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Pain, cognition and quality of life associate with structural measures of brain volume loss in multiple sclerosis

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Abstract

BACKGROUND—Multiple sclerosis (MS) is characterized by physical and mental impairments that often result in pain and reduced quality of life.

OBJECTIVE—To understand the relationship of pain, quality of life, and cognition to structural measures of brain volume.

METHODS—Behavioral measures were assessed in a single session using standardized questionnaires and rating scales. Brain volume measures were assessed with structural magnetic resonance imaging (MRI).

RESULTS—Twenty-nine individuals with relapsing-remitting MS and 29 age-matched controls participated in this study. Pain, quality of life, and cognition were significantly interrelated. Higher fluid attenuation inversion recovery weighted lesion volume was significantly associated with increased reports of pain ($p = 0.01$), lower physical quality of life ($p < 0.0001$), and lower cognitive performance ($p = 0.001$) in our cohort.

CONCLUSIONS—Assessment of pain and quality of life along with structural MRI highlights the importance of understanding structure-function relationships in MS and suggests that

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Conflict of interest

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therapists should not only evaluate individuals for cognition and quality of life, but should consider rehabilitation goals that target these areas.

Keywords

Multiple Sclerosis; quality of life; pain; cognition; MRI; brain volume; lesion volume

1. Introduction

Multiple sclerosis (MS) is the most common disabling neurologic disorder in young adults (Amato, 2010). Individuals with MS present with impairments in mobility, including weakness and difficulty with walking and balancing. Individuals with MS receive physical therapy intervention many times throughout their disease course to address these impairments. However, the heterogeneous nature of the disease presentation and course complicates exercise prescription. In addition, physical mobility is influenced by many factors, such as pain, cognition, quality of life, and the underlying structural integrity of the brain tissue.

Reports of pain and reduced quality of life are common among individuals with MS regardless of disease severity. Approximately 50% of individuals with MS report pain (O'Connor, 2008), and 12% report pain as their worst symptom (Kenner, 2007). Pain is an important contributor to health-related quality of life for persons with MS (Kalia, 2005; Svendsen, 2005) and is associated with lower quality of life as measured by the SF-36 (Forbes, 2006) as well as activity limitations and participation restrictions. Health-related quality of life comprises several domains, including self-reported social, emotional, physical and mental functioning. Quality of life has been associated with fatigue and sleep in individuals with MS (Tabrizi, 2015), and the mental domain is particularly influenced by pain (Kalia, 2005).

Cognitive dysfunction, particularly in processing speed, is also common in individuals with MS, with up to 50% reporting impairments (Benedict, 2006). Interestingly, poor quality of life also correlates with cognitive impairment, and neuropsychological impairments negatively impact quality of life (Cutajar, 2000). Also, the presence of pain influences cognition, particularly the domain for memory that pertains to intention, i.e., the execution of future behaviors (Miller, 2014). These interrelationships are complicated by a complex pathology in MS. One way of making sense of this information is to evaluate the structure-function relationships among the variety of behavioral measures with brain and lesion volumes.

The majority of structural magnetic resonance imaging (MRI) studies have examined relationships of whole brain lesion and volume measures to pain, cognition, and quality of life individually. Recent imaging studies have linked lower brain volume with poorer performance on the Symbol Digit Modalities Test (SDMT) (Vollmer, 2015; Maghzi, 2014) in both relapsing and progressive MS subtypes. White matter lesion volume (Papadopoulou, 2013) and focal white matter damage (Patti, 2015) have been found to significantly predict long-term cognitive performance, including SDMT performance. The presence and location

of demyelinating lesions have been linked with reports of pain in individuals with MS (Seixas, 2014).

The emotional well-being and thinking/fatigue subscales of the Functional Assessment in Multiple Sclerosis, a measure of quality of life, were found to correlate with higher lesion loads and lower grey matter volume (Mowry, 2009), while the Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54) was also associated with T1 lesion load (Janardhan, 2000). Despite these studies, there remains an incomplete knowledge of how physical and social well-being relate to each other and structural MRI measures.

Engagement theory (Danzl, 2012) suggests that a better understanding of the factors that mediate physical mobility can facilitate neurorehabilitation. Therefore, a clearer understanding of structure-function relationships would advance our understanding of targeted rehabilitation for individuals with MS. The objective of this study was to better understand the relationship of pain, quality of life, and cognition to structural measures of brain volume. We hypothesized that pain and quality of life measures are related, and that these measures correlate with whole brain volume. Furthermore, we hypothesized that lesion volume is related to cognitive performance.

2. Methods

2.1. Subjects

Individuals with clinically definite MS and age and gender-matched healthy controls volunteered for this cross-sectional study. Clinically definite MS was determined by the 2005 McDonald Criteria (Polman, 2005). All participants gave written, informed consent prior to participation. The Institutional Review Boards at the Kennedy Krieger Institute and Johns Hopkins Medical Institutes approved all procedures. To be included in the study, MS participants carried a diagnosis of relapsing-remitting MS with an Expanded Disability Status Score (EDSS) between 1.0 and 6.5, had been stable on immunomodulatory therapy for at least 6 months, demonstrated full understanding of study-related tests, and were ambulatory with or without an assistive device. This study was part of a larger parent study examining exercise responsiveness for which ambulation was a key component. Participants were excluded from the study if they reported an MS exacerbation in the last eight weeks or experienced other neurological, cognitive or orthopedic conditions that might interfere with study procedures.

2.2. Experimental procedure

In a single visit, pain, quality of life, self-perceived walking, and cognition were assessed in our laboratory. To minimize fatigue, the order of these assessments was randomized and subjects were permitted to take rest breaks throughout the testing. Imaging measures were collected within 1 month of the laboratory measures.

2.2.1. Pain measure—Pain was assessed using the Brief Pain Inventory-Short Form (BPI) (Cleeland, 1994). The BPI is a short questionnaire that assesses both pain intensity and pain interference. It is a reliable and valid assessment for pain interference in individuals with MS (Osborne, 2006).

2.2.2. Quality of life measures

1. The Multiple Sclerosis Quality of Life-54 (MSQOL-54) (Vickrey, 1995) is a 54-question survey that specifically assesses the health-related quality of life for persons with MS in a way that allows comparison to quality of life in the general population. The MSQOL-54 is based upon the SF-36 with 18 additional items specific to MS. The MSQOL-54 is a valid and reliable (Miller, 2005) measure of health-related quality of life in persons with MS.
2. *The Short Form-36 (SF-36)* (Ware, 1992) is a questionnaire measuring eight health concepts including physical functioning, social functioning, general mental health, vitality, and general health perceptions. The SF-36 is a commonly used measure of quality of life and is reliable and valid across diverse populations (McHorney, 1994).

2.2.3. Self-perceived walking—Self-perceived walking was assessed with the Multiple Sclerosis Walking Scale-12 (MSWS-12) (Hobart, 2003). In this 12-item questionnaire, subjects are asked to rate their degree of limitation in ambulation due to MS in the past 2 weeks. The MSWS-12 has established reliability and validity (Hobart, 2003) and has been shown to correlate with quantitative walking tests such as the Timed 25 Foot Walk and 6 Minute Walk Test (Kieseier, 2012).

2.2.4. Cognition—Cognition was assessed with the oral Symbol Digit Modalities Test (SDMT). The SDMT (Smith, 1982) is commonly used in MS to assess processing speed. The SDMT provides participants with a symbol-digit key; participants then have 90 seconds to name as many of the numbers that belong with the associated symbols on the page. The oral version of this test was utilized to minimize the influence of upper extremity motor impairments (Benedict, 2002). The oral SDMT is sensitive to MS-related cognitive dysfunction (Benedict, 2002, 2006).

2.3. Structural neuroimaging

2.3.1. Image acquisition—Whole brain MRI scans were acquired for all participants on the same 3-Tesla Intera scanner (Philips Medical Systems, Best, The Netherlands). We collected two axial whole-brain sequences: a) T2-weighted fluid-attenuated inversion recover (FLAIR; acquired resolution: $0.9 \times 0.9 \times 1.0$; TE: 365 ms; TR: 4.8 s; TI: 1.6 s; SENSE factor: 1); and b) 3D magnetization-prepared rapid acquisition of gradient echoes (MPRAGE; acquired resolution: $0.8 \times 0.8 \times 1.2$ mm; TE: 6 ms; TR: 10 ms; flip angle: 8 degrees; SENSE factor: 1).

2.3.2. Image processing—Lesions and other brain tissue segmentations were segmented for each subject using corresponding T₁-w and FLAIR images using a publicly available software package TOADS-CRUISE (<https://www.nitrc.org/projects/toads-cruise/>). For each subject, the FLAIR image was rigidly registered (Jenkinson, 2002) to the MPRAGE image. The MPRAGE was then skull-stripped (Carass, 2011) and the co-registered FLAIR was also stripped using the same stripping mask. Then all the subjects were transformed into a

common space by rigidly registering the MPRAGE images to an atlas, as described in Shiee et al. (Shiee, 2010). The FLAIR image of each subject was then transformed into the atlas space by the transformation found using its corresponding MPRAGE. This atlas, having 0.83 mm^3 isotropic voxel size and $218 \times 262 \times 218$ image size, was previously registered to the standard MNI-152 (Fonov, 2011) template. MPRAGE and FLAIR images were then corrected for image intensity inhomogeneity using N4 (Tustison, 2010). Lesions were first segmented from the MPRAGE and FLAIR images using a patch-based segmentation method (Roy, 2014, 2015). Briefly, instead of looking at individual voxel intensities, this method uses intensities from 3D patches (e.g., $3 \times 3 \times 3$ blocks of voxels) from the MPRAGE and FLAIR to estimate lesions, thereby improving lesion segmentation accuracy from traditional voxel based methods. Then brain tissues were segmented using Lesion-TOADS (Shiee, 2010), which segments multiple structures from the MPRAGE, including cerebellar and cerebral WM, cortical, subcortical and cerebellar GM, ventricles, brainstem, and sulcal cerebrospinal fluid (CSF). Volumes of each structure were computed and normalized by the intra-cranial volume, computed as the sum of the volumes of all brain tissues.

2.4. Statistical analyses

Statistical analyses were performed using SPSS version 23 (IBM Corp, Armonk, NY). The data distribution was assessed for normality using the Skewness and Kurtosis test. *T*-tests were used to examine differences in behavioral and imaging measures among MS and control participants. Non-parametric statistics were utilized in conditions where the assumptions for normality were not satisfied. Spearman correlations were used to determine relationships among behavioral measures and imaging measures; boot-strapping was performed to examine 95% confidence intervals. Corrections for multiple comparisons were not performed, as the relationships examined were based upon a priori hypotheses. Furthermore, these corrections assume that the variables are unrelated; MRI substructures are all related to some extent.

3. Results

Twenty-nine individuals with relapsing remitting MS and 29 age and gender-matched controls participated in this study (Table 1). We excluded 7 individuals from the imaging analyses: the first six participants with MS were scanned with an inferior quality FLAIR sequence that could not be included in the LesionTOADS algorithm, and one control subject failed segmentation through the TOADS algorithm due to motion in the scan. Analyses with the MSQOL-54 and MSWS-12 includes only the MS participants, as the healthy control subjects did not complete these assessments.

3.1. Comparisons among individuals with MS and healthy controls

There was no significant difference in age or gender among MS participants and controls (Table 1). Individuals with MS reported significantly more pain ($p < 0.009$), reduced quality of life ($p < 0.036$) and performed more poorly on the SDMT ($p < 0.0001$) compared to their healthy control counterparts.

Individuals with MS demonstrated significantly higher lesion load than healthy controls on brain imaging ($p = 0.0007$), as well as significantly larger sulcal CSF and ventricle volumes ($p = 0.025$ and 0.0006 , respectively). Individuals with MS also had significantly smaller thalamic ($p = 0.0095$) and brainstem ($p = 0.039$) volumes compared to matched healthy controls (Table 2).

3.2. Whole-group relationships among pain, quality of life, and cognition and brain imaging

3.2.1. Relationships among behavioral measures—Pain, cognition, and quality of life were significantly interrelated. Reports of increased pain interference and severity were significantly associated with lower scores on both mental and physical quality of life subscales as well as lower SDMT cognitive performance (Table 3).

Surprisingly, only reports of lower quality of life on the physical subscale of the SF36 were significantly associated with lower SDMT performance, while the mental subscale was not related to cognitive performance (Table 3).

3.2.2. Relationships among behavioral and imaging measures—Higher lesion volume was significantly associated with increased reports of pain, lower quality of life, and lower cognitive performance in our cohort. The relationships between lesion volume and quality of life, pain interference, and SDMT were particularly striking (Table 4).

Reports of high pain interference and lower mental quality of life were associated with lower cortical GM volume, while reports of high pain severity were associated with reduced thalamic and brainstem volumes.

Larger ventricular volume was associated with lower physical quality of life and poorer performance on the SDMT (Table 4; Fig. 1A), while lower caudate and thalamic volumes were associated with reports of low physical quality of life and poorer performance on the SDMT (Table 4; Fig. 1B-C). Pain, quality of life, and cognition were not related to cerebellar GM or WM measures, putamen volume, or cerebral WM volume.

3.3. Sub-analyses: Examining relationships in the MS group

3.3.1. Relationships among behavioral measures—In keeping with the results from the full group analyses, higher reports of pain interference were linked with lower quality of life on the MSQOL-54 fatigue ($r = -0.42$; $p = 0.01$), mental ($r = -0.63$; $p < 0.0001$) and physical ($r = -0.62$; $p = 0.001$) subscales as well as the SF36 mental ($r = -0.61$; $p = 0.001$) and physical ($r = -0.45$; $p = 0.02$) subscales. Interestingly, higher reports of pain severity were not linked to fatigue, but were linked to both mental and physical quality of life on both the MSQOL-54 and SF36 ($r > -0.48$; $p < 0.01$ for all).

Lower self-reported walking status on the MSWS-12 was significantly related to lower reports of quality of life on all three subscales of the MSQOL-54 (Mental: $r = -0.52$; $p = 0.006$; Physical: $r = -0.73$; $p < 0.0001$; and Fatigue: $r = -0.39$; $p = 0.04$), higher pain severity ($r = 0.51$; $p = 0.007$), lower physical quality of life on the SF 36 ($r = -0.81$; $p <$

0.0001) and poorer performance on the SDMT ($r = 0.46$; $p = 0.02$). Interestingly, none of the MSQOL-54 subscales were related to SDMT performance.

3.3.2. Relationships among behavioral and imaging measures—Similar to the combined group analysis, higher lesion volume was significantly associated with reports of lower physical quality of life on the SF36 ($r = -0.48$; $p = 0.02$) and MSQOL-54 ($r = -0.61$; $p = 0.003$) as well as lower mental quality of life on the MSQOL-54 ($r = -0.57$; $p = 0.006$).

Poorer performance on the SDMT was associated with larger ventricular volume ($r = -0.54$; $p = 0.01$) and lower caudate volume ($r = 0.57$; $p = 0.006$), in keeping with the results of the full group analysis. Larger ventricular volume was also associated with lower physical quality of life on the MSQOL-54 ($r = -0.423$; $p = 0.047$). Pain, self-perceived walking function (MSWS-12), and the fatigue subscale of the MSQOL-54 were not significantly related to any of the MRI measures, while cortical GM and WM, cerebellar GM and WM, thalamic, brainstem, and putamen volumes were not related to any of the behavioral measures.

4. Discussion

This study explores relationships among pain, quality of life, cognition and structural brain imaging in a cohort of individuals with MS and healthy age-matched controls. Our results demonstrate that performance on cognitive measures and participants' perceptions of pain and quality of life correlate with MRI lesion burden and brain volumes. Given the complexity of individuals with MS, a better understanding of what clinical measures correlate with brain pathology would improve quantification of this heterogeneity and aid in goal-setting for rehabilitation. A clearer understanding of factors mediating physical function underscores the use of engagement theory, which may improve the results of treatment directed at function.

Beginning early in the disease course, individuals with MS accrue brain atrophy both directly, as a result of axonal damage, and indirectly, with aging. Others have linked reduced thalamus volume to MS disability level (Shiee, 2012), and lower GM volume to reports of lower quality of life (Mowry, 2009). In our cohort, lower thalamic volume was significantly associated with reports of lower physical quality of life and higher pain severity scores. Interestingly, we found that reports of high pain interference were significantly linked with lower cortical GM volume, suggesting that our results build upon the work of Mowry et al. (Mowry, 2009) and now specify that pain influences quality of life reports. Others have shown the relationships among selective GM atrophy and upper extremity motor function (Sbardella, 2013); however, the usefulness of global GM atrophy as an indicator of present and future motor function is unknown. Finally, our data shows that lower caudate volume was significantly associated with poorer performance on the SDMT (caudate: $r = 0.53$; $p < 0.0001$; Fig. 1) and lower physical quality of life ($r = 0.30$; $p = 0.04$), adding to previous literature demonstrating relationships among thalamic atrophy and neuropsychological test performance in individuals with clinically isolated syndrome (Štecková, 2014).

Our results show that higher FLAIR lesion volume was associated with lower quality of life, higher pain and lower cognitive performance. This builds upon earlier work suggesting that lesion burden may be a useful clinical tool for demonstrating the impact on patients' well-being (Mowry, 2009). Additionally, the strong relationship between lesion volume and SDMT performance ($r = -0.46$; $p = 0.001$) extends recent work linking performance on the SDMT and other neuropsychological tests with lesion load (Lazeron, 2005) and suggesting that white matter lesion volume significantly predicts longitudinal SDMT performance (Papadopoulou, 2013). Future work should examine whether lesion volume measures may be useful for understanding long-term quality of life and pain scores.

Although limited by a small sample size, our subanalysis of the MS cohort alone demonstrates that disease-specific survey measures, such as MSWS-12 and MSQOL, are useful for understanding how impairments influence the participants' function. Indeed, the MSWS-12 was significantly associated with all three sub-scales of the MSQOL and cognitive performance. Furthermore, lower reported physical and mental quality of life on the MSQOL was linked with higher lesion volume ($r = -0.61$; $p = 0.003$ and $r = -0.57$; $p = 0.006$, respectively). These data contribute to our knowledge base on structure-function relationships in individuals with MS. A better understanding of the factors that mediate physical mobility, such as these structure-function relationships may help rehabilitation professionals direct treatment planning and goal-setting for individuals with MS and are in agreement with engagement theory principles. Future studies should examine pain, cognition, and quality of life measures in combination with more commonly-measured motor impairments (e.g., strength). We have previously shown that quantitative strength, balance, and walking measures are useful for assessing function in MS (Fritz, 2015a, 2015b) and are amenable to rehabilitation (Keller, 2016). Rehabilitation can impact quality of life, pain, and cognition; given the results of this study, future work should also examine structural brain changes that might accompany these behavioral improvements. A recent intervention study combining cognitive and motor training demonstrated enhancement of both functional and structural brain plasticity (Prosperini, 2015), lending support to the examination of a wide variety of impairments and the potential for improving the efficacy of rehabilitative therapies.

4.1. Limitations

This study is limited by a small sample size. Within our analyses, we did not control for disease modifying therapy. We were underpowered to examine drug effects on quality of life; eight MS participants were taking natalizumab, which has been associated with improvements in self-reported quality of life in a single longitudinal study (Rudick, 2007). However, all of these participants had been stable on their immunotherapy for at least six months prior to beginning our cross-sectional study. We did not measure depression or fatigue directly. Although pain, fatigue, and depression have been shown to be related to one another (O'Connor, 2008), there is no evidence to suggest that depression or fatigue are risk factors for the development of pain.

4.2. Future directions

In the future, we plan to examine the relationship of quantitative physical measures such as strength and walking to pain, cognition, quality of life, and structural imaging measures cross-sectionally as well as longitudinally and in response to therapeutic interventions, both pharmacological and rehabilitative.

5. Conclusion

Relationships among pain, cognition, and quality of life with structural imaging underscore the importance of structure-function relationships in MS and highlights the need for rehabilitation professionals to not only evaluate these measures, but also to consider rehabilitation goals that targets these areas. Finally, this work reinforces the idea that engagement theory may be an important driver of function in individuals with neurologic disease.

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Fig. 1.

Scatter plot showing the relationship among the Symbol Digit Modalities Test (SDMT), a measure of cognition, and A) ventricular volume; B) caudate volume; and C) thalamic volume. Each filled in circle represents one participant. The line is the correlation between the two variables. Poorer performance on the SDMT is significantly associated with larger ventricular volume ($r = -0.51$; $p < 0.0001$) and smaller caudate and thalamic volumes ($r = 0.53$; $p < 0.0001$ and $r = 0.38$; $p = 0.007$, respectively).

Table 1

Subject demographics

	Multiple Sclerosis N=29	Controls N=29	<i>p</i> -value
Age (years)	48.7 (11.5)	50.8 (11.6)	0.4974
Gender	17F; 12M	20F; 9M	0.4165
Symptom Duration (years)	11.9 (8.7)	–	–
EDSS	4 [1–6.5]	–	–
SDMT	47.6 (12.5)	59.7 (6.04)	<0.0001
BPI Interference	1.95 (2.59)	0.261 (0.625)	0.0003
BPI Severity	2.23 (2.27)	0.754 (0.855)	0.0088
MSQOL Fatigue	44.9 (20.9)	–	–
MSQOL Mental	68.1 (21.5)	–	–
MSQOL Physical	58.9 (16.2)	–	–
MSWS-12	41.6 (26.6)	–	–
SF36 Mental	48.2 (11.3)	55.3 (5.16)	0.0359
SF36 Physical	38.1 (9.34)	51.4 (7.03)	<0.0001

All values listed are mean (SD) with the exception of EDSS, which is listed median [range]. Bolded values indicate significance at $p < 0.05$. Brief Pain Inventory (BPI); Expanded Disability Status Scale (EDSS); Multiple Sclerosis Quality of Life scale (MSQOL); Multiple Sclerosis Walking Scale-12 (MSWS-12); Symbol Digit Modalities Test (SDMT); Short Form 36 (SF36).

Table 2

Comparison of individuals with MS and healthy controls on MRI volume measures

	Multiple Sclerosis N=23	Controls N=28	p-value
Lesion Volume (cm ³)	8.50 (7.88)	3.26(0.94)	<0.0001*
Sulcal CSF (cm ³)	330.57 (29.15)	308.43 (37.40)	0.0247
Ventricles (cm ³)	31.90 (13.05)	20.07(9.84)	0.0006*
Caudate (cm ³)	5.95(1.00)	6.55 (0.97)	0.0353
Thalamus (cm ³)	11.07 (1.45)	11.96 (0.86)	0.0095*
Putamen (cm ³)	9.32 (0.79)	9.29 (0.98)	0.9039
Brainstem (cm ³)	21.31 (3.87)	22.49(2.95)	0.0391*
Cerebellar GM (cm ³)	91.32 (16.29)	90.32 (15.93)	0.8946*
Cortical GM (cm ³)	474.58 (45.12)	463.68 (38.52)	0.3565
Cerebellar WM (cm ³)	24.69 (6.98)	26.59 (7.28)	0.0512*
Cerebral WM (cm ³)	409.77 (39.15)	422.76 (55.52)	0.3493
ICV (cm ³)	1088.40 (83.87)	1076.96 (96.13)	0.6564

All values are listed mean (SD). Bolded values indicate significance at $p < 0.05$.

Cerebrospinal Fluid (CSF); Grey Matter (GM); Intracranial Volume (ICV); White Matter (WM).

*
Indicates Mann-Whitney test.

Table 3

Combined group relationships among behavioral measures

		Spearman's Rho	<i>p</i> -value	95% Confidence Interval
BPI Severity	SF36 Mental	−0.33	0.01	−0.60 to −0.004
	SF36 Physical	−0.52	<0.0001	−0.71 to −0.27
	SDMT	−0.39	0.003	−0.63 to −0.12
BPI Interference	SF36 Mental	−0.48	<0.0001	−0.69 to −0.20
	SF36 Physical	−0.61	<0.0001	−0.78 to −0.36
	SDMT	−0.35	0.008	−0.60 to −0.06
SDMT	SF36 Mental	0.20	0.14	−0.08 to 0.45
	SF36 Physical	0.51	<0.0001	0.32 to 0.66

Bolded values indicate significance at $p < 0.05$. Brief Pain Inventory (BPI); Short Form 36 (SF36); Symbol Digit Modalities Test (SDMT).

Table 4

Combined group relationships among behavioral measures and brain imaging

		Spearman's Rho	p-value	95% Confidence Interval
Lesion Volume	SF36 Mental	-0.31	0.03	-0.58 to -0.02
	SF36 Physical	-0.60	<0.0001	-0.76 to -0.38
	BPI Severity	0.29	0.04	-0.04 to 0.58
	BPI Interference	0.37	0.01	0.07 to 0.62
	SDMT	-0.46	0.001	-0.71 to -0.13
Ventricular Volume	SF36 Mental	-0.20	0.17	-0.52 to 0.14
	SF36 Physical	-0.45	0.001	-0.64 to -0.19
	BPI Severity	0.25	0.08	-0.03 to 0.14
	BPI Interference	0.24	0.09	-0.08 to 0.52
	SDMT	-0.51	<0.0001	-0.71 to -0.23
Cortical GM Volume	SF36 Mental	-0.28	0.048	-0.57 to 0.09
	SF36 Physical	-0.11	0.45	-0.37 to 0.50
	BPI Severity	0.06	0.68	-0.21 to 0.33
	BPI Interference	0.29	0.045	-0.01 to 0.55
	SDMT	0.05	0.72	-0.23 to 0.34
Thalamus Volume	SF36 Mental	-0.01	0.97	-0.32 to 0.29
	SF36 Physical	0.40	0.004	0.18 to 0.58
	BPI Severity	-0.32	0.02	-0.57 to -0.02
	BPI Interference	-0.24	0.10	-0.49 to 0.03
	SDMT	0.38	0.007	0.13 to 0.58
Brainstem Volume	SF36 Mental	0.05	0.74	-0.27 to 0.35
	SF36 Physical	0.26	0.07	-0.01 to 0.51
	BPI Severity	-0.30	0.04	-0.55 to -0.01
	BPI Interference	-0.12	0.46	-0.38 to 0.19
	SDMT	0.19	0.20	-0.10 to 0.45
Caudate Volume	SF36 Mental	-0.09	0.55	-0.40 to 0.25
	SF36 Physical	0.30	0.04	0.04 to 0.51
	BPI Severity	-0.22	0.14	-0.48 to 0.08
	BPI Interference	-0.003	0.98	-0.32 to 0.30
	SDMT	0.53	<0.0001	0.26 to 0.72

Bolded values indicate significance at $p < 0.05$. Brief Pain Inventory (BPI); Grey Matter (GM); Short Form 36 (SF36); Symbol Digit Modalities Test (SDMT).