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Information processing deficits in multiple sclerosis: A matter of complexity

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Abstract

This study examined the relationship between processing speed (PS) and working memory (WM), as measured by performance on an *n*-back task, in relapsing-remitting multiple sclerosis (RRMS) patients. Simple PS was defined as reaction time (RT) on the 0-back task and complex PS was defined as RT on both the 1-back and 2-back tasks. Participants were administered all three *n*-back tasks (0-, 1-, and 2-back). Total correct responses, total dyads, and RTs were recorded. As expected, RT for all participants slowed as WM load increased. MS patients had slower RTs than controls across all tasks, and the difference between groups for RT was greatest during the 2-back task. When RT for simple PS (0-back) was parsed from the 1- and 2-back tasks, MS patients still showed impaired complex PS compared to controls. MS patients also made significantly fewer total correct responses and had fewer dyads than controls only on the 2-back task. These findings suggest that both WM and PS deficits are present in RRMS, and that as WM demand increases (from 1- to 2-back) both PS and WM deficits become more prominent. (*JINS*, 2007, *13*, 417–423.)

Keywords: Working memory, Processing speed, *N*-back, Cognitive dysfunction, Relapsing-remitting multiple sclerosis, Reaction time

INTRODUCTION

Multiple sclerosis (MS) is a degenerative disorder of the central nervous system characterized by demyelination (Perry, 1994), axonal transection (Ferguson et al., 1997; Raine & Cross, 1989; Trapp et al., 1998), and gray matter atrophy (Benedict et al., 2004; Simon et al., 1999; Zivadinov et al., 2001). The resulting neurologic damage can cause various symptoms, including motor impairments, somatosensory deficits, cognitive dysfunction, and fatigue (Miller, 1996). Between 30 and 70% of patients with MS suffer from cognitive dysfunction, ranging from cognitive impairment, mild in degree, to dementia (Heaton et al., 1985; Peyser et al., 1980; Rao et al., 1991). Two commonly impaired cognitive domains are working memory (WM) and information processing speed (D'Esposito et al., 1996; Diamond et al., 1997; Grigsby et al., 1994; Lengenfelder et al., 2003).

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According to Baddeley (1992; 2003), WM is a limited-capacity system enabling the storage, processing, and manipulation of information. WM consists of a central executive system, which is an attentional control system, and two slave systems, the phonological loop and the visuospatial sketchpad. The phonological loop holds and manipulates speech based information, and the visuospatial sketchpad performs similar processes for visuospatially presented information (Baddeley & Hitch, 1974; Baddeley & Hitch, 1994).

Processing speed (PS) refers to the rate at which cognitive processes can be executed (Krail & Sanan, 1994). There is a careful balance between the rate that information can be processed and the rate at which information becomes unavailable secondary to decay or displacement (Nebes et al., 2000). Two types of PS have been discussed in the literature: simple and complex. Simple PS refers to the amount of time needed for simple attentional tasks such as target detection. Complex PS, on the other hand, is the amount of time necessary to process more complicated tasks, such as those requiring mental manipulation (Chiaravalloti et al., 2003).

Studies by Archibald and Fisk (2000) and DeLuca et al. (2004) suggest that early in the disease course of MS [i.e., relapsing-remitting (RR) form of the disease], WM deficits

are caused by deficits in PS. DeLuca et al. discuss this notion in terms of two models: a *Relative Consequence Model* and an *Independent Consequence Model*. The *Relative Consequence Model* suggests that patients' fundamental slowing of PS affects their abilities to perform other cognitive tasks, such as WM. As such, impaired performance on cognitive measures may be misleading; patients may have intact cognitive functioning that is masked by PS difficulties. Deluca and colleagues proposed that actual WM deficits are present only in more advanced cases of the disease [i.e., the secondary progressive (SP) type of the disease]. At this point, there is a marked increase in deficient PS that now begins to affect WM.

Alternatively, cognitive deficits in MS may be explained using an *Independent Consequence Model* (DeLuca et al., 2004), which suggests that deficits in WM are independent of impaired PS. The investigators noted that the "particular pattern of cognitive deficits would then be determined by individual factors such as lesion location in the brain or perhaps depression" (p. 558). In fact, this idea was suggested in a study by Landro et al. (2003). They administered tasks of PS and WM along with a measure of depression. They found that depression could explain the deficits in PS, but not WM. However, it is important to note that WM was measured using the Paced Auditory Serial Addition Task (PASAT), which has a significant PS component. Although not all studies have found performance on WM tasks to be independent of depression (Arnett et al., 1999), the study by Landro and colleagues highlights WM and PS as independent constructs, which is consistent with the *Independent Consequence Model*.

In the clinical setting, the PASAT is frequently used to assess WM in patients with MS, and it was recommended by an international consensus group as one of the standard measures of WM in this population (Benedict et al., 2002). The PASAT is a continuous performance task. Patients are aurally presented with a number (between 1 and 9) at a predetermined rate (i.e., every 2 or 3 seconds depending on the trial) and asked to add it to the preceding number. Sixty-one numbers are presented and the total score is the number correct out of 60. However, Fisk and Archibald (2001) suggested that tallying the total number of correct responses on this task may not be an accurate measure of WM performance for patients with MS. In their study, they found that patients were more likely to "chunk" their responses. In other words, patients skip items and "chunk" responses to make the task less demanding, thereby reducing the load on WM. The authors suggest calculating both the number of "chunking" responses as well as the number of the "dyad" responses, or correct answers provided in a sequence. As such, dyad responses are a better indicator of WM capacity on the PASAT than total correct responses. Fisk and Archibald found that compared to healthy controls, patients with MS had more "chunking" responses and fewer "dyad" responses despite having similar total correct scores. Shucard et al. (2004), using the same scoring method, found similar results in patients with systemic lupus erythematosus. Because of the predetermined fixed presentation rates of the stimuli for the PASAT, performance on this measure is dependent on a person's PS abilities. Thus, the PASAT may not be the best pure measure of WM ability.

In a previous study, we proposed that the *n*-back task, which is frequently used as a measure of WM in experimental studies, allows for the parsing of PS and WM (Parmenter et al., 2006). During the *n*-back task, participants have to decide whether a currently presented visual stimulus matches one previously presented "*n*" trials back, with "n" equaling 0, 1, or 2. For example, in the 0-back task, participants simply respond when a specified letter is presented; whereas in the 1-back task, participants have to decide if the presented letter matches the one just prior to it, or presented one back. As "*n*" increases, so does the level of difficulty of the task, and thus WM burden. In other words, a 2-back task is more challenging than a 1-back task because two stimuli must be simultaneously held in WM while one is being matched with the stimulus two back. Similar to the PASAT, WM performance on the 2-back can be measured by either total correct or correct dyads (Parmenter et al., 2006). Unlike the PASAT, the *n*-back task provides an indicator of simple PS without a WM component, as measured by reaction time (RT) on the 0-back, and a measure of complex PS, as measured by RT on the more complicated tasks (i.e., the 1- and 2-back). Thus, both PS and WM can be examined separately.

The current study was designed to explore further the distinction between PS and WM deficits in MS using the *n*-back task. We compared *n*-back performance between healthy controls and RRMS patients. Patients with RRMS have a milder form of the disease compared to those with secondary progressive MS. We hypothesized that on the *n*-back task MS patients and healthy controls would have increasingly longer RTs on each subsequent condition of the *n*-back task. In other words, for both groups, RTs will be longer on the 1-back compared to the 0-back, and on the 2-back compared to the 1-back. We also hypothesized that compared to healthy controls, MS patients would demonstrate impaired simple PS based on RT latencies on the 0-back, and impaired complex PS based on the RT latencies on the 1- and 2-back tasks, both before and after simple PS is parsed from the 1- and 2-back PS scores. Furthermore, as indicated by previous findings that PS and not WM is impaired in patients with RRMS, we hypothesized that there would be no group differences on the 2-back for total correct and total dyad responses.

METHOD

Participants

Twenty-two patients with clinically definite MS according to standard diagnostic criteria (McDonald et al., 2001) and 20 healthy controls participated in the study. All MS patients

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were diagnosed with relapsing-remitting MS at the time of the study. There were 10 female and 12 male patients. There were 15 female and 5 male controls. Participants were excluded from the study if they had a history of head trauma, hearing or visual problems, or learning disorder. Additional exclusionary criteria included psychiatric, neurologic, or medical conditions other than MS. However, because of the high prevalence rate of depression in MS, depression was allowed in the patient sample only. Informed consent was obtained for all participants and the project met the standards of the Internal Review Board of the State University of New York at Buffalo.

Participants completed a neuropsychological battery and the *n*-back tasks (0-, 1-, and 2-back) as part of an electrophysiological study of WM. The MS participants in the present study are the RRMS patients from Parmenter et al. (2006), in which PASAT and *n*-back performance was compared in a sample with RR and secondary progressive MS.

Measures

Three *n*-back tasks were administered to all participants: 0-, 1-, and 2-back. The tasks were always presented in the same order (0-, 1-, 2-back) for all participants. A practice trial preceded each condition. For the 0-back condition, the participant identified a target letter, "X," in a sequence of letters presented one at a time. For the 1-back condition, the participant compared each letter with the previously presented letter (the letter 1-back). For the 2-back condition, the participant compared each letter presented with the letter two back. The participant pressed two outer buttons of a response pad with their left and right thumbs when a match was detected, and two inner buttons with their thumbs when a nonmatch was detected. Ten letters of the alphabet were repeated and case (lower or upper) did not determine correct response. A total of 150 letters were present in each trial, and one third of the trials were a "match" and two thirds were a "nonmatch." Each condition was divided into two 75 trial blocks. Stimulus duration was 400 msec, with a 2000 msec ISI.

Correct and incorrect responses were recorded for matches and nonmatches. The number correct for the 0-, 1-, and 2-back conditions, and the number of dyads for the 1- and 2-back conditions were obtained. Dyad scores were calculated following the procedure described by Fisk and Archibald (2001) and Shucard et al. (2004). Specifically, a response was scored as a dyad if it was preceded by a correct response (e.g., consecutive correct responses). Although the dyads do not measure overall performance accuracy for the *n*-back, dyad scores reflect performance according to test instructions and, thus, WM ability.

In order to obtain full scale IQ estimates, all participants were also administered the North American Adult Reading Test (NAART). Depression was measured using the Beck Depression Inventory-II (BDI-II). Expanded Disability Status Scale (EDSS) scores were obtained for all MS patients to document neurologic functioning. The Stanford Sleepiness Scale (Hoddes et al., 1973) was administered to all participants before beginning the *n*-back task and after each *n*-back condition to obtain levels of alertness throughout the testing procedure. This scale is a brief subjective measure of arousal with a choice of seven items ranging from very alert to very sleepy.

Statistical Analyses

Independent samples *t*-tests were used to compare the two groups (healthy controls *versus* MS patients) on demographic variables, such as age, level of education, and estimated full scale IQ based on the NAART. Chi-square analyses were used to compare the two groups according to proportion of gender. Multivariate analyses of covariance (MANCOVA) were used to compare the two groups on RT for each level of the *n*-back (0-, 1-, and 2-back). Two-way ANCOVAs (group by gender) were used to compare the two groups on performance measures (total correct and total dyads) on each level of the *n*-back. One-way analyses of covariance (ANCOVA) were used to examine main effects. To control statistically for depression, total score on the BDI-II was used as the covariate in the aforementioned analyses.

To examine complex PS, difference scores were derived for each participant by subtracting RT on the 0-back condition (i.e., simple PS) from RT on the 1-back and 2-back conditions separately. These difference scores allowed us to remove simple PS from measures of more complex PS. ANCOVAs were then used to examine group differences for RT for the 1- and 2-back conditions, again using total score on the BDI-II as the covariate. Unless otherwise indicated, the *p*-value was set at 0.05.

RESULTS

Participant Characteristics

Table 1 presents demographic and health characteristics for healthy controls and MS patients. The two groups did not differ on age [$F(1,40) = 0.01$, n.s.], education [$F(1,40) =$

Table 1. Patient and control group characteristics

	MS		Healthy controls	
	M	*SD*	*M*	*SD*
Age	45.03	8.77	44.63	8.98
Education (years)	14.64	2.89	14.26	1.73
NAART	105.28	7.76	108	7.84
Health Characteristics				
EDSS	3.02	1.62	—	—
Disease duration (years)	8.72	8.74	—	—
BDI-II	11.45	10.24	2.25	3.19

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1.32, n.s.], or estimated full scale intelligence based on scores on the NAART [$F(1,40) = 0.03$, p = n.s.]. Differences in the proportion of males and females in each group approached significance ($\chi^2 = 3.80$, $df = 1$, n.s.). A significant difference between groups was found for reported subjective depression [$F(1,36) = 12.00$, $p < .01$], with MS patients reporting significantly higher levels of depression on the BDI-II ($M = 11.45$, $SD = 10.24$) compared to healthy controls ($M = 2.25$, $SD = 3.19$). Neurologic involvement according to the EDSS and disease duration are also presented for patients in Table 1.

Stanford Sleepiness Scale scores were compared to determine if level of alertness differed between the groups at four different administration times during the *n*-back task. No differences in level of alertness were found at the beginning, during, or at the end of the testing session ($t = -.761$, $t = -.512$, $t = -.828$, $t = -1.303$, all n.s.). Further, all mean scores for both groups were in the alert to very alert range.

Table 2. Group performance on the *n*-back task

	RR MS patients		Healthy controls		
	M	*SD*	*M*	*SD*	*p*
Total correct					
0-back	144.50	3.07	145.37	2.19	n.s.
1-back	138.64	6.75	141.70	3.13	n.s.
2-back	111.73	24.96	124.30	13.69	0.03
Total dyad					
1-back	130.00	5.54	135.00	5.54	n.s.
2-back	90.00	31.06	107.65	19.59	0.01
RT (sec)					
0-back	0.64	0.16	0.48	0.06	0.02
1-back	0.78	0.21	0.61	0.16	n.s.
2-back	1.02	0.24	0.75	0.15	<0.01
1-back minus 0-back	0.14	0.11	0.13	0.14	n.s.
2-back minus 0-back	0.39	0.21	0.27	0.12	<0.01

*p-values based on ANCOVAs, with total score on the BDI-II used as the covariate

Group Differences on Reaction Time

A 2 (group) × 2 (gender) × 3 (condition) analysis of covariance (ANCOVA) was used to examine the differences between groups with regard to RT on each condition of the *n*-back while statistically controlling for depression. The group × gender × condition and the group × gender interactions were not significant [$F(2,37) = .34$, n.s., $F(2,37) = 1.26$, n.s., respectively]. The group × condition interaction was significant [$F(2,35) = 4.19$, $p = .02$] and post-hoc analyses were conducted. As can be seen in Figure 1, RT for the two groups differed on the 2-back [$F(1,36) = 16.61$, $p < .01$], 1-back [$F(1,36) = 4.61$, $p = .04$], and 0-back [$F(1,36) = 6.96$, $p = .01$]. Using the Bonferroni correction method (each simple effect was tested at the $p < .02$ level), RT significantly differed between the groups for the 2- and 0-backs, and approached significance for the 1-back. The BDI-II was not a significant covariate in any of these analyses. Mean RTs are presented in Table 2. In sum, compared to controls, MS patients responded more slowly on each condition of the *n*-back, but more so for the 2-back condition relative to the 0- or 1-back.

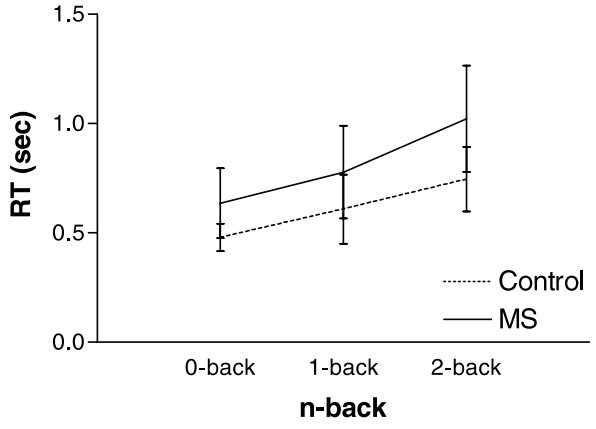

Fig. 1. Mean RT (in seconds) with standard error on each condition of the *n*-back for MS and control participants.

Analyses were also conducted on the RT difference scores (0-back RT subtracted from 1-back and 2-back conditions separately) to examine group differences after eliminating simple PS. A 2 (group) × 2 (gender) × 2 (RT/complex PS) ANCOVA was performed. Neither the group × gender × condition nor the gender × condition interactions were significant [$F(1,36) = 1.04$, n.s., $F(1,36) = 3.32$, n.s., respectively]. The group × condition interaction was significant [$F(1,36) = 5.56$, $p = .02$]. Again, using the Bonferroni correction model, each simple effect was tested at the $p < .02$ significance level. The groups did not differ significantly for complex PS/RT on the 1-back [$F(1,36) = 0.43$, n.s.]. A significant simple effect was present, however, between the MS and control groups for complex PS/RT on the 2-back [$F(1,36) = 8.36$, $p < .01$], with MS patients having significantly slower RTs compared to controls. Again, the BDI-II was not a significant covariate for any of these analyses. Thus, when complex PS was compared between the groups after the effects of simple PS were eliminated, MS patients did not differ from controls for 1-back RT, but continued to show significantly slower RTs than controls for the 2-back condition, indicating impaired complex PS during the most demanding WM task.

Group Differences in Accuracy

Two (group) × 2 (gender) ANCOVAs were also conducted between groups for performance measures (total correct and total dyads) separately for each condition of the *n*-back task (i.e., 0-, 1-, and 2-back). None of the interactions were significant. The mean performance scores for each group are presented in Table 2. There were no significant main

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effects for group for total correct on the 0- or 1-back [$F(1,35) = 0.51$, n.s.; $F(1,36) = 1.61$, n.s., respectively] or for total dyads on the 1-back [$F(1,33) = 0.96$, n.s.]. Significant main effects for group were found for total correct and total dyad on the 2-back only [total correct: $F(1,36) = 5.49$, $p = .03$; total dyad: $F(1,36) = 6.78$, $p = .01$]. The BDI-II was not a significant covariate for any of these analyses. In sum, compared to healthy controls, MS patients performed more poorly than controls only on the highest WM demand task (i.e., the 2-back; see Table 2).

DISCUSSION

The present study was designed to explore PS and WM deficits in patients with RRMS using the *n*-back task. As expected, we found that both groups had increasingly longer RTs on each subsequent trial of the *n*-back. In other words, both controls and patients had longer RTs as the complexity or WM load of the task increased from the 0-back to the 1-back to the 2-back. However, compared to controls, RRMS patients showed greater increases in RT from the 0-back to the 2-back, with more time to respond on the tasks requiring greater WM. Additionally, even when controlling for motor speed/simple PS by subtracting RT on the 0-back, MS patients had significantly longer RTs on the 2-back compared to controls, indicating that slowed motor speed alone cannot sufficiently explain these findings. In sum, both simple and complex processing speeds were impaired in patients with RRMS compared to healthy controls.

WM was measured by the total number of correct responses and the total number of dyad responses on the 1- and 2-back tasks. We found that compared to controls, patients with RRMS achieved significantly fewer total correct and total dyads on the 2-back, the condition that places the greatest demand on WM. According to the *Relative Consequence Model*, impaired processing speed accounts for deficits in WM and other cognitive domains, particularly in patients with the less severe disease course of RRMS (DeLuca et al., 2004). Therefore, if patients are allowed adequate time, they should perform within normal limits on tasks measuring these other cognitive domains. It is not until later in the disease course that true impairments occur in other domains. This notion of relative consequence has been suggested by several researchers (Archibald & Fisk, 2000; DeLuca et al., 2004; Lengenfelder et al., 2006). However, this model was not supported in the current study. Rather, we found impairments in both PS and WM in RRMS. The findings of the present study are more supportive of the *Independent Consequence Model*, which states that patients may have deficits in other domains that are not solely caused by impaired PS (DeLuca et al., 2004).

The *Independent Consequence Model* suggests that impairments in separate domains are relatively independent of each other; although, this is not to imply that the cognitive domains are mutually exclusive (DeLuca et al., 2004). On the contrary, PS is an important component of many cognitive domains including WM (Salthouse, 1996). However, according to the results of the current study, deficient PS cannot fully account for the impairments in RRMS seen in WM. Rather, at least one component of WM is also affected, either one of the slave systems (i.e., visuospatial sketchpad or phonological loop) or the central executive system. This finding is true even for patients with RRMS, the least severe form of the disease, and this could be related to white matter and gray matter changes reported to occur early in the disease course (Amato et al., 2004; Deloire et al., 2005; Tiberio et al., 2005; Valsasina et al., 2005).

One possible explanation for the differences in findings between the current study and previous studies (Archibald & Fisk, 2000; DeLuca et al., 2004) involves the tasks used to measure WM. In previous studies, WM was assessed using either an experimental measure developed by Salthouse (Archibald & Fisk, 2000), or the Working Memory Index from the Wechsler Memory Scale-III (DeLuca et al., 2004). The Working Memory Index is comprised of the Spatial Span and Letter-Number Sequencing subtests. However, these tests are broken up into trials and are relatively brief. Specifically, during the Letter-Number Sequencing subtest, a patient is provided with up to eight numbers and letters. They are allowed to take as much time as needed to mentally reorganize them and respond. Then the next series of letters and numbers are presented. In other words, the task is not continuous, but rather broken up into short trials. The *n*-back task, on the other, is continuous and requires approximately six minutes to complete each condition. As such, it may be that the *n*-back paradigm is either a more sensitive measure of WM than the Working Memory Index, or that these tests measure different abilities.

A potential limitation of the study is that patients had to respond to each stimulus within 2.0 seconds. It could be argued that patients achieved fewer total correct and fewer total dyad scores because of impaired complex PS. Thus, their impaired performance may have been because of a PS deficit and not a deficit in WM. This conclusion is not likely, however, because the mean response times for patients and controls were always less than two seconds. For example, for the 2-back trial, the mean response time for patients was 1.02 seconds with a standard deviation of 0.24 seconds. The longest length of time required to respond correctly by anyone in the study was 1.51 seconds. Therefore, lack of adequate time, or impaired complex processing speed, cannot adequately explain why patients performed more poorly than controls on the WM component of the task.

The length of time to complete the version of the *n*-back used in the current study could have potentially produced fatigue, which, in turn, could have influenced the results. Each trial lasted approximately six minutes, with one short break in the middle of each trial and a longer break between trials. Total time to complete the *n*-back, including administering task instructions, was approximately 20 minutes. It is possible that the patients experienced significant fatigue, especially by the time they were administered the 2-back trial. Although we did not measure fatigue directly, we did

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administer the Stanford Sleepiness Scale (SSS) before the *n*-back commenced and after each *n*-back condition, and found no differences in mean scores between patients and controls. Fatigue and sleepiness are unique constructs; however, research has shown that scores on the SSS are significantly correlated with scores on subjective measures of fatigue, such as the Fatigue Severity Scale and the Chadler Fatigue Scale (Bailes et al., 2006). The research examining the relationship between fatigue and cognitive functioning in MS is mixed, however, as some studies have found a significant relationship (Cohen & Fisher, 1989; Geisler et al., 1996; Krupp & Elkins, 2000), whereas others have not (Beatty et al., 2003; Parmenter et al., 2003). Nonetheless, future research should specifically look at the unique construct of fatigue and its relationship to performance on the *n*-back task.

Another limitation of this study is the relatively small sample size. There were only 20 healthy controls and 22 RRMS patients. Furthermore, the MS sample was not representative of the proportion of females to males in the MS population because there were more males than females (12 *versus* 10, respectively); whereas MS more commonly affects women than men. Even though we did not find any gender effects in our analyses the current results should be replicated with a larger sample size and with a sample more representative of the gender ratio in MS.

The findings of the present study, with the *n*-back paradigm as a measure of PS and WM, are interesting and provide new information about the relationship between PS and WM in RRMS. By using the *n*-back paradigm, we are able to show that both cognitive domains are impaired, even early in the course of the disease. This is in direct contrast to previous research that suggested that only PS was impaired in patients with RRMS and that if provided with adequate time, these patients could perform normally on measures of WM. It is possible that the WM deficits in RRMS patients are subtle and that many WM measures commonly used are not sensitive enough to detect them. The *n*-back, on the other hand, may allow for earlier detection of such impairments.

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