

The Relationship between Perceived Cognitive Impairment and the Experience of Pain in Individuals with Multiple Sclerosis

Tierra L. Willis

University of West Florida

Tammy Lowery Zacchilli

Saint Leo University

Rebecca Liller

University of South Florida

Abstract

The purpose of this study was to assess whether cognitive impairment was related to the experience of pain in individuals with multiple sclerosis. Participants included 239 women and 33 men recruited through the National Multiple Sclerosis Society and the Multiple Sclerosis World support group website. It was predicted that, as cognitive impairment and cognitive general concerns increased for individuals diagnosed with multiple sclerosis, neuropathic pain, pain intensity, and pain interference would increase as well. Cognitive concerns was the only significant predictor of neuropathic pain ($\beta = .33, t = 2.97, p = .003$). Cognitive impairment was the only significant predictor of pain intensity ($\beta = .26, t = 2.41, p = .017$). Finally, both cognitive general concerns ($\beta = .25, t = 2.39, p = .018$) and cognitive impairment ($\beta = .26, t = 2.46, p = .015$) were significant predictors of pain interference.

Keywords: multiple sclerosis, pain intensity, neuropathic pain, cognitive impairment

In 2011, DeLuca and Nocentini reported that multiple sclerosis affects about 400,000 individuals in the United States and approximately 2.1 million people throughout the world. Multiple sclerosis is most often referred to as a neurological autoimmune disease characterized by the progressive demyelination of nerve cells located in the brain and throughout the spinal cord. There are typically four different phases of disease progression for multiple sclerosis: relapsing remitting, secondary progressive, primary progressive, and progressive relapsing. These different types of phases can often cause a multitude of symptoms to emerge including cognitive impairment and the experience of pain (DeLuca & Nocentini, 2011). The prevalence and comorbidity of these two symptoms for individuals with multiple sclerosis suggests that a possible relationship between cognitive impairment and the experience of pain exists (Attal et al., 2014; Bushnell, Ceko, & Low, 2013).

Nearly half of all patients diagnosed with multiple sclerosis will eventually develop some degree of cognitive impairment or concern for perceived cognitive ability (Baumstarck-Barrau et al., 2011). The areas of cognition predominantly impacted include memory, attention, executive function, visual perception, and the efficiency with which information is processed (DeLuca & Nocentini, 2011).

Correspondence concerning this article should be addressed to Tierra S. Willis, 7200 Cypress Lakes Apt Blvd., Apt. 934, Baton Rouge, LA 70808. Email: tierrawillis0@gmail.com.

Individuals with multiple sclerosis also experience and often report concerns for any perceived difficulties with different areas of cognition (Beier, Amtmann, & Ehde, 2015). Therefore, for the purpose of the present study, cognitive impairment was characterized as experiencing perceived deficits with a cognitive process such as memory, attention, or processing speed. Cognitive general concerns were characterized as experiencing any perceived difficulties over the past seven days with multitasking, attention, or concentration. Along with cognitive impairment and cognitive general concerns, the experience of pain can also cause difficulties or deficits throughout several areas of the body for individuals diagnosed with multiple sclerosis.

Pain can be described as any unpleasant sensory experience associated with definite or potential tissue damage and, in chronic cases, can be considered a brain disease that influences how the brain functions (Borsook, 2012; Solaro, 2006). According to Melzack and Wall's (1965) gate control theory of pain, the underlying physiological mechanisms associated with the psychological experience of pain depend on the activation and transmission of varying nerve signals throughout the dorsal horn in the spinal cord. The substantia gelatinosa, a functional group of densely-packed cells along the spinal cord, acts as a gate control system for synapses that regulates the transmission of nerve signals to the brain. For example, the activation of nociceptive fibers, or nerves that transmit pain signals, rely on the opening or closing of the presynaptic gate in order to modulate the appropriate level of activity for coinciding cells and fibers (Melzack & Wall, 1965).

For individuals with multiple sclerosis, this gate control process may be hindered by the progressive demyelination of nerves. Myelinated nerves transmit quick signals that are generally experienced as intense pain while unmyelinated nerves transmit slow signals that are generally experienced as throbbing or chronic pain. Without the myelination of specific nerve cells, the gate control system for pain, or substantia gelatinosa, can transmit inaccurate pain signals to the dorsal horn and subsequently jeopardize areas where the experience of pain is produced or felt (Borsook, 2012). Consequently, individuals with multiple sclerosis may psychologically experience various types and levels of pain throughout different anatomical areas instead of primarily where the most demyelination occurs. For example, Marchettini, Formaglio, and Lacerenza (2006) investigated the reports of several patients' experiences with pain that were related to the eventual diagnosis and treatment of multiple sclerosis. These experiences of pain spanned several different anatomical areas and were perceived differently for each patient. Reports described the experience of pain as an intense squeezing sensation ranging in intensity over time, burning sensations of severe intensity, and numbness (Marchettini et al., 2006).

Additionally, Pöllmann and Feneberg (2008) reported that up to 86% of individuals diagnosed with multiple sclerosis have experienced some degree or level of pain including both intense and chronic pain. Therefore, to provide a more comprehensive scope of pain for individuals with multiple sclerosis, four main pain related categories were constructed. The first category is comprised of neuropathic pain or pain directly related to multiple sclerosis, the second category consists of pain indirectly related to multiple sclerosis, the third category is treatment related pain, and the fourth category is characterized by pain unrelated to multiple sclerosis (Pöllmann & Feneberg, 2008). For the purpose of this study, neuropathic pain along with the intensity and interference of pain were primarily examined. Pain intensity was characterized according to the degree of unpleasantness or severity of pain; pain interference was characterized according to how often pain interfered with daily activities or the enjoyment of life (Kratz, Hirsh, Ehde, & Jensen, 2013).

Pain and cognitive impairment are prevalent and often comorbid symptoms that are found throughout many different diseases and older age groups. As a result, these symptoms are the primary variables for many studies that examine the relationship between various cognitive areas and pain. For example, Weiner, Rudy, Morrow, Slaboda, and Lieber (2006) investigated the relationship between chronic low back pain, physical function, and neuropsychological function in older adults. Results from both correlational and multiple linear regression analyses indicated that an overall increase in pain intensity was significantly related to the decrease in specific neuropsychological functions such as attention and mental flexibility. Similarly, multiple linear regression analyses also indicated that the impairment of mental flexibility increased when the severity of pain also increased for older adults at a pain clinic (Karp et al., 2006). This result can be attributed in part to the cognitive interference produced by the experience of pain. Morone, Abebe, Morrow and Weiner (2014) also examined how chronic knee pain, rather than chronic back pain, influenced cognitive impairment. Results, unlike the findings for chronic back pain, indicated no relationship between pain scores and cognitive test scores. This result suggests that different locations and types of chronic pain can differentially influence cognitive performance for older adults. Along with the influence of chronic pain, several studies have also suggested that acute episodes of pain are associated with cognitive impairment as well. For example, Lorenz and Bromm (1997) found that when acutely painful stimuli were presented to younger adults, attention related processes were impaired. Overall, results suggest that the intensity and severity of both chronic and acute pain impacts several different areas of cognitive function often related to attention, processing speed, memory, and executive function (Hart, Martelli & Zasler, 2000).

However, despite these findings and conclusions, further examination of the relationship between pain and cognitive impairment due to neurological diseases, such as multiple sclerosis, is crucial. Providing further examination of this relationship is crucial because it would provide practitioners with a more succinct understanding of how to treat these specific symptoms, either together or individually, and, ultimately, make important steps in trying to improve the overall well-being of individuals with multiple sclerosis. Consequently, the aim of the present study was to investigate the relationship between cognitive impairment and the experience of pain for individuals diagnosed with multiple sclerosis. It was predicted that as cognitive impairment and cognitive general concerns increased, neuropathic pain, pain intensity, and pain interference would increase as well.

Method

Participants

Participants included 239 women and 33 men with a mean age of 45.53 years ($SD = 12.02$). Participants represented all four levels of disease progression. The mean age of participants with relapsing remitting was 44.17 ($SD = 11.52$), for secondary progressive was 55.63 ($SD = 8.98$), for primary progressive was 48.00 ($SD = 14.92$), and for progressive relapsing was 47.00 ($SD = 14.07$). Participants were recruited from the National Multiple Sclerosis Society and the Multiple Sclerosis World support group websites. Most participants were European American/White (77.7%). Additionally, 9.5% were African American/Black, 6.2% were Hispanic/Mexican/Puerto Rican/Cuban/Dominican Republic/Spanish/Central/South American, 2.9% were Biracial/Mixed, and 1.8% were Asian/Pacific Islander.

With regard to disease course, 81.3% ($n = 222$) of participants selected relapsing remitting as the type of multiple sclerosis, 10.6% ($n = 29$) of participants selected secondary progressive, 3.3% ($n = 9$) selected primary progressive, and 3.3% ($n = 9$) selected progressive relapsing. The mean age of diagnosis was 36 years ($SD = 10.38$) with a minimum of 12 years and a maximum of 64 years. Additionally, participants were asked if they were currently taking any disease modifying or pain related medications, and if so, which ones. A total of 225 participants indicated whether they were taking any medications. Out of those 225 participants, 40.9% ($n = 92$) were taking one medication, 21.3% ($n = 48$) were taking two medications, 18.7% ($n = 42$) were taking three or more medications, and 19.1% ($n = 43$) were not taking any medications. The most frequently reported medications included Gabapentin (22.5%), Baclofen (21.4%), Ibuprofen (13.5%), Lyrica (5.5%), and Cymbalta (4.9%).

Materials and Procedure

Prior to conducting this study, approval was given by the institutional review board (01212016). Participants read and agreed to an implied consent form. The survey was completed online using Qualtrics. Participants responded to a demographic questionnaire, which included disease course or type and the age of diagnosis. Participants also responded to two scales related to cognitive impairment. These include the Patient-Reported Outcomes Measurement Information System (PROMIS) Applied Cognition—General Concern scale (Cella et al., 2007) and the Multiple Sclerosis Neuropsychological Screening Questionnaire (Benedict et al., 2003). Additionally, two scales were used that measured the experience of pain. One of these was Cleeland's (1991) Brief Pain Inventory Short Form. Galer and Jenson's (1997) Neuropathy Pain Scale was also used in the current study.

Cognitive general concerns. PROMIS's (Cella et al., 2007) Applied Cognition—General Concerns Short Form was used to examine cognitive general concerns regarding perceived cognitive ability. This scale is typically used to measure perceived cognitive ability and quality of life for individuals with neurological disorders. It is comprised of eight questions and participants responded to a 5-point Likert-type scale from 1 (never) to 5 (very often, several times a day). A total score was calculated for each participant with higher scores indicating more general cognitive concern. Total scores can range from 8 to 40, respectively. Sample items include "I have had trouble shifting back and forth between different activities that require thinking," "I have had to work harder than usual to keep track of what I was doing," and "I have had trouble forming thoughts." The measure demonstrated high reliability in the current study ($\alpha = .95$). For the current study, the minimum score was 8 and the maximum score was 40.

Cognitive impairment. The Multiple Sclerosis Neuropsychological Screening Questionnaire (Benedict et al., 2003) was used to examine cognitive impairment. This scale is typically used to detect early signs of cognitive impairment for individuals diagnosed with multiple sclerosis. It is comprised of 15 questions, and participants responded to a 5-point Likert-type scale from 0 (never, does not occur) to 4 (very often, very disruptive). A total

score was calculated for each participant with higher scores indicating higher cognitive impairment. Total scores can range from 0 to 60, respectively. Sample items include “Do you have difficulty keeping track of two things at once,” “Are you slow when trying to solve problems,” and “Do you lose your thoughts while listening to somebody speak?” This measure demonstrated high reliability in the current study ($\alpha = .93$). For the current study, the minimum score was 15 and the maximum score was 60.

Pain intensity and interference. Cleeland’s (1991) Brief Pain Inventory Short Form was used to examine pain intensity and pain interference. This scale is typically used for individuals experiencing pain from a chronic disease. This inventory is comprised of an anatomical diagram for locating areas of pain. Participants were asked to click on the diagram to indicate which areas of pain they experienced. Specifically, participants clicked once on the area of the diagram where they experience pain and twice where they experienced the most pain. There are also four questions related to pain intensity ($\alpha = .90$) and seven questions related to pain interference ($\alpha = .94$). These items were measured using a Likert-type scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine). A total score was calculated with higher scores indicating more pain. Total scores for pain intensity can range from 0 to 40 while total scores for pain interference can range from 0 to 70. In the current study, the minimum score for pain interference was 7 and the maximum score was 70. For pain intensity, the minimum score was 4 and the maximum score was 40.

Neuropathic pain. Galer and Jenson’s (1997) Neuropathy Pain Scale was used to examine neuropathic pain in multiple sclerosis and is comprised of 10 questions (eight questions pertain to physical qualities of pain and two questions pertain to sensations of pain). The scale is measured on a Likert-type scale from 0 (none) to 10 (most). Total scores were calculated with higher scores indicating more pain. Total scores can range from 0 to 100, respectively. For the current study, the minimum score was 13 and the maximum was 97. This measure also demonstrated high reliability in the current study ($\alpha = .87$).

Results

A nonexperimental design was used to examine the hypotheses of this study. Previous studies (Karp et al., 2006; Weiner et al., 2006) examined similar relationships between cognitive impairment and pain by using descriptive statistics such as correlations and multiple linear regressions. Similarly, the variables of interest for this study could not be manipulated and, consequently, a descriptive design was employed. Means and standard deviations were calculated for all the measures. These results are found in Table 1.

Table 1
Means and Standard Deviations for the Pain and Cognitive Impairment Variables

| Variables | <i>M</i> | <i>SD</i> |
|---|----------|-----------|
| Cognitive General Concerns | 27.47 | 7.73 |
| MSNSQ- Cognitive Impairment | 46.01 | 12.36 |
| Brief Pain Inventory- Pain Intensity | 20.10 | 8.75 |
| Brief Pain Inventory- Pain Interference | 40.27 | 19.46 |
| Neuropathic Pain | 54.00 | 19.28 |

Correlational Data Analysis

Correlations were calculated between neuropathic pain, pain interference, pain intensity, cognitive general concerns, and cognitive impairment. Neuropathic pain was significantly, positively correlated to pain interference ($r = .77, p < .001$) pain intensity ($r = .79, p < .001$), cognitive impairment ($r = .31, p < .001$), and cognitive general concerns ($r = .37, p < .001$). Pain interference was also significantly, positively correlated to cognitive impairment ($r = .44, p < .001$) and cognitive general concerns ($r = .45, p < .001$). Finally, pain intensity was significantly, positively related to cognitive impairment ($r = .37, p < .001$) and general cognitive concerns ($r = .36, p < .001$). The effect sizes ranged from small to moderate with the strongest effect sizes being between neuropathic pain and pain intensity ($r^2 = .62$) and neuropathic pain and pain interference ($r^2 = .60$).

Multiple Regression Analysis

Simultaneous multivariate regression analyses were calculated to predict the three measures of pain (i.e., neuropathic pain, pain interference, and pain intensity). Cognitive general concerns and cognitive impairment were included as predictors of the three measures of pain. A simultaneous regression analysis involves entering all the predictor variables in one step (Cohen, Cohen, West, & Aiken, 2003) and allows examination of “the extent to which the set of variables predicts an outcome” (Keith, 2006, p. 76). For neuropathic pain, the model was significant, $F(2, 193) = 16.45, p < .001$. This model accounted for 13.7% of the variance. Cognitive concerns was the only significant predictor ($\beta = .33, t = 2.97, p = .003$). For pain intensity, the model was significant, $F(2, 213) = 18.70, p < .001$. This model accounted for 14% of the variance. Cognitive impairment was the only significant predictor of pain intensity ($\beta = .26, t = 2.41, p = .017$). Finally, the model for pain interference was also significant, $F(2, 209) = 31.96, p < .001$. The model accounted for 23% of the variance. Both cognitive concerns ($\beta = .25, t = 2.39, p = .018$) and cognitive impairment ($\beta = .26, t = 2.46, p = .015$) were significant predictors of pain interference.

Discussion

The overall aim of this study was to investigate how cognitive impairment is associated with the experience of pain amongst individuals diagnosed with multiple sclerosis. It was predicted that as cognitive general concerns and cognitive impairment increased, neuropathic pain, pain intensity, and pain interference would increase as well. Results indicated that cognitive impairment was related to the experience of pain. More specifically, both cognitive impairment and cognitive general concerns were related to pain intensity, pain interference, and neuropathic pain. Additionally, results indicated that cognitive general concerns was the only significant predictor of neuropathic pain, and cognitive impairment was the only significant predictor of pain intensity. A possible reason for these findings could be attributed to the previously established relationship between pain intensity, pain interference, and perceived cognitive ability for older adults with chronic pain (Karp et al., 2006; Morone et al., 2014; Weiner et al., 2006). Both cognitive impairment and cognitive general concerns were predictive of pain interference. These findings have both practical and empirical implications. For example, practitioners can use these findings during clinical assessments to better explain why pain might influence the performance on tasks related to executive function. Practitioners can also use these findings to simultaneously target multiple symptoms related to pain and cognitive impairment thus allowing for the development of more efficient and specialized treatment plans.

The empirical implications of these findings are best established throughout the recommendations for future research. For example, the data collected in this study were gathered using a self-selected sample through an online survey distributed on a multiple sclerosis website. Online surveys, while helpful in determining relationships between specific variables, do not provide the opportunity to produce causal statements or conclusions for results. Thus, the generalizability of the results for this study are limited in scope. Future studies that use these variables for individuals with multiple sclerosis should, therefore, seek to use a more experimental design. Also, a more representative sample could potentially be recruited through multiple sclerosis centers or by using other related sampling techniques rather than just primarily through a multiple sclerosis website.

Large disparities also existed throughout this study with regard to demographic information such as age, ethnicity, and sex. According to the National Multiple Sclerosis Society (2016), most ethnicities are affected by multiple sclerosis, although it is more common in European Americans, and it is two to three times more common in women than in men. Additionally, most people are diagnosed between 20 and 50 years of age. The current sample was mostly European American and female as one would expect given data on multiple sclerosis. However, these

two groups were overrepresented in the current study. Also, in the current study, the sample sizes of men and women who were diagnosed with multiple sclerosis were predominantly skewed toward women. The overall prevalence ratio of multiple sclerosis for women to men has increased from 2:1 to 3:1 over the past decade, indicating a significant discrepancy between the prevalence of women and men who are diagnosed with multiple sclerosis (Harbo, Gold, & Tintoré, 2013). Future research should seek to better include the variable of sex to investigate how this discrepancy between men and women with regard to prevalence influences the relationship between cognition and pain for individuals diagnosed with multiple sclerosis. Understanding how sex influences this relationship for individuals with multiple sclerosis allows practitioners to develop targeted and specific treatment plans not just for women but also for men. Additionally, the mean age of participants for both overall and specific disease phases tended to be middle aged. Consequently, current age and age of diagnosis should be included throughout future research as more prominent variables in examining the relationship between cognitive impairment and the experience of pain.

Although the results of this study support the hypotheses, previous research suggests that this relationship needs to be more specifically examined in respect to different cognitive areas and types of pain. For example, Morone et al. (2014) specifically examined parts of executive function and memory in relation to pain for older adults with osteoarthritis. Karp et al. (2006) also examined specific areas of cognition, such as mental flexibility and psychomotor speed, in relation to chronic pain. Consequently, future research should seek to include distinct areas of cognition or executive function when examining the relationship between pain and cognitive impairment for individuals diagnosed with multiple sclerosis. Further examination of these specific areas of cognition would allow practitioners to succinctly assess specific declines in cognitive ability or executive function. With succinct and specific assessments, practitioners would be able to develop and implement targeted treatment plans.

Previous research also demonstrates the importance of examining different locations of pain. For example, Morone et al. (2014) found that the impact of chronic knee pain on cognitive impairment was less severe when compared to the impact of chronic back pain. This finding suggests that the location of pain may influence the overall experience of pain and, consequently, influence the degree of cognitive impairment. Future hypotheses should include location as a primary variable as it pertains to better explaining the relationship between cognitive impairment and pain. Further examining how these specific variables for both pain and cognition are related would provide researchers with more in depth and focused variables allowing for results and conclusions to be better generalized.

Along with examining different cognitive areas and types or locations of pain, future research should also seek to include more variables or measures that control for any confounding variables such as severity of disease, overall level of disability, fatigue, or depression. For example, this study collected and reported data regarding disease progression and how many individuals were diagnosed with each type of multiple sclerosis but, due to the small sample sizes for different types, no other analyses were performed. Planche, Gibelin, Cregut, Pereira, Clavelou (2016), however, did have adequate sample sizes for each type of multiple sclerosis and found that participants with progressive types of multiple sclerosis demonstrated more cognitive impairment when compared to participants with less progressive types of multiple sclerosis. Thus, future research that examines the relationship between cognitive impairment and pain for individuals with multiple sclerosis should strive to include screening tools or measurements that control for disability or disease severity, such as the disability status scale or the mini mental status exam. Other variables such as fatigue or depression can also influence the overall experience of pain and degree of cognitive impairment or perceived cognitive concerns (Amato, Ponziani, Rossi, Liedl, Stefanile, & Rossi, 2001). Therefore, future research should include measures that examine and control for these variables as part of the experimental design to avoid any confounds related to how these variables might influence the relationship between cognitive impairment and pain.

Lastly, the design of this study was non-experimental. Rather, this study was designed according to a descriptive and correlational framework. This framework provided an opportunity to ascertain a rudimentary yet important understanding of the given variables from a psychological, rather than purely medical, perspective. Neurological diseases, such as multiple sclerosis, require an in-depth examination from multiple perspectives as the individuals impacted by this disease often suffer from a compilation of symptoms and issues. Thus, while this approach and design warrant several limitations, which must be taken into consideration when interpreting these results, it also provided an excellent platform for researchers to gain a basic psychological understanding of these variables or symptoms when applied to individuals with multiple sclerosis. While rudimentary in scope and execution, this study is a stepping stone for researchers and practitioners to develop more in depth and experimental studies that holistically examine symptoms that are related to this disease. Consequently, future studies should seek to include both self-report and behavioral measures within an experimental design for the variables of pain and cognition. By incorporating behavioral measures into an experimental design, future conclusions and implications

would be more easily generalized and understood among the multiple sclerosis community while also adding value to therapeutic techniques used by practitioners.

Overall, the results of this study supported previous research that indicated a relationship between cognitive impairment and pain (Bushnell et al., 2013; Karp et al., 2006; Morone et al., 2014; Weiner et al., 2006). More importantly, the findings from this study demonstrated a positive relationship between cognition and pain specifically for individuals diagnosed with multiple sclerosis. Examining these variables for individuals with multiple sclerosis is important because it provides further insight into how these comorbid symptoms function and, consequently, how factors related to pain and cognitive impairment can be jointly assessed, targeted, and managed. By understanding how these symptoms function and how they can be managed, practitioners can seek to elevate pain management techniques, improve cognitive performance on everyday tasks, and build a better sense of well-being for individuals diagnosed with multiple sclerosis.

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