

Expanding the Connection Between Cognition and Illness Intrusiveness in Multiple Sclerosis

Aprille Gangi, BS*; Sarah A. Raskin, PhD; Aaron P. Turner, PhD; Frederick W. Foley, PhD; Lindsay O. Neto, MPH; and Elizabeth S. Gromisch, PhD

ABSTRACT

BACKGROUND: Multiple sclerosis (MS) disease factors, such as cognitive impairment, can cause disruptions in meaningful activities, also known as illness intrusiveness. Although the association between specific objective measures of cognition and illness intrusiveness has been documented in MS, the contributions of individuals' perceptions of their cognition or whether any psychological factors can buffer the relationship have yet to be explored. This study aimed to (1) simultaneously examine objective processing speed and subjective cognition as disease factors contributing to illness intrusiveness and (2) explore whether resilience moderates the relationship between cognition and illness intrusiveness.

METHODS: Participants (N = 112) were individuals with MS who completed the Illness Intrusiveness Ratings Scale (IIRS), Symbol Digit Modalities Test (SDMT), Perceived Deficits Questionnaire (PDQ), and MS Resiliency Scale (MSRS) as part of a larger cross-sectional study. A hierarchical linear regression was done, followed by individual moderation analyses.

RESULTS: Both the PDQ ($b = .43, P = .001$) and SDMT ($b = -4.17, P = .003$) were independent predictors of the IIRS. There was no evidence of moderation in either model, although the MSRS independently contributed to the IIRS.

CONCLUSIONS: Among individuals with MS, objective processing speed and subjective cognition were independently associated with illness intrusiveness, highlighting the importance of considering both cognitive performance and perceptions as contributing factors to life disruptions.

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Multiple sclerosis (MS) is a neurological disorder that affects millions of individuals worldwide.¹ With an average onset at age 32 years, it is the most common neurological cause of disability for young adults.² As a result of disease-related changes, individuals with MS can experience diminished health-related quality of life (HRQOL).³ A significant component of HRQOL is illness intrusiveness, or the extent to which chronic illness disrupts daily life activities such as relationships, work, and other interests.⁴ Individuals with MS tend to endorse higher levels of illness intrusiveness compared with individuals with other conditions, such as rheumatoid arthritis and end-stage renal disease.⁵ Illness intrusiveness has been conceptualized as the outcome of several factors, including both the direct impact of various characteristics of a disease and/or its treatments and the extent to which these characteristics are moderated by psychological, contextual, and social risk and protective factors.⁶ Consequently, examinations of illness intrusiveness should consider the potential contribution of both of these influences.

Several disease factors have been explored as contributing to illness intrusiveness in individuals with MS,^{5,7-11} including cognitive impairment, which is estimated to occur in up to 70% of individuals with MS.¹² Processing speed is the most common cognitive deficit in MS^{13,14} and an underlying contributor of other cognitive issues, such as executive function, working memory, and attention.^{15,16} Examination of the role of cognition in illness intrusiveness has produced mixed findings, likely due to differences in the cognitive domains assessed. Two studies did not find a relationship between complex attention (measured with the Paced Auditory Serial Addition Test; PASAT) and illness intrusiveness.^{8,9} However, both verbal learning (via the California Verbal Learning Test first edition; CVLT)⁹ and processing speed (via the Symbol Digit Modalities Test; SDMT)¹⁰ were associated with illness intrusiveness, with the latter study noting that illness

Neuroscience Program (AG, SAR) and Department of Psychology (SAR), Trinity College, Hartford, CT; Multiple Sclerosis Center of Excellence West, Veterans Affairs, Seattle, WA (APT); Rehabilitation Care Service, VA Puget Sound Health Care System, Seattle, WA (APT); Department of Rehabilitation Medicine, University of Washington, Seattle, WA (APT); Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, NY (FWF); Holy Name Medical Center Multiple Sclerosis Center, Teaneck, NJ (FWF); Mandell Center for Multiple Sclerosis, Mount Sinai Rehabilitation Hospital, Trinity Health of New England, Hartford, CT (LON, ESG); Department of Rehabilitative Medicine (LON, ESG) and Department of Medical Sciences (ESG), Frank H. Netter MD School of Medicine, Quinnipiac University, North Haven, CT; Department of Neurology, University of Connecticut School of Medicine, Farmington, CT (ESG). *Correspondence:* Elizabeth S. Gromisch, PhD, 490 Blue Hills Avenue, Hartford, CT 06112; email: elizabeth.gromisch@trinityhealthofne.org.

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intrusiveness acted as a significant intermediary between cognition and mood.¹⁰

To date, all studies investigating the role of cognitive impairment in illness intrusiveness among individuals with MS have used performance-based measures (ie, objective cognition).⁸⁻¹⁰ The potential role of self-reported cognitive functioning (ie, subjective cognition) remains unknown. Although subjective cognition can be influenced by factors such as depression and fatigue,¹⁷ it can provide insights into individuals' perceptions of their functioning, which may influence how intrusive they view their MS to be. The association between subjective cognition and illness intrusiveness has been documented in individuals with metastatic non-small cell lung cancer; those who reported clinically significant cognitive concerns had higher levels of illness intrusiveness.¹⁸ However, illness intrusiveness was not associated with performance-based cognitive impairment in this population, as determined through a multidomain cognitive battery.¹⁸ In those with MS, there is evidence that both objective and subjective cognition contribute to HRQOL, though they may influence HRQOL through different pathways.¹⁹

Based on the theoretical model of illness intrusiveness,⁶ the relationship between a disease factor and illness intrusiveness may be moderated by psychological factors. Using this conceptualization, a protective psychological factor could buffer the negative effects that cognitive impairment has on illness intrusiveness. Buffering effects that are amenable to psychological modification hold considerable promise as potential targets for interventional strategies. One consideration is resilience, a positive psychological construct associated with adjustment to chronic conditions, including better functional outcomes.^{20,21} Resilience has been positively associated with HRQOL²²⁻²⁴ and processing speed²⁵ in individuals with MS, although the latter was no longer significant after controlling for mood and fatigue. In populations without MS, resilience has been related to fewer cognitive problems²⁶ and better cognitive performance.^{27,28}

This study aims to expand the literature on the role of cognition in illness intrusiveness in MS. The primary aim is to examine simultaneously the association of objective processing speed and subjective cognition as disease factors associated with illness intrusiveness. The hypothesis is that both slowed processing speed and greater perceived cognitive difficulties will be independently associated with illness intrusiveness. A secondary aim is to explore whether resilience moderates the relationship between cognition and illness intrusiveness. Given the positive associations of resilience with HRQOL in MS²²⁻²⁴ and reported cognitive difficulties²⁶ and performance^{27,28} in other populations, we believe that the strength between illness intrusiveness and objective processing speed and between illness intrusiveness and subjective cognition will be buffered by higher resilience.

METHODS

Participants

Study data used were part of a secondary analysis of a cross-sectional study conducted at the Trinity Health of

New England Mandell Center for Multiple Sclerosis Care and Neuroscience Research and were collected between June 2019 and September 2020.²⁹ The variables used for current analyses were extracted from the existing data set. As noted in the parent study, inclusion criteria for participants (N = 112) were (1) MS diagnosis, (2) age 18 to 89 years, (3) English speaker, and (4) relapse-free period for the past 2 months.²⁹ Individuals with MS and other comorbidities, such as chronic medical (eg, hypertension) and mental health (eg, depression) conditions, were eligible. The sample size for the parent study was calculated to have adequate power for a linear regression, allowing for a medium effect size, up to 11 variables, and an α of 0.05.^{29,30} The study was approved by the Trinity Health of New England Institutional Review Board and all participants were required to sign an informed consent before participation.

As previously reported,²⁹ the average participant was 51.03 years old (SD=12.23) with 15.21 years (SD=2.29) of education. Most participants were women (74.1%), White (85.7%), and non-Hispanic (92.0%) and had moderate levels of disability (median 2; range, 0-7) as measured by the Patient Determined Disease Steps (PDDS) scale.³¹⁻³⁴ The most common type of MS was relapsing-remitting (n=90). On average, participants had a disease duration of 14.40 years (SD=9.31).

Measures

Demographics

Participants completed a questionnaire designed specifically for the parent study²⁹; for the current study, gender, age, race, ethnicity, and education were extracted for analyses, with type of MS and disease duration used for descriptive purposes only. Race was recategorized as White and non-White secondary to low counts of other categories (Black, multiracial, or other). Disability was self-reported using the PDDS, in which responses ranged from 0 (normal) to 8 (bedridden).³¹⁻³⁴

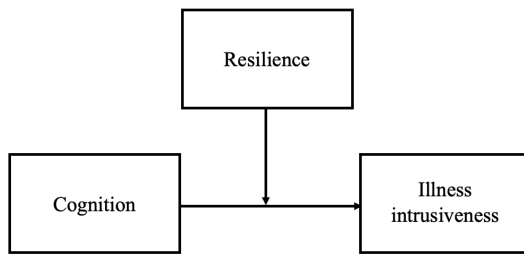
Illness Intrusiveness Ratings Scale (IIRS)

The IIRS is a 13-item self-report measure in which participants rate the level of intrusiveness of their MS in different aspects of their lives (eg, health, work, and relationships) using a Likert scale ranging from 1 (not very much) to 7 (very much).⁶ The total score (range, 13-91) is calculated by summing all the items, with higher scores indicative of greater intrusiveness.⁶ The IIRS has been used in MS,⁶ with an internal consistency (α) of 0.88 noted in the current sample.

SDMT

The SDMT is a performance-based measure of cognitive functioning that taps into multiple domains, including processing speed.³⁵ It was selected as the measure of objective cognition as it is a sensitive measure for MS-related cognitive impairment³⁶ and is often used as a screening measure.³⁶⁻³⁸ The oral version of the test was used, in which participants stated the number that corresponded with the symbol.³⁹ A z score was generated based on the number of correct responses within 90 seconds using published normative data adjusted for age and education.³⁹ The

FIGURE 1. Theoretical Model of Resilience Moderating the Relationship Between Cognition and Illness Intrusiveness



same normative data were used in a previous study examining the SDMT in relation to the IIRS.¹⁰

Perceived Deficits Questionnaire (PDQ)

The PDQ assesses participants' perceptions of their attention/concentration, retrospective memory, prospective memory, and planning/organization.^{40,41} The measure contains 20 cognitive difficulties, and participants rate how often they have experienced them over the past 4 weeks using a Likert scale ranging from 0 (never) to 4 (almost always).⁴¹ The total score (range, 0-80) is calculated by summing all the items, with higher scores indicative of greater cognitive difficulties.⁴¹ In the current sample, the PDQ had an internal consistency of 0.94.

Multiple Sclerosis Resiliency Scale (MSRS)

Resilience was measured with the MSRS, which taps into the psychological, social, and physical factors associated with resilience in MS.⁴² For each of the 25 items, participants use a Likert scale to indicate their level of agreement. The total score (range, 25-100) is calculated by summing all the items, with higher scores indicative of greater resilience.⁴² The MSRS has strong psychometric properties,⁴²⁻⁴⁴ and the measure had an internal consistency of 0.86 in the current sample.

Statistical Analyses

IBM SPSS version 26 was used for data analyses. A hierarchical linear regression was used to examine the associations of objective processing speed and subjective cognition with illness intrusiveness. Age, gender, race, ethnicity, and education were included in the first step to control for demographics that might influence the model. For instance, the PDQ does not have demographically corrected scores, while race/ethnicity differences have been noted on the SDMT.⁴⁵ In addition, a study has shown that men with MS can present with more cognitive impairment than women.⁴⁶ The PDQ and SDMT were entered into steps 2 and 3 of the regression, respectively, to assess their individual contributions to illness intrusiveness. All assumptions for a hierarchical regression were met including linearity, homoscedasticity, and independence.

Hayes' PROCESS macro for SPSS⁴⁷ was used to conduct the moderation analyses, with cognition as the independent variable, illness intrusiveness as the dependent variable, and resilience as the moderator (FIGURE 1). As the macro allows for only 1 independent variable in the model, 2 separate moderation analyses were conducted: 1 with the PDQ and 1 with the SDMT. Based on the nonsignificance of the covariates in the hierarchical linear regression, none were included in the mediation analyses. Moderation was considered to have occurred if the interaction term was significant.⁴⁸

Results

Participants' scores on the IIRS, SDMT, PDQ, and MSRS are reported in TABLE S1. The PDQ was significantly associated with the IIRS ($b = 0.53$, 95% CI [.29-.77]; $P < .001$), accounting for 15% of the variance in the model. The association remained significant when the SDMT was added in the next step (TABLE 1). The SDMT was also a significant factor ($b = -4.17$, 95% CI [-6.90 to -1.45]; $P = .003$), accounting for 7% of the model's variance.

Although both the PDQ ($b = 0.31$, 95% CI [.09-.53]; $P = .006$) and MSRS ($b = -0.61$, 95% CI [-.90 to -.33]; $P < .001$) were independently related to the IIRS, there was no evidence of moderation (FIGURE S1). Similarly, there was no evidence of moderation when the SDMT was the cognition variable (FIGURE S2).

DISCUSSION

This study aimed to expand upon the literature examining the role of cognition in illness intrusiveness in MS. As hypothesized, both objective processing speed and subjective cognition were found to be independently associated with illness intrusiveness in MS. The current findings are consistent with previous work documenting the connection between the SDMT and IIRS,¹⁰ in which slower processing speed was associated with higher illness intrusiveness. These results support the conceptualization that cognitive impairment is a disease factor in the model of illness intrusiveness⁶ for individuals with MS. Worse performance on the SDMT has been associated with greater difficulties with functional activities.³⁶ Due to these increased functional issues, individuals with slowed processing speed may view their MS as more intrusive.

The discrepancy in the literature⁸⁻¹⁰ on the relationship between objective cognition and illness intrusiveness in MS may be due to the measures used. Although both the SDMT and PASAT are recommended for use in MS,⁴⁹ the 2 tasks vary in cognitive demands. In addition, the SDMT has been found to be the most sensitive measure for MS-related cognitive impairment³⁶ and may be a better representation of cognition as a disease factor in the theoretical model. That said, as the SDMT does not measure all the cognitive domains that can be affected by MS, that some aspects of cognition do not contribute to illness intrusiveness cannot be ruled out.

Not only was subjective cognition significantly associated with illness intrusiveness, but it also accounted for slightly more variance than objective processing speed.

and quality of life, as well as changes in their perceptions.⁵⁴ While the IIRS has yet to be an outcome measure for a cognitive-focused intervention in MS, future studies may consider this to evaluate whether these approaches can help reduce illness intrusiveness.

Although it was hypothesized that resilience would buffer the relationship between cognition and illness intrusiveness, this was not observed. Instead, resilience independently contributed to illness intrusiveness, regardless of whether cognition was measured subjectively or objectively. In both models, higher resilience was associated with lower illness intrusiveness, consistent with other research in MS showing a positive association between resilience and HRQOL.²²⁻²⁴ Although the role of resilience as a moderator was conceptualized using the theoretical model of illness intrusiveness,⁶ in which psychological factors moderate between disease factors and illness intrusiveness, these findings suggest that resilience may contribute to illness intrusiveness through another pathway. Given the direct effects of resilience on illness intrusiveness in both models, resilience may be reconceptualized as a *treatment factor* in the illness intrusiveness model, which acts similarly in the model to a *disease factor*.⁶ It has been suggested that resilience can be learned over time,⁵⁵ with several studies in MS focusing on building resilience.⁵⁶⁻⁶⁰

If resilience is still to be conceptualized as a *psychological factor* in the theoretical model, then it may either moderate the relationship between illness intrusiveness and subjective well-being or act directly on subjective well-being.⁶ Vissicchio and colleagues¹⁰ found that cognition contributed to illness intrusiveness, which, in turn, influenced depressive symptom severity. In MS, it is possible that resilience could moderate between illness intrusiveness and mood, given the inverse relationship between resilience and psychological distress.⁶¹ As subjective and objective cognition have been found to act on HRQOL in MS through different pathways,¹⁹ there are likely other factors involved in the relationship between cognition and illness intrusiveness, including other potential moderators. Although a path model would allow for an examination of different interactions of several factors, that would require a more robust sample size than that of the current study.

In addition to the restrictions on the complexity of the model that we examined, there are other limitations that need to be considered. Only the SDMT was used to measure objective cognition, and although sensitive to MS-related cognitive impairment,³⁶ it does not assess other aspects of cognition, such as executive functioning, language, and visuospatial skills. Future studies could explore whether global cognition or only specific cognitive domains contribute to illness intrusiveness. Although the current study assumed causal relationships based on the theoretical model of illness intrusiveness,⁶ it is important to note that the study was cross-sectional. To definitively state that cognitive impairment leads to greater illness intrusiveness, a longitudinal investigation, where changes in both metrics can

PRACTICE POINTS



While addressing factors that contribute to illness intrusiveness in individuals with multiple sclerosis (MS), clinicians need to consider not only individuals' objective processing speed but also their perceptions of their functioning.

Resilience does not buffer the relationship between cognition and illness intrusiveness, but it is independently associated with the latter, suggesting that it can play a protective role through another pathway. ■

be observed over time, would be needed. Finally, although demographics such as race and ethnicity were not significant in the hierarchical linear regression, the sample was largely White and non-Hispanic, which may have influenced the generalizability of the results. As such, future studies should consider a more diverse sample, which would allow for the examination of demographics in the model.

CONCLUSIONS

Among individuals with MS, both objective processing speed and subjective cognition were independently associated with illness intrusiveness. Resilience, however, did not moderate the relationship between cognition and illness intrusiveness, although it directly affected illness intrusiveness. Not only do these findings bolster previous work on the role of cognition as a disease factor in the theoretical model of illness intrusiveness, but they also highlight the importance of considering both cognitive performance and perceptions as contributing factors to illness intrusiveness in MS. Addressing cognitive concerns may be an avenue for future interventions targeting illness intrusiveness in this population.

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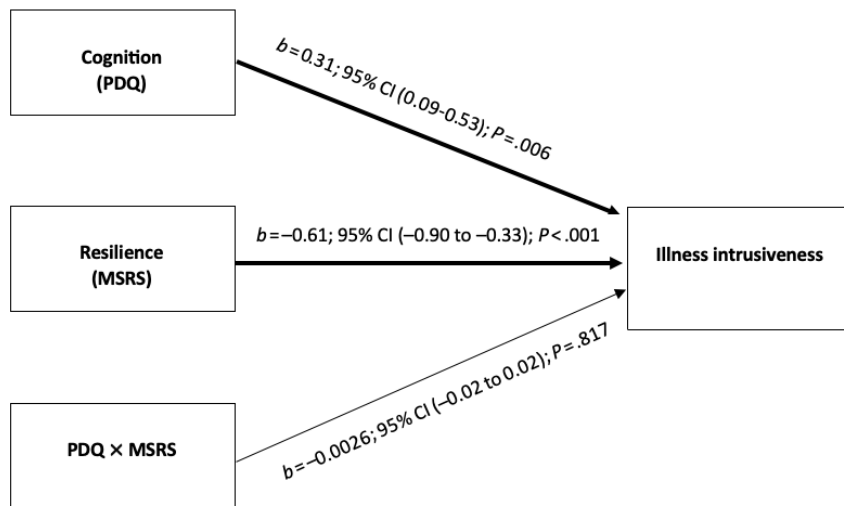
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TABLE S1. Participants' Scores on Illness Intrusiveness, Cognition, and Resilience Measures

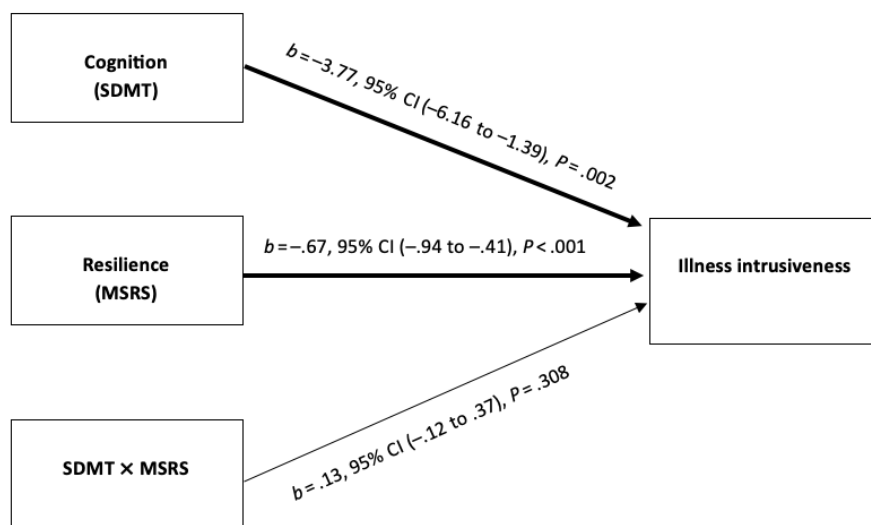
Measure	Mean (SD)	Observed range
Illness Intrusiveness Ratings Scale total score	47.55 (17.15)	17-91
Symbol Digit Modalities Test z score	-0.71 (1.19)	-4 to 3
Perceived Deficits Questionnaire total score	37.61 (13.77)	5-75
Multiple Sclerosis Resiliency Scale total score	76.08 (10.52)	54-100

FIGURE S1. Moderation Analysis With Illness Intrusiveness as Outcome and PDQ as Cognition Variable



Note: Thicker arrows indicate a significant effect. $R^2 = 0.27$; $F(3, 108) = 13.51$; $P < .001$.
MSRS, Multiple Sclerosis Resiliency Scale; PDQ, Perceived Deficits Questionnaire.

FIGURE S2. Moderation Analysis With Illness Intrusiveness as Outcome and PDQ as Cognition Variable



Thicker arrows indicate a significant effect. $R^2 = 0.30$; $F(3, 108) = 15.24$; $P < .001$.
MSRS, Multiple Sclerosis Resiliency Scale; SDMT, Symbol Digit Modalities Test.