4) and may not have resulted in conflicting Stroop-like responses, we also calculated a composite RT score by standardizing and collapsing across these RT measurements. RTs did not significantly correlate with any of the memory performance measures (all ps≥.19; Table 4).

Table 3. Response times in the interference task

	Different RTs			*Same RTs*		
	Mean	Median	*SD*	Mean	Median	*SD*
HC	1,258	1,196	292	1,079	990	272
MS-U	1,288	1,336	235	1,152	1,209	208
MS-I	1,370	1,366	208	1,204	1,195	157

Mean, median and standard deviations (*SD*).

Table 4. Processing speed [response time (RT) & symbol digit modalities test (SDMT)] × memory correlations for MS participants

	Different RTs	Same RTs	Composite RT	SDMT	Immediate Recall	Delayed Recall
Different RTs	—					
Same RTs	.93**					
Composite RT	.98**	.98**				
SDMT	−.52**	−.46*	−.50*			
Immediate Recall	−.26	−.20	−.24	.43*		
Delayed Recall	−.28	−.18	−.24	.47*	.92**	
Proportion Retained	−.21	−.13	−.18	.51*	.70**	.89**

Note: *$p \leq .05$; **$p \leq .01$.

SDMT and memory. The MS memory-impaired and unimpaired groups differed on the SDMT total raw scores (see Table 1) and the SDMT is often interpreted and discussed as an index of information processing speed in MS (Benedict et al., 2017; Costa et al., 2017). Thus, we evaluated the correlation between the SDMT and memory performance. There were significant positive correlations between SDMT scores and immediate recall, delayed recall and consolidation (Table 4).

Response time, SDMT and memory. There is a clear discrepancy when evaluating the correlational results comparing processing speed and memory. Processing speed measured with RT was not related to memory performance while processing speed measured with the SDMT was related to memory performance. RTs and the SDMT were negatively correlated with each other (Table 4), corroborating a processing speed component to the SDMT and demonstrating that participants who performed worse on the SDMT also had slower RTs. However, RT only accounted for one-quarter of the variance on the SDMT so there are clearly other cognitive, motor or sensory processes that contribute to performance on this commonly used test.

We further evaluated the same relationships between the SDMT and the memory variables but controlled for RT using linear regressions in order to determine whether the relationship between the SDMT and memory variables remain when accounting for processing speed variance associated with RT. When controlling for RT (composite score), the model predicting immediate recall from SDMT was not significant, $F(2,21) = 2.32$, $p = .12$, the model predicting delayed recall from SDMT was marginally significant, $F(2,21) = 2.97$, $p = .07$. The model predicting consolidation from SDMT was significant, $F(2,21) = 3.73$, $p = .04$, $R^2 = .26$, however, while the SDMT was a significant predictor of consolidation $\beta = .56$, $p = .02$, RT was not, $\beta = .10$, $p = .65$. Variability on the RT task may have also included motor response variability. To control for differences in motor response speed we computed a percentage change score (Reicker et al., 2007) between the Same and Different trials and tested the same regression models. The general pattern of results did not change aside from the model predicting delayed recall from SDMT surpassing conventional significance levels, $F(2,21) = 3.74$, $p = .04$, $R^2 = .26$, and only SDMT remaining in that model as a significant predictor of delayed recall, $\beta = .43$, $p = .04$, while RT was not, $\beta = -.21$, $p = .29$. The correlational analyses provide divergent results and raise critical issues related to process purity in measurement that we address in the discussion.

Exploratory Analysis: Dual Components of Working Memory

Given there were both encoding (low immediate memory) and consolidation (low proportion retained) deficits in the MS memory-impaired group we directly investigated memory performance on immediate recall trials to better understand how working memory is related to long-term memory impairment in MS (Sandry, 2015; Sandry & Sumowski, 2014). One established theory of working memory assumes that dual-components make up working memory, primary memory and secondary memory, respectively (Unsworth & Engle, 2007). Primary memory is capacity limited and maintains the activated contents of working memory and information that exceeds this capacity is processed and transferred into secondary memory (Mogle, Lovett, Stawski, & Sliwinski, 2008; Unsworth & Engle, 2007; Unsworth & Spillers, 2010). On the basis of the dual-component model, three alternative hypotheses can be proposed to explain the relationship between working memory and long-term memory impairment in MS. First, it is possible that impaired long-term memory is linked to reduced capacity and this would be evident if MS memory-impaired participants performed worse on the estimate of primary memory. Second, it is possible that impaired long-term memory is linked to inefficient processing between primary and secondary memory and this would be evident if MS memory-impaired participants performed worse on the estimate of secondary memory. The third possibility is that both capacity and processing are reduced for memory-impaired MS participants compared to memory-unimpaired participants.

The design of the present study comprising an immediate free recall task provides an opportunity to begin to test these hypotheses. Output of an immediate free recall task can be classified as retrieval either from primary memory or secondary memory and these components can be differentiated using a procedure developed by Tulving and Colotla (1970). The number

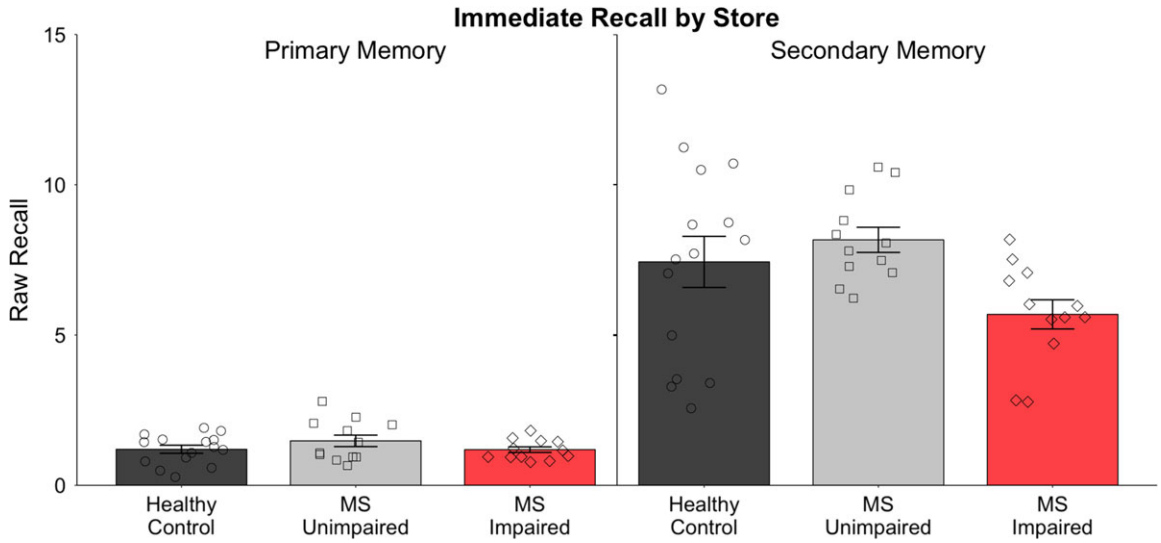

Fig. 3. Raw recall at immediate test and classified as working memory retrieval from either primary memory (quantitative capacity) or secondary memory (processing efficiency), as a function of Group (collapsed across Interference Onset conditions).
Note. Error bars represent ±1 standard error. Points represent scores for each participant, plotted for each of the three Groups. Healthy control (black); multiple sclerosis (MS) memory-unimpaired (gray); MS memory-impaired (red).

of intervening words, both recalled and presented, that come between the retrieved item is used to infer retrieval from either primary or secondary memory. If seven or fewer items intervened then this was considered retrieval from primary memory and this can be interpreted as an index of storage capacity. Lags greater than seven were considered retrieval from secondary memory and this can be interpreted as an index of processing efficiency. Processing efficiency may involve successful transfer out of or into the capacity limited primary component of working memory. This measurement approach corresponds well with lab based measures of complex span working memory tasks that include both a storage and processing component (Unsworth & Engle, 2007). Decomposing immediate recall trials may provide additional insight into what aspect of working memory (storage capacity or processing efficiency) is impaired and contributes to long-term memory impairment in MS.

Immediate freely recalled words were coded as retrieval from either primary or secondary memory and averaged across the four interference conditions, rendering separate estimates for the dual-components of working memory. Group differences in primary and secondary memory were evaluated using a three Group × two Store (Primary vs. Secondary Memory) mixed ANOVA. The main effects of Group, $F(2,36) = 4.10$, $p = .025$, $\eta_p^2 = .17$ and Store, $F(1,36) = 209.20$, $p < .001$, $\eta_p^2 = .85$ were both significant and the Group × Store interaction trended towards significance, $F(2,36) = 2.61$, $p = .087$, $\eta_p^2 = .13$. We completed the same analysis but restricted it to only to the MS groups using a 2 × 2 mixed ANOVA. The main effects of Group, $F(1,22) = 16.62$, $p < .001$, $\eta_p^2 = .43$ and Store, $F(1,22) = 278.76$, $p < .001$, $\eta_p^2 = .93$ were both significant as was the Group × Store interaction, $F(1,22) = 10.66$, $p = .004$, $\eta_p^2 = .33$. The interaction was driven by the finding that MS memory-impaired participants showed a reduction in access to the secondary memory component of working memory on the immediate recall task compared to MS memory-unimpaired participants, $t(22) = 3.90$, $p =< .001$, $d = 1.63$, however, the MS groups did not differ in their retrieval from primary memory, $t(15.94) = 1.37$, $p = .19$ ((equal variances not assumed and degrees of freedom adjusted; Fig. 3). This exploratory analysis supports the hypothesis that long-term memory deficits in MS are related to the secondary memory component (processing efficiency) of working memory.

Discussion

In the present study, we evaluated a number of research questions directed at understanding and improving memory impairment in MS. We discuss the results for each hypothesis and the related implications in turn.

Susceptibility to Interference & Forgetting

Our first research question comprised two parts. First, we sought to determine whether susceptibility to retroactive interference differs between MS participants with and without a priori defined memory impairment. On the basis of past research, we

hypothesized that MS memory-impaired participants would be more susceptible to interference than MS memory-unimpaired and healthy control participants. If this first hypothesis was correct, the related goal was to evaluate whether minimizing interference would improve memory in the memory-impaired MS participants. The data from the current study did not support either hypothesis (no interaction as a function of interference onset). In past research, Dewar and colleagues (2009) reported a striking finding of a dose-dependent effect of minimizing interference. Reducing interference during early consolidation improved memory in patients with dense amnesia as well as other populations with lesser forms of memory impairment. We did not replicate this finding, suggesting that delaying the onset of interference did not improve consolidation in the present sample. While it would be valuable to replicate the current study in a separate MS sample, these findings do suggest that minimizing interference is not an effective memory rehabilitation approach for persons with MS.

While the present findings did not support interference as an underlying cause of memory impairments in MS, the findings do provide evidence that some aspect of early consolidation is impaired (specifically in MS participants who perform poorly on the delayed recall trial of the Hopkins Verbal Learning Test). The MS memory-impaired participants lost proportionally more information over the consolidation interval than the MS memory-unimpaired and healthy control groups who did not differ. This finding suggests that the MS memory-impaired participants were able to successfully initially encode some of the to-be-remembered information (but see *Dual-Components of Working Memory* section), however, they also lost more of this initial information over the retention interval than the unimpaired groups. This finding is congruent with an account that attributes some aspects of memory problems in MS to accelerated forgetting over the retention interval (Andrade et al., 2003).

How then, does accelerated forgetting over the retention interval occur with the absence of retroactive interference effects? One possibility is that cognitive mechanisms related to time-based forgetting (Brown, 1958; Ricker, Vergauwe, & Cowan, 2016) are impacted by MS and this causes information to decay more rapidly with the passage of time, similar to the older Law of Disuse (Pratt, 1936). The cues that are generated at encoding may fade or no longer be available or the cues may no longer match the memory trace (Roediger & Guynn, 1996) making it impossible to retrieve the memory. It is also possible that the memory representation itself fades. An alternative explanation for the increased forgetting over the retention interval may be that when freely recalling words aloud, MS participants experience a type of output or retrieval interference where the act of recalling information makes it difficult to retrieve or access other information stored in memory (Anderson, Bjork, & Bjork, 1994; Smith, D'Agostino, & Reid, 1970). Time-based forgetting and output interference accounts are both plausible explanations for the observed patterns of reduced memory performance over the retention interval in the current study. These alternatives may prove to be useful concepts to understand the present findings and accelerated forgetting in MS. Future research in this area may also reveal whether these postulated forgetting mechanisms occur at acquisition or at retrieval and whether they depend on the specific type of memory impairment that different MS patients experience – ultimately leading to a patient-specific approach to rehabilitation.

Inconsistencies between the present research and earlier work (Dewar et al., 2009) raise questions about why we did not observe a benefit from minimizing interference while a number of other studies have reported the hypothesized effect. We closely followed the design of Dewar and colleagues (2009), however, we made a few minor changes so direct comparisons should be considered with those differences in mind. For example, we required a concurrent button press on the interference task to also capture RTs, introducing a concomitant motor or dual-tasking component to the design. Additionally, Dewar et al. used a forward–backward counterbalancing strategy and we used a graeco-latin square. Dewar et al. reported a benefit of minimizing interference for both memory-impaired and memory-unimpaired participants. We did not replicate this benefit in any of the groups we tested; however, sample size of the present study was compatible with Dewar et al. who demonstrated large effect sizes for both memory-impaired and healthy participants. A main difference from Dewar et al.'s sample is that the degree of memory impairment in the present sample may have been less extreme. The amnesiac participants in that report scored approximately 3.5 standard deviations below the mean when standardized to the healthy control comparison group on a verbal list learning test (cf., González, Mungas, Reed, Marshall, & Haan, 2001). This degree of memory impairment is more than two times as extreme as the MS memory-impaired participants in the present study. It may be that the degree of memory impairment or other individual differences factors serve as indicators for who will and will not benefit from minimizing interference. The differences in degree of memory impairment cannot completely explain the discrepancy between the present research and earlier work because we also did not find the predicted effect in our healthy control sample.

It is unclear why the healthy controls did not show an improvement in proportion retained scores in the minimal interference conditions. Although the healthy control group did not undergo a neuropsychological assessment, their performance in the experiment was comparable to the memory-unimpaired MS group. To evaluate the degree that effort or motivation may have played a role we performed a supplemental analysis and divided the healthy control group into high and low memory performers by median split on proportion retained (collapsed across Interference Onset conditions). Group and condition differences were evaluated using a two Group × four Interference Onset mixed ANOVA. The main effect of Interference Onset and Interaction were not significant ($ps > .19$), suggesting the lack of improvement as a function of Interference Onset was

similar across high and low performers. If low effort was responsible for masking any benefit, we would have expected the high performing group to benefit from minimal interference, however, this was not observed. This post-hoc analysis provides some evidence against an alternative explanation that lack of effort was responsible for no observable benefit of minimizing interference in the healthy control group.

Psychiatric comorbidities including depression and fatigue are common in MS and are related to cognitive functioning (Diamond, Johnson, Kaufman, & Graves, 2008; Feinstein, 2006). These factors, if present in this group of MS participants, could have suppressed any benefits from minimizing interference. Scores on psychiatric variables were not available in the present study. Despite no observed benefit of minimizing interference, the present findings do provide some insight into how acquisition is impaired in MS. Before interpreting this finding and the exploratory analysis, we first discuss the findings for the secondary aim.

Processing Speed and Memory

The secondary aim of the present study was to investigate the correlation between processing speed and memory. Evidence from past research suggests that MS patients with slowed information processing speed also experience poorer memory performance (Chiaravalloti & DeLuca, 2015; Chiaravalloti et al., 2013; DeLuca et al., 1994; Litvan et al., 1988), something also reported in other populations (Dunlosky & Salthouse, 1996; Salthouse, 1993, 1996; Salthouse & Coon, 1993). While our concern is with memory and memory acquisition in general, no past research has evaluated this question with respect to consolidation performance in MS. In the first analysis, we focused on investigating differences between individuals with and without a priori specified memory impairment and found no difference across these participants for Same trials or Different trials measured using the choice RT task. Further, no correlations supported the relationship between RT and memory in MS participants. The null relationship reported here along with other research that reported no correlation between simple or complex processing speed and immediate *verbal* list memory (Berrigan et al., 2013), may imply that processing speed is not an underlying mechanism responsible for verbal memory acquisition deficits observed in MS patients. It remains possible that processing speed is related to other types of memory, e.g., visual memory, verbal story memory, other modalities or other stimulus types.

Contrary to the RT findings, the SDMT was positively related to the memory variables. The SDMT has increasingly become the main cognitive screening tool used in MS (Benedict et al., 2012; Brochet et al., 2008; Drake et al., 2010; López-Góngora, Querol, & Escartín, 2015; Sandry, Paxton, & Sumowski, 2016) and it is commonly interpreted as a measure of processing speed. Importantly, the SDMT is likely a multifaceted measure of cognition (Smith, 1982, 2002), that includes components of visual scanning, learning and associative memory for symbol–digit pairings during early trials, working memory maintenance, motor or oral responses depending on administration, as well as processing speed. There was a clear relationship between the SDMT and RTs, verifying a speed component to the SDMT. In order to isolate whether the direct effect between the SDMT and memory was driven by variability due to processing speed we controlled for RT in the regression analysis. The findings revealed minimal to no change in the strength of the direct relationship and no overlap with RT. If replicated, this finding may have far reaching implications in that it questions whether the relationship between the SDMT and memory is due to overlapping variability in processing speed or some other cognitive processes.

If there was strong evidence for a relationship between processing speed and memory, then there should have been converging evidence for this relationship across alternate processing speed measurements. Converging evidence was absent in the present study. Discrepant correlations between the RT and SDMT measures of processing speed and memory raise an important point regarding a process purity assumption in neuropsychological measurement. Processing speed, when operationalized as the amount of time it takes to complete a mental operation or the *rate* at which cognitive operations can be performed, might be most easily measured using participants' RT. When measuring processing speed, simple tasks that are not influenced by other cognitive processes or general knowledge are preferable (Salthouse, 1996). The RT task is simpler and less confounded by alternative cognitive processes than the multifaceted SDMT. It is possible that processing speed measured with RT is not correlated with memory, however, the other cognitive processes besides processing speed that are captured by the SDMT are what *is* correlated with memory. The speed-memory relationship might only be captured when neuropsychological assessments measure more than processing speed (e.g., working memory, attention, etc.) or when efforts are taken to control for other disease-related symptoms (Diamond et al., 2008). Earlier investigations suggesting a relationship between processing speed and memory in MS that relied on PASAT and SDMT as the measure of processing speed (DeLuca et al., 1994; Litvan et al., 1988; Olivares et al., 2005) may need to be reevaluated under the context of the present findings and consideration of process purity assumptions. Those relationships may have resulted from memory impairment correlating with variance from cognitive processes other than processing speed that are captured by the PASAT or SDMT.

Our understanding of how diseases like MS impact cognition depend upon our understanding of the psychometric properties of the assessments being used. Some of the MS literature seems to have redefined the processing speed construct so it is compatible with commonly used instruments (e.g., SDMT, digit-symbol substitution) rather than operationalizing, creating and refining sensitive instruments that tap into processing speed. One recent report stated that the SDMT is currently undergoing classification by the FDA as a measure of "information processing speed" (LaRocca et al., 2017). Such a conceptualization may invite an uninformed researcher or clinician to miss or overlook other cognitive processes that contribute to performance on the test and this could negatively impact patient treatment or lead to misdiagnosis. Despite a lack of process purity, a non-specific measure of general cognitive function like the SDMT does serve as a quick and efficient initial assessment of cognition.

One important direction for future research will be to tease apart the underlying cognitive components of the SDMT and operationalize how those processes correspond with memory and other cognitive processes in MS. The ability of the SDMT to detect cognitive changes in MS may largely be a result of the multiple cognitive processes that are required to complete the assessment. For example, patient A could be impaired in memory, patient B could be impaired in visual scanning ability and patient C could be impaired in oral or motor response speed. Scores for all of these patients might be lower on the SDMT than a healthy control given the general nature of the assessment but they may not directly reflect impairments in information processing speed. It would be a mistake and disservice to MS patients to only administer and interpret a low SDMT score as indicative that "information processing speed" is impaired. While useful as a general measure of cognition, the SDMT may lack precision when it comes to diagnosing what specific aspect of cognition is impaired, something that may be better reserved for a larger test battery. The present hypothesis regarding processing speed was specified a priori and the design was modified to record RTs to enable these analyses. Additional prospective studies designed to directly test this relationship as the primary aim will be a valuable next step in understanding the relationship (or lack of a relationship) between processing speed and memory impairment in MS. Future work in this area will lead to a refined understanding of the underlying mechanisms responsible for memory deficits in MS patients. This understanding will likely lead to an upsurge in the design of novel rehabilitation strategies because the impaired cognitive process can be directly targeted (Sandry, 2015; Sandry, Akbar, et al., 2016).

Dual-Components of Working Memory

Early consolidation was not the only impaired acquisition process in the memory-impaired MS group. Upon initial encoding (immediate recall trials) the MS memory-impaired participants recalled a lower proportion of words than the unimpaired participants. This cannot be attributed to a failure to read the information because all participants vocalized the words aloud. We further evaluated this finding in a theoretically motivated exploratory analysis by dichotomously classifying immediate memory performances as retrieval from either primary or secondary memory (Tulving & Colotla, 1970). This approach allowed us to further evaluate the role of working memory in long-term memory impairment (Sandry, 2015). Specifically, in the dual-component/controlled attention view of working memory (Unsworth & Engle, 2007), information that exceeds the capacity limit of primary memory is processed and shifted into secondary memory. The secondary memory component of the Tulving and Colotla procedure is one measure that positively correlates with complex span working memory tasks that include both a processing and storage component (Engle, Tuholski, Laughlin, & Conway, 1999; Shipstead, Lindsey, Marshall, & Engle, 2014).

The exploratory analysis on the dual-components (primary memory [capacity] and secondary memory [processing]) of working memory revealed no group differences in retrieval from primary memory, however, MS memory-impaired participants showed reduced access to secondary memory compared to MS memory-unimpaired participants. This finding supports prior research demonstrating that long-term memory deficits in MS are related to individual differences in working memory (Sandry & Sumowski, 2014). The present findings extend this initial observation in further decomposing what working memory differences exist between MS memory-impaired and unimpaired participants. Specifically, there were no differences between MS groups on the primary memory component of immediate recall, this suggests that working memory differences are not due to reductions in quantitative storage capacity (e.g., Cowan, 2001; 2005). Instead, the present findings suggest that working memory differences related to long-term memory impairment in MS may be driven by inefficient or dysfunctional working memory processing between primary and secondary memory. This may be a result of inefficient *integration* from primary memory into secondary memory, it may be due to poor *access* to (or retrieval from) secondary memory, or it may be a combination of inefficient integration and poor access. Further, these patterns may change at an individual difference level or at different stages of the disease. It will be useful to begin to translate the substantial body of individual differences research in working memory (Engle, 2002; Unsworth & Engle, 2007) and the relationship to long-term memory (Loaiza, McCabe, Youngblood, Rose, & Myerson, 2011; Rose & Craik, 2012; Rose, Myerson, Roediger III, & Hale, 2010; Unsworth, 2016) to further unpack how the working memory–long-term memory relationship is altered as a function of MS disease (Sandry, 2015).

The present findings, with respect to the dual-component view of working memory, share some similarities and differences with earlier research. For example, some have reported differences between MS and controls on the primary memory portion of immediate free recall (Beatty & Gange, 1977), which would imply a quantitative capacity issue. Similar to the present research, others have reported no difference on the primary memory component but significant differences on the secondary memory component (Rao et al., 1993, 1989). Akin to much research in MS, this early work differs from the present study in that it did not evaluate differences between memory-impaired and unimpaired MS participants. In line with the present findings, other studies of memory-impaired populations using this same procedure also revealed a similar pattern. Alzheimer's disease patients show preserved primary memory and reduced secondary memory (Bäckman, Jones, Berger, Laukka, & Small, 2005; Simon, Leach, Winocur, & Moscovitch, 1994). Similarly, primary memory remains intact in healthy aging while secondary memory shows a subtle decline (Wahlin, Backman, & Winblad, 1995).

Neurologically, secondary memory deficits may be correlated with hippocampal damage (Moscovitch, 1982). For example, primary memory scores did not differ between stroke patients with either left or right hippocampal lesions, commissurotomy patients and healthy controls while secondary memory scores for the hippocampal patients were far lower than the other two groups (Dobbins, Kroll, Tulving, Knight, & Gazzaniga, 1998). Additionally, hippocampal activation in healthy controls is greater when completing complex span working memory tasks compared to arithmetic control tasks (Faraco et al., 2011). This pattern may be because the hippocampus is involved in encoding, active maintenance and retrieval of information that exceeds the capacity of primary memory, (i.e., information maintained and retrieved from secondary memory) (Faraco et al., 2011). The low secondary memory behavioral performance among the memory-impaired participants in the present study may serve as a behavioral marker for hippocampal-related working memory dysfunction or hippocampal-mediated cognitive change in MS. This interpretation is congruent with recent findings that suggest working memory capacity is related to long-term memory impairment in clinical populations (Chiou, Sandry, & Chiaravalloti, 2015; Constantinidou et al., 2014; Sandry, 2015; Sandry, DeLuca, & Chiaravalloti, 2015; Sandry & Sumowski, 2014) and research implicating the hippocampus as a vulnerable structure susceptible to MS disease-related pathology (Anderson et al., 2010; Geurts et al., 2007; González Torre et al., 2017; Hulst et al., 2015; Kiy et al., 2011; Longoni et al., 2015; Muhlert et al., 2014; Papadopoulos et al., 2009; Paulesu et al., 1996; Roosendaal et al., 2008; Sicotte et al., 2008; Sumowski et al., 2017; Sumowski et al., 2016). Necessarily, this suggestion remains a hypothesis that needs to be directly evaluated in the future with complimentary measurement from neuroimaging data.

Working memory assessments that only tap into primary memory or quantitative capacity may not accurately capture working memory ability as it relates to long-term memory impairment in MS and it may be more appropriate to use tasks that include a processing component that displaces information into secondary memory (e.g., complex span tasks, Conway et al. 2005). It is reasonable to hypothesize that the memory-impaired participants in the present study would perform worse on a complex span working memory task but those performance differences may not be noticeable if only traditional clinical assessments were used. One study that included complex span measures of working memory reported that 55% of the variability in learning ability in relapsing remitting MS was accounted for by a general working memory factor composed of reading span and letter number sequencing, both complex span tasks. In line with the current study, that same investigation also reported that only 11% of the variability in learning ability was accounted for by a general processing speed factor (Berrigan et al., 2013). Our quasi-experimental design included mostly relapsing remitting MS participants and generally corroborates this finding.

Limitations

One limitation is that we relied on recent neuropsychological assessments. It is possible that some of the participants experienced cognitive changes between the initial assessment and the time they participated in the current study and this should be considered when interpreting the present findings. The MS memory-impaired participants did exhibit substantially worse memory than the MS memory-unimpaired and healthy control participants in the present task, which corroborates the neuropsychological assessments used for recruitment. While the data from the additional analyses of primary and secondary memory are informative in furthering our understanding of how working memory is related to long-term memory impairment, those findings should be replicated in a prospectively designed study that also takes memory status into account. For example, one where participants are compared on the basis of their long-term memory ability, similar to the present approach, and their performances on complex span working memory tasks are assessed. This will help to further isolate what specific working memory processes contributed to long-term memory problems in MS.

We did not intentionally block or prevent rehearsal with any type of articulatory suppression procedure. Similar to Dewar and colleagues (2009), we assumed the introduction of interference and requirement for overt articulation during the same/different choice task would stop any ongoing rehearsal in those conditions. There would only be an opportunity to consistently

rehearse over the retention interval in the unfilled condition. Our results suggest an invariance between the unfilled and filled conditions across all three groups so it is unlikely that rehearsal as a maintenance strategy can explain the findings. The 15-item verbal list used in the present investigation is also outside of the capacity of working memory (Cowan, 2005) or the two-second capacity of the phonological storage buffer (Baddeley, 1986; Baddeley, Thomson, & Buchanan, 1975), where rehearsal would take place, further reducing a rehearsal explanation.

The present study cannot rule out retrieval failure hypotheses because recognition memory was not assessed. Importantly, this study was not designed to test a retrieval failure hypothesis. This is because the present study was designed on the basis of ample empirical evidence that suggests retrieval remains intact while acquisition is the fundamental underlying mechanism driving memory impairment in MS (DeLuca et al., 1994; DeLuca et al., 1998; DeLuca et al., 2013; Demaree et al., 2000; Johnen et al., 2017; Lafosse et al., 2013; Olivares et al., 2005). Some of this past research has used multiple learning opportunities in order to successfully equate MS participants to healthy controls on initial acquisition (DeLuca et al., 1994). Improving acquisition through multiple learning opportunities may serve to strengthen the memory trace by acting on initial encoding whereby multiple learning opportunities lead to more efficient integration of information into secondary memory. Multiple learning opportunities may also act on early consolidation, considering weak consolidation does seem to be a contributor to the acquisition problem. A major difference between those multi-trial acquisition studies and the present research is that the design of the present study used single-trial learning to replicate the design of Dewar and colleagues (2009). The data from the present study do not empirically inform how increasing learning trials will improve memory and we suggest that these ideas be evaluated in future research. Evaluating what aspect of acquisition is improved through multiple learning opportunities will be one additional way to understand the contributions of encoding and consolidation to memory acquisition deficits in MS and is a direction for future research.

The sample size in the present study was also set to test the primary aim of understanding the role of retroactive interference in memory impairment in MS. The secondary analysis relating processing speed to memory may be somewhat underpowered and this should be considered when evaluating the lack of a significant relationship between speed and memory.

Conclusion

The primary aim of this research was to evaluate whether retroactive interference plays a role in memory impairment in MS and test whether minimizing interference would be a useful memory rehabilitation strategy. The findings did not support retroactive interference as a cause of memory acquisition problems in the present sample. The evidence does suggest that poor initial encoding and weakened early consolidation processes both underline memory acquisition deficits in MS. The secondary aim of the present research was to evaluate whether processing speed is related to memory performance. The processing speed findings were mixed and the methodology used to measure processing speed seems to be a crucial factor in whether or not this relationship manifests. In an exploratory analysis, we evaluated and found support that the secondary memory processing component and not the primary memory capacity component of working memory is related to memory impairment in MS. Together, these data help further our understanding of memory impairment in MS and suggest rich theoretical directions to pursue going forward.

Conflict of Interest

None declared.

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