MAYO CLINIC

BRIEF REPORT

Predictive Bidirectional Relations Between Pain, Fatigue, and Dyscognition in Fibromyalgia

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Abstract

Fibromyalgia (FM) is a common and disabling disorder characterized by chronic widespread pain, fatigue, and dyscognition. Previous studies have shown strong positive correlations between pain, fatigue, and dyscognition. However, bidirectional relationships, particularly with dyscognition modeled as a predictor, have rarely been established. The purpose of this study was to examine the bidirectional, predictive nature of the relationships between these FM symptoms. Pain, fatigue, and dyscognition were measured via the Brief Pain Inventory, Multidimensional Fatigue Inventory, and Multiple Ability Self-Report Questionnaire at baseline and a 2-year follow-up in a large sample of 450 well-characterized female patients with FM. Relationships between FM symptoms were evaluated using a cross-lagged, longitudinal model. Dyscognition, pain, and fatigue were positively correlated at both baseline and follow-up (*r*s .13 -.53, *P*s<.01). Dyscognition at baseline was predictive of dyscognition (*B*=.76, β=.75, *P*<.001), pain, (*B*=.01, β=.09, *P*=.033) and fatigue (*B*=.05, β=.08, *P*=.050) at follow-up. Pain at baseline was predictive of pain (*B*=.59, β=.59, *P*<.001), dyscognition (*B*=.88, β=.07, *P*=.022), and fatigue (*B*=.85, β=.11, *P*=.004) at follow-up. Fatigue at baseline was only associated with fatigue (*B*=.61, β=.60, *P*<.001) at follow-up. Dyscognition is predictive of future pain and fatigue in patients with FM. Continued work should examine dyscognition as a clinical predictor of future severity of core symptoms such as pain and fatigue.

 ■ Mayo Clin Proc Inn Qual Out 2022;6(2):143-147

Fibromyalgia (FM) is a disorder characterized by chronic widespread pain that is accompanied by fatigue, sleep difficulties, mood and anxiety disorders, and dyscognition.[1] It is one of the most common chronic pain disorders, possibly present in as much as 8% of the population, although prevalence estimates can vary widely.[1,2] Although the pathophysiology is not fully understood, contributing factors likely include disordered pain regulation (central sensitization), genetic predisposition, and environmental factors; and limited research has suggested peripheral pain mechanisms.[2-5]

Previous research has shown a high degree of correlation between the symptoms of pain, fatigue, and dyscognition in patients with FM.[6,7] The majority of studies suggest that dyscognition is, in part, driven by pain and/or fatigue. For instance, Reyes Del Paso et al[6] reported that pain may mediate deficits in cognitive functioning in patients with FM, although causal relationships cannot be confidently determined because of the cross-sectional nature of the study. Similarly, Williams et al[7] reported that perceived dyscognition was strongly associated with increased fatigue in patients with FM compared to healthy controls, and that pain levels were uniquely correlated with perceived language deficits. A meta-analysis of 23 case-controlled studies, in contrast, found insufficient evidence for these relationships between dyscognition, pain, and fatigue.[8] Although the majority of studies to date model dyscognition as an outcome, few studies have evaluated whether dyscognition predicts pain or fatigue. For example, Turk and Okifuji[9] suggested that the presence of pain behaviors, theorized to be a behavioral manifestation of pain, could be in part explained by the interaction of cognitive factors with other physical and psychological

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factors. Knowledge of symptoms and their predictors is key for health care providers to accurately diagnose FM and understand its progression over time. It is therefore clear that more research is needed to examine the bidirectional relationships between dyscognition, pain, and fatigue in patients with FM.

To our knowledge, no longitudinal study has examined dyscognition as a predictor of both pain and fatigue in patients with FM. Although a 7-day study conducted by Whibley et al[10] reported that decreased cognitive function (specifically, decreases in working memory functioning) predicted future increases in pain intensity, the very short-term nature of the study could not definitively determine if these predictive relationships persisted over a longer period, nor did the study include fatigue as an outcome. Similarly, McBeth et al[11] assessed cognitive problems as a predictor of new-onset widespread pain in a population of patients without FM and reported that cognitive complaints and nonrestorative sleep predicted new-onset widespread pain. This study, however, did not examine fatigue as a predictor or outcome, nor did it examine reciprocal associations between cognitive complaints and pain. Together, these studies allude to the possibility that dyscognition could predict future pain, and perhaps fatigue.

The purpose of the present study was to evaluate bidirectional relationships between pain, fatigue, and dyscognition in a previously described[12,13] large sample of well-characterized patients with FM and extend this work to examine if dyscognition itself was an important predictor of pain and fatigue. A cross-lagged, longitudinal model allows for the simultaneous examination of bidirectional effects. We hypothesized that pain and fatigue would be significant predictors of later dyscognition and that dyscognition would be a significant predictor of later pain and fatigue.

METHODS

The study was approved by the Mayo Clinic Institutional Review Board (IRB #11-002884) and all participants provided written informed consent.

Sample

Baseline and follow-up data from the participants of two previously published studies (N=450) were used for this analysis.[12,13] Women who met FM research survey criteria at baseline were eligible to participate.[14] Baseline data were extracted from the survey responses of randomly selected patients with FM found within an existing registry of patients seen at the Mayo Clinic and diagnosed with FM since January 1, 2000.[15] Two-year follow-up data were collected via questionnaires mailed to eligible participants.

Measures

Participants completed the Brief Pain Inventory,[16] the Multidimensional Fatigue Inventory,[17] and the Multiple Ability Self-Report Questionnaire.[18] The symptom domain of pain was captured through completion of the Brief Pain Inventory, which has a pain severity subscale and a pain interference subscale. The Multidimensional Fatigue Inventory total score was used to measure the symptom domain of fatigue. Multiple Ability Self-Report Questionnaire patient scores were used to quantify perceived dyscognition. All three measures are frequently used in FM studies.[13] Estimated internal reliability of the measures was excellent at both baseline and follow-up and ranged from α=.90-.95.

Statistical Analysis

Bivariate correlations at baseline and follow-up were included as the first step in the analysis. The second step included examining a cross-lagged model where dyscognition, pain, and fatigue at both baseline and follow-up were included, as well as control variables at baseline. No variable had more than 2% missing data and data were determined to be missing completely at random χ^2 (43)=58.6, P=.06. Hence, full-information maximum likelihood was used to address missing data in the analyses. Data met assumptions of parametric statistical inference testing, and statistical significance was set at P<.05. Although all variables met assumptions of statistical inference testing, five univariate outliers were detected using the median absolute deviation method. These outliers were all within one or less points of non-outlying values in the distributions. The five identified outlying values were recoded to the value of the nearest non-outlying value. Multivariate outliers were then examined. None were found. Analysis of the original dataset and the recoded dataset

Mayo Clin Proc Inn Qual Out ■ April 2022;6(2):143-147 ■ https://doi.org/10.1016/j.mayocpiqo.2021.12.007
www.mcpiqojournal.org

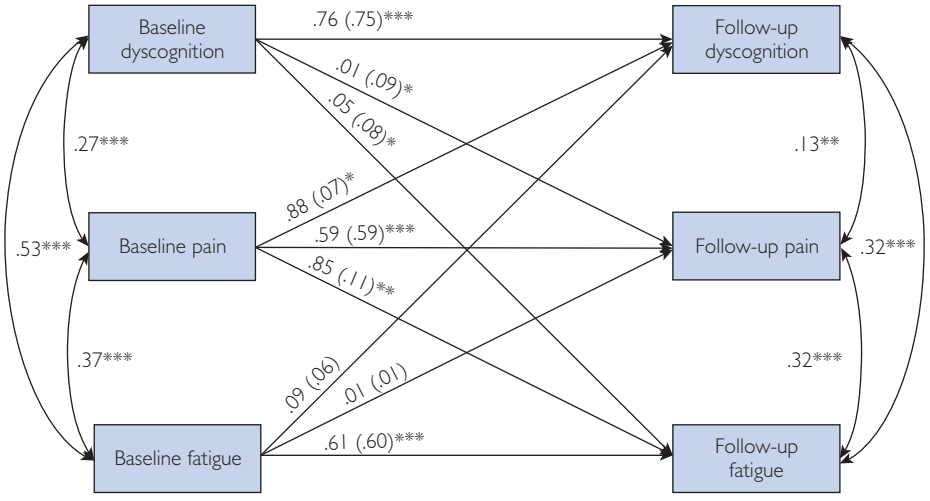

FIGURE. Longitudinal associations between dyscognition, pain, and fatigue in fibromyalgia patients. Unstandardized and standardized (in parentheses) coefficients for the longitudinal associations of cognitive problems, pain, and fatigue. All coefficients are adjusted for the effects of age, sex, ethnicity, and treatments (pain medications, physical therapy, and complementary/alternative treatment). Paths between variables at the same time point are bivariate correlations. *$P<.05$, **$P<.01$, ***$P<.001$.

resulted in no changes to the results. All analyses were conducted in SPSS[19] and the Lavaan package in R.[20]

RESULTS

Demographics for this cohort have been previously described.[13] The average patient age was 56 (range, 20 to 85) years and the median body mass index was 29 kg/m^2. All participants were female. Results of our hypothesized cross-lagged model are included in the Figure. Dyscognition, pain, and fatigue were positively correlated with each other at both baseline and follow-up (*r*s .13 -.53, *P*s<.01). Longitudinal associations were more varied. Dyscognition at baseline was predictive of dyscognition (*B*=.76, β=.75, *P*<.001), pain, (*B*=.01, β=.09, *P*=.03) and fatigue (*B*=.05, β=.08, *P*=.05) at follow-up. Pain at baseline was predictive of pain (*B*=.59, β=.59, *P*<.001), dyscognition (*B*=.88, β=.07, *P*=.02), and fatigue (*B*=.85, β=.11, *P*=.004) at follow-up. Fatigue at baseline was only associated with fatigue (*B*=.61, β=.60, *P*<.001) at follow-up.

DISCUSSION

This study shows an interesting pattern of longitudinal associations. Dyscognition at baseline was predictive of later dyscognition and later pain and fatigue. Pain at baseline likewise predicted later pain, fatigue, and dyscognition. Fatigue at baseline was only predictive of later fatigue, but not pain or dyscognition. We consider each of these patterns of association below, in turn.

Perhaps most interestingly, we found that dyscognition in FM was a significant long-term predictor of later pain and fatigue, which is previously undocumented in patients with FM. This confirms prior work[11] in patients with chronic widespread pain from a large population-based sample and extends this work to patients with FM, as well as examines reciprocal effects simultaneously in the present model. This finding might be cause for reflection and further investigation. For example, the question of what mechanisms might explain why dyscognition serves as a predictor of future pain and fatigue can be considered. One possibility is that central dysregulation, which is part and parcel of FM, may manifest itself earlier in cognitive disruption. This disruption then signals later pain and fatigue symptoms that arise from a similar, if not the same, central nervous system source. For instance, the prefrontal cortex is not only reported as the most frequently

activated brain area during chronic pain, but it also plays an important role in cognition, perhaps suggesting that dysfunction of this brain region plays a role in dyscognition in patients with chronic pain.[11] Additionally, patients with FM seem to lose more grey matter per year than patients without FM and have lower volumes of white matter, possibly related to increased dyscognition, fatigue, and impaired pain modulation.[21-23]

This study also confirms that pain, but not fatigue, was a predictor of later dyscognition. This is consistent with several previous studies showing positive associations between pain and dyscognition.[6,7] However, these results are in conflict with past findings that momentary increases in pain do not predict dyscognition in the short-term,[10] possibly suggesting that pain is only predictive of long-term cognitive changes. As previously suggested, pain may be disruptive to efficient cognitive functioning[24] and fatigue is a known contributor to compromised cognitive processing,[25] although that was not in evidence here. The present study offers supportive evidence of these research findings in a sample of patients with FM.

Study Limitations

The present study possesses some limitations. First, the sample is a well-characterized patient sample of individuals with FM, but broader generalizations to people living with chronic pain cannot be made. Second, all measures are self-reported and future work should consider incorporating neuropsychological testing of dyscognition, as well as objective measures of fatigue and pain. Last, although this study offers the first insight into longitudinal and reciprocal relationships between pain, fatigue, and dyscognition, there are just two time points separated by 2 years. More phasic changes on day-to-day, week-to-week, or month-to-month bases will be overlooked in this design, as will nonlinear trajectories of change. Future studies might use more intensive longitudinal designs.

CONCLUSION

To our knowledge, this is the first long-term study reporting the reciprocal, longitudinal effects of pain, fatigue, and cognitive problems. Specifically, it has been found that dyscognition is predictive of future pain and fatigue. Knowing this, continued work should aim to refine measurements, understand mechanisms, and consider whether dyscognition might be more than simply one symptom among many in FM, but also an important and useful clinical predictor of future severity of core symptoms such as pain and fatigue in FM.

ACKNOWLEDGMENTS

The study was approved by the Mayo Clinic Institutional Review Board (IRB #11-002884) and all participants provided written informed consent.

Potential Competing Interests: The authors report to potential competing interests.

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