Reduction in Cognitive Processing Speed Surrounding Multiple Sclerosis Relapse

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Objective: The purpose of this study was to explore the longitudinal relationship between multiple sclerosis (MS) relapses and information processing efficiency among persons with relapsing–remitting MS.
Methods: We conducted a Swedish nationwide cohort study of persons with incident relapsing–remitting MS (2001–2019). Relapse information and symbol digit modalities test (SDMT) scores were obtained from the Swedish MS Registry. Follow-up was categorized into 2 periods based on relapse status: "relapse" (90 days pre-relapse to 730 days post-relapse, subdivided into 10 periods) and "remission." Linear mixed models compared SDMT scores during the relapse periods to SDMT scores recorded during remission (reference) with results reported as β-coefficients and 95% confidence intervals (CIs), adjusted for age, sex, SDMT type (written vs oral), time-varying, disease-modifying therapy exposure and sequence of SDMT.
Results: Over a mean (SD) follow-up of 10.7 (4.3) years, 31,529 distinct SDMTs were recorded among 3,877 persons with MS. There was a significant decline in information processing efficiency that lasted from 30 days pre-relapse up to 550 days post-relapse, with the largest decline occurring 0 to 30 days post-relapse (β-coefficient: −4.00 (95% CI = −4.61 to −3.39), relative to the period of remission.
Interpretation: We found evidence of cognitive change up to 1 month prior to relapse onset. The reduction in SDMT lasted 1.5 years and was clinically significant up to 3 months post-relapse. These results suggest that the effects of a relapse on cognition are longer than previously thought and highlight the importance of reducing relapse rates as a potential means of preserving cognitive function.

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system (CNS), with a varied symptomology, including both mental and physical changes. Impaired cognition, in particular, is common in MS, with prevalence estimates ranging from 34% to 65%.[1] Cognitive impairment can occur at all stages of disease and can even precede its clinical recognition.[2] Despite its integral role in quality of life,[3] medication adherence,[4] and ability to work,[5] cognitive impairment remains a largely overlooked and undertreated symptom of MS.[1]

Acute inflammation in the CNS is a hallmark of MS, particularly in the early stages of disease.[6] Depending on the location of inflammation, relapses can present in a myriad of ways, including sensory and motor impairments, fatigue, and bladder dysfunction.[6] Prior research has shown that relapses can impair cognition temporarily, but it typically rebounds after a few months.[7] However, most research has focused on this 3-month period post-relapse[7–9]; therefore, little is known about the longer-term effects of a relapse on cognition[1] or the period directly preceding a relapse. We aimed to explore the longitudinal relationship between MS relapses and information processing efficiency among persons with relapsing–remitting MS across Sweden.

Methods

Study Cohort

Cases were derived from the Swedish MS registry (SMSreg), a nationwide web-based platform in which neurologists prospectively collect and input detailed clinical data from patients with MS (nationwide start date: January 1, 2001).[10] Information in the SMSreg relevant to this study includes date of MS onset and diagnosis, disease course, year of conversion to secondary-progressive MS (SPMS), disease-modifying therapy (DMT) exposure (product name, and start and stop dates), relapses, and symbol digit modalities (SDMT) scores (Table 1).

To be included, persons must have met the following criteria:

- Clinically definite relapsing–remitting MS with an onset between January 1, 2001, and December 31, 2016.
- A minimum of 1 relapse recorded during follow-up (to ensure inclusion of only participants with active disease followed in clinics which recorded relapses).
- A minimum of 2 SDMT scores recorded.
- A minimum of 3 years of follow-up in the SMSreg from MS onset.

Participants were followed from their MS onset until January 1 of the year that they converted to SPMS, their date of death or emigration from Sweden, or the last date of follow-up (December 31, 2019), whichever came first.

Exposures

Relapses are recorded by the neurologist and include information on the start date and symptoms (isolated optic neuritis, afferent or efferent symptoms, and monofocal or multifocal symptoms). They are defined as "new symptoms or worsening of prior symptoms, lasting ≥24 hours, separated from a previous relapse by at least 30 days, and occurring in the absence of fever or infections."

We categorized the complete follow-up time into 2 periods based on relapse status: "relapse" and "remission." The relapse period covered the time surrounding a relapse: 90 days pre-relapse (categorized into 3 periods: 90–61 days, 60–31 days, and 30–1 day pre-relapse), and 2 years post-relapse (categorized into 7 distinct periods following the onset of a relapse: 0–30 days; 31–60 days; 61–90 days; 91–180 days; 181–365 days; 366–550 days; and 551–730 days). The "remission" period encapsulated all

TABLE 1. Clinical and Demographic Characteristics of the Cohorts

n	3,877
Onset age in yr (mean [SD])	31.64 (9.51)
Age at first SDMT in yr (mean [SD])	36.63 (10.13)
Disease duration at first SDMT in yr (median [IQR])	4.19 [1.64, 7.40]
Female sex	
n (%)	2,741 (70.7)
Region of Sweden, n (%)	
South	1,660 (42.8)
Central	1779 (45.9)
North	438 (11.3)
Total relapses recorded during follow-up (median [IQR])	2.00 [1.00, 3.00]
Baseline SDMT score (mean [SD])	52.39 (11.91)
Cognitively impaired at baseline[a]	
n (%)	1,035 (38.5)
ARR in first 3 yr of disease (median [IQR])	0.33 [0.33, 0.67]
Follow-up time in yr (mean [SD])	10.74 (4.34)
DMT at baseline (%)	
None	468 (12.1)
First-line	329 (8.5)
Second-line	3,080 (79.4)

Baseline was the date of the first SDMT evaluation.
[a]Including only participants who completed the oral SDMT at baseline (n = 2,687).
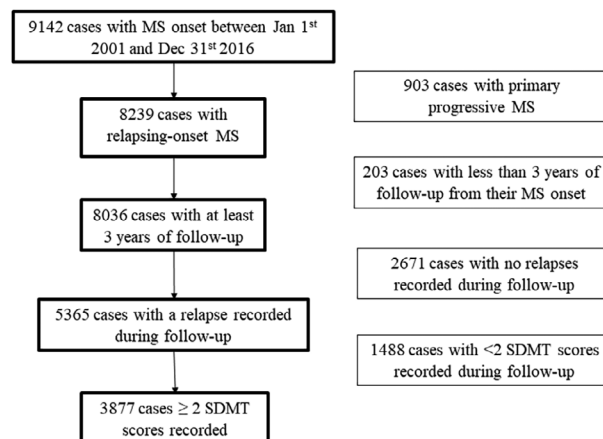ARR = Annualized relapse rate; DMT = disease-modifying therapy; IQR = interquartile range.

FIGURE 1: Flowchart of cohort selection. MS = multiple sclerosis; SDMT = symbol digit modalities test.

follow-up time outside of this window (>90 days pre-relapse or >730 days following a relapse). If a second relapse occurred within 2 years of an earlier relapse, the later relapse then became the "index" relapse and the SDMTs that followed were considered in relation to that relapse. Further, if an SDMT fell within the post-relapse period of an earlier relapse, as well as the pre-relapse period of a subsequent relapse, the earlier relapse acted as the index relapse.

Outcome

The SDMT is a cognitive screener which measures a component of cognition, information processing efficiency.[11] In 2006, the SDMT was introduced into clinical practice

TABLE 2. Results of the Linear Mixed Models Analyses of SDMT Scores During the Relapse Period in Comparison to the Remission Period

	Unadjusted model β-coef (95% CI)	Adjusted model 1[a] β-coef (95% CI)	Adjusted model 2[b] β-coef (95% CI)
(Intercept)	57.07 (56.67 to 57.48)	58.85 (57.57 to 60.13)	72.38 (71.11 to 73.65)
Time in relation to relapse			
In remission (ref)	0	0	0
−90 to −61 days	−1.64 (−3.34 to 0.05)	**−1.71 (−3.41 to −0.02)**	−0.61 (−2.19 to 0.96)
−60 to −31 days	**−2.74 (−4.42 to −1.05)**	**−2.80 (−4.48 to −1.11)**	−1.52 (−3.09 to 0.05)
−30 to −1 days	**−3.65 (−5.25 to −2.04)**	**−3.72 (−5.33 to −2.11)**	**−2.10 (−3.60 to −0.60)**
0–30 days	**−5.86 (−6.50 to −5.22)**	**−5.97 (−6.61 to −5.32)**	**−4.00 (−4.61 to −3.39)**
31–60 days	**−5.70 (−6.31 to −5.09)**	**−5.81 (−6.43 to −5.19)**	**−3.54 (−4.12 to −2.95)**
61–90 days	**−5.64 (−6.31 to −4.96)**	**−5.74 (−6.42 to −5.06)**	**−3.26 (−3.89 to −2.62)**
91–180 days	**−5.48 (−5.94 to −5.03)**	**−5.59 (−6.05 to −5.12)**	**−2.72 (−3.16 to −2.28)**
181–365 days	**−4.01 (−4.33 to −3.69)**	**−4.10 (−4.43 to −3.77)**	**−1.64 (−1.96 to −1.32)**
366–550 days	**−2.52 (−2.83 to −2.21)**	**−2.60 (−2.92 to −2.28)**	**−0.59 (−0.89 to −0.28)**
551–730 days	**−1.67 (−2.00 to −1.34)**	**−1.73 (−2.07 to −1.40)**	−0.11 (−0.43 to 0.20)
Age at SDMT	N/A	−0.03 (−0.06 to 0.00)	**−0.44 (−0.47 to −0.41)**
Sex	N/A		
Female (ref)		0.00	0.00
Male		**−1.76 (−2.63 to −0.89)**	**−1.86 (−2.68 to −1.04)**
SDMT type	N/A	N/A	
Oral (ref)			0.00
Written			**−0.91 (−1.24 to −0.59)**
DMT exposure	N/A	N/A	
None (ref)			0.00
First-line			−0.19 (−0.53 to 0.14)
Second-line			−0.08 (−0.31 to 0.15)
SDMT sequence (continuous)	N/A	N/A	**0.50 (0.49 to 0.52)**

Statistically significant findings are in bold text.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, SDMT type, DMT exposure, and SDMT sequence.
β-coef = beta coefficient; CI = confidence interval; DMT = disease-modifying therapy; N/A = not applicable; SDMT = symbol digit modalities test.
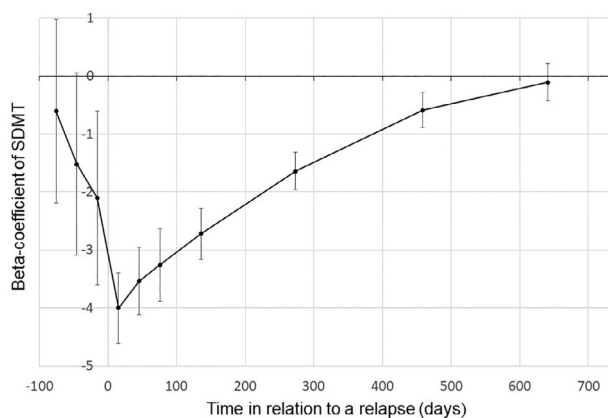
FIGURE 2: Difference in SDMT score during the relapse period compared to the remission period (reference, represented by 0 on the y-axis). SDMT = symbol digit modalities test.

in Sweden as part of a postmarketing observational study of newly available DMTs, and gradually became a component of routine clinical care across the country, regardless of treatment status. The number of annual tests increased steadily from 2006 to 2014, at which time the total number of tests stabilized between 7,500 and 8,500 per year, nationwide.[12] The SDMT follows a normal distribution, with scores ranging from 0 to 110 (higher scores represent faster information processing). Across Sweden, MS clinics used the oral SDMT, apart from clinics within Stockholm county, which used the written form between 2006 and 2017, after which the oral form was used.

Statistical Analysis

We summarized categorical variables using frequency (percent) and continuous variables using mean (standard deviation [SD]) or median (interquartile range [IQR]). The first recorded SDMT was considered the baseline visit. Persons were classified as "cognitively impaired" or "unimpaired" at baseline based on regression-based norms for the oral SDMT (persons who completed the written form were excluded).[13,14] The change in SDMT over follow-up was measured per year using linear mixed models and stratified by cognitive status at baseline. Linear mixed models were used to compare the SDMT score over the pre- and post-relapse periods to SDMT scores recorded during remission (reference period). Results were reported as β-coefficients with 95% confidence interval (CI). Covariates included age at each SDMT, sex, form of the SDMT (written versus oral), SDMT sequence, and DMT exposure (first- or second-line relative to no DMT) at the time of the SDMT. First-line DMTs included interferons, glatiramer acetate, teriflunomide, and dimethyl fumarate. Second-line DMTs included

fingolimod, hematopoietic stem cell transplantation, alemtuzumab, rituximab, ocrelizumab, cladribine, mitoxantrone, daclizumab, and natalizumab.

Sensitivity Analyses. We completed 2 sensitivity analyses. In the first analysis, we removed all persons who had optic neuritis given that visual difficulties could reduce one's ability to perform the SDMT. In the second analysis, we excluded all persons who had completed the written form of the SDMT, as the physical symptoms of a relapse may have influenced their performance.

Results

Over a mean (SD) follow-up of 10.7 (4.3) years, 31,529 distinct SDMTs were recorded among 3,877 persons with incident relapsing–remitting MS across Sweden (see Fig 1 for cohort selection). Most participants were women (70.7%) and the mean (SD) onset age was 31.6 (9.5) years. The majority of participants were receiving a second-line therapy as of their baseline visit (79.4%).

At the baseline visit, 38.5% of the cohort met the definition for "cognitive impairment," based on their age- and sex-expected norms.[13,14] On average, the SDMT score declined 0.85 points per year (95% CI = −0.97 to −0.73) in the full cohort. When stratified by cognitive status at baseline, the annual decline on the SDMT was higher in those who were unimpaired (−1.22; 95% CI = −1.41 to −1.04) than impaired (−0.45; 95% CI = −0.68 to −0.22). Of the SDMTs recorded, 10,531 occurred within 90 days pre- or 730 days post-relapse, whereas 20,998 occurred during the remission period. The median (IQR) annualized relapse rate (ARR) in the first 3 years of disease was 0.33 (0.33, 0.67).

In the unadjusted linear mixed model, there was a significant decline in information processing efficiency that lasted from 60 days pre-relapse up to 730 days post-relapse, with the largest decline occurring 0 to 30 days post-relapse (Table 2), β-coefficient: −4.00 (95% CI = −4.61 to −3.39). Adjusting for age at SDMT and sex did not meaningfully alter the results. However, following adjustment for age, sex, SDMT type and sequence, and DMT exposure, the results were attenuated. The decline in SDMT score began up to 30 days pre-relapse and was no longer significant at 551–730 days post-relapse (Table 2, Fig 2). The change in results was largely driven by the inclusion of SDMT sequence; each additional SDMT that a person completed was associated with a 0.50 (95% CI = 0.49 to 0.52) improvement in score (see Table 2).

Sensitivity Analyses. After excluding all SDMTs which were recorded during a relapse for which optic neuritis

TABLE 3. Results of the Sensitivity Analyses of SDMT Scores During the Relapse Period in Comparison to the Remission Period, Excluding Persons with Optic Neuritis Relapse (Analysis 1) and Excluding the Written Form of the SDMT (Analysis 2)

	Analysis 1[a] Excluding optic neuritis	Analysis 2[b] Excluding written form of SDMT
(Intercept)	71.78 (70.49 to 73.07)	70.84 (72.2 to 73.57)
Time in relation to relapse		
In remission (ref)	0	0
−90 to −61 days	−0.63 (−2.47 to 1.21)	−0.74 (−2.63 to 1.14)
−60 to −31 days	−1.70 (−3.59 to 0.18)	−1.36 (−3.19 to 0.48)
−30 to −1 days	**−2.41 (−4.31 to −0.52)**	**−2.41 (−4.12 to −0.71)**
0–30 days	**−3.53 (−4.25 to −2.80)**	**−4.03 (−4.75 to −3.32)**
31–60 days	**−3.55 (−4.25 to −2.85)**	**−3.45 (−4.13 to −2.77)**
61–90 days	**−3.09 (−3.85 to −2.32)**	**−3.25 (−3.99 to −2.50)**
91–180 days	**−2.62 (−3.15 to −2.08)**	**−2.85 (−3.37 to −2.34)**
181–365 days	**−1.65 (−2.03 to −1.28)**	**−1.63 (−2.00 to −1.25)**
366–550 days	**−0.63 (−1.00 to −0.27)**	**−0.48 (−0.83 to −0.13)**
551–730 days	−0.30 (−0.68 to 0.09)	−0.10 (−0.47 to 0.26)

Statistically significant findings are in bold text.
[a]Adjusted for age, sex, SDMT type and sequence, and DMT exposure.
[b]Adjusted for age, sex, SDMT sequence, and DMT exposure.
DMT = disease-modifying therapy; SDMT = symbol digit modalities test.

was noted as the primary characteristic of the relapse, there were 3,815 persons and 27,945 SDMTs available for analysis. The results were consistent with the primary analysis. Removing all written SDMTs (26,106 SDMTs were included among 3,783 individuals) did not alter the findings (Table 3).

Discussion

In this nationwide study of nearly 4,000 patients with MS followed for an average of 10 years, we found a distinctive pattern of cognitive changes surrounding the relapse period. Up to 30 days prior to a relapse, there was evidence of cognitive decline, which worsened immediately following a relapse, and subsequently improved, only reaching the "remission" levels after 1.5 years.

The mechanistic basis of cognitive impairment in MS is still not fully understood, and its manifestation is highly variable between patients.[1] Cortical lesions, grey matter atrophy, and altered patterns of connectivity within the cerebral cortex have consistently been associated with impairments to cognition, and likely contribute to the declining cognition seen over time.[15] We also know that inflammation can alter the capacity of synapses to function as a component of the circuitry necessary for the storage, organization, and recovery of information,[15] perhaps leading to temporary declines in cognitive functioning. Both gadolinium-enhancing lesions on magnetic resonance imaging (MRI)[16] and circulating pro-inflammatory cytokines[17] (representing acute inflammation) have been linked to reductions in cognitive performance. Here, we have shown that acute inflammation, as measured by clinical relapse, can lead to transitory changes in cognition as well.

Our study identified a pre-relapse decline in information processing efficiency, suggestive of a subclinical period of inflammation immediately preceding the clinical recognition of a relapse. Risk factors for relapse include stress and infection,[18] both of which are associated with systemic heightened inflammation.[19,20] It is possible that the measurable change in information processing efficiency that we observed may be an indication or consequence of this pre-relapse inflammation. From a clinical perspective, this could also represent an opportunity to efficiently screen for disease activity.

The SDMT is considered a valid and reliable measure of cognition in MS.[21] It has been evaluated in the context of clinical relapses previously and the change associated with this period of time contributed to the notion of a "clinically important change" of 3 to 4 points on the scale.[21] This change has been associated with increased odds of converting from gainful employment to unemployment.[22] In the analysis which did not include practice effects, our results showed a clinically important change up to 1 year post-relapse. However, when accounting for the improvements that people experienced as they practiced the SDMT, this time was reduced to 90 days post-relapse.

Multiple studies have explored the relationship between relapses and cognition, using the SDMT,[7–9,23] 2 of which focused on isolated cognitive relapses.[24,25] Follow-up time from relapse ranged from 1 month to 1 year, and only 3 studies had ≥100 patients.[7,8,23] All studies compared a relapsing group to a stable group, such that the differences observed were entirely between groups. Consistently, these studies have demonstrated a clinically significant drop in the SDMT, followed by recovery. However, the scale of this reduction varied widely between studies, from −13.9 to −2.3 below the stable (non-relapsing) control group.[1] Further, there was variability in the time to recovery; some groups reported lasting effects on the SDMT at 12 months post-relapse (maximum follow-up), whereas others reported a return to remission levels at 1 month post-relapse.[1] The 2 studies which reported the most extreme results (in terms of effect size and time to recovery) focused on isolated cognitive relapses (ICRs), defined as "a transient reduction in cognitive functioning not associated with other subjective or objective neurological symptomatology."[24] Although the sample size was small in each study (fewer than 20 patients who experienced an ICR), they highlight that cognitive decline can, in and of itself, act as evidence of a relapse, verifiable by the presence of gadolinium-enhancing lesions. Our own study did not include ICRs, as they were not recognized as relapses in Sweden during the study period. It is expected that the inclusion of such relapses would lead to even higher effect sizes than we observed.

Our study was unique in that we were able to include within-person differences, as individuals contributed to both relapsing and remission periods. Further, the long follow-up enabled us to track people over time and determine, on average, when most persons return to the "remission" SDMT level. Excluding persons with optic neuritis and those who completed the written form of the SDMT, further strengthened our findings to show that these changes do not appear to be caused by visual or physical impairments experienced during the relapse. Nevertheless, it is possible that other noncognitive effects may have contributed to the reduction in SDMT that was observed during an active relapse, such as increased fatigue,[26] for which we lacked information.

There was robust evidence of a learning effect over time on the SDMT. Each additional SDMT that a person completed was associated with a 0.5-point higher SDMT score. Practice effects have been noted in prior studies of repeated SDMT administration among persons with MS.[27,28] Whether this improvement is due to DMT exposure has also been addressed. A prior study was able to disentangle the effects of natalizumab exposure and practice effects, and showed that the improvements over time were related to practice and not the effect of therapy.[28] Similarly, we found no effect of being on a first- or second-line therapy on SDMT, although our measure of DMT exposure did not account for duration of exposure, nor the potential influence of lack of adherence or confounding by indication.

Our study has several limitations. First, the relapse data in the Swedish MS Registry is not complete. A validation of a subset of clinic charts in the registry found that the registry data was highly accurate in recording relapses (94% were confirmed by medical record review), but that many were not recorded (35%).[29] For this reason, we elected to only include persons with a minimum of one relapse recorded during follow-up in our analyses. Persons with zero relapses recorded were assumed to be more likely related to missing data. Nevertheless, it is still possible that SDMTs which were analyzed as "in remission" were, in fact, occurring during a relapse. This would have had the effect of diminishing our effect estimates. Further, the only cognitive measure we had access to was the SDMT. Although the SDMT is a sensitive tool, it lacks specificity, meaning that it does not inform us about the underlying mechanisms of cognitive impairment,[30] and captures only the domain of information processing efficiency.

This large, population-based study provides evidence of a transient pre- and post-relapse effect on cognition, which lasted substantially longer than previous reports. How this contributes to the longer-term accumulation of cognitive disability is an important question to be addressed in future research. From a clinical perspective, this provides evidence of the importance of reducing the occurrence of relapses as a potential means of mitigating the cognitive effects of the disease.

Acknowledgments

Author Contributions

K.A.M., K.F., and A.M. contributed to the conception and design of the study. K.A.M., J.H., L.S., and T.O. contributed to the acquisition and analysis of data. K.A.M., S.B., A.M., L.S., T.O., J.H., and K.F. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

K.A.M., S.K.B., A.M., L.S., T.O., J.H., and K.F. report no conflicts of interest for this work.

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