Clinical Pain Research

Rogier J. Scherder*, Angela J. Prins, Marit J. van Dorp, Chris van Klaveren, Ilja Cornelisz, Joep Killestein and Henry Weinstein

Pain, cognition and disability in advanced multiple sclerosis

https://doi.org/10.1515/sjpain-2021-0067
Received April 3, 2021; accepted August 9, 2021;
published online September 2, 2021

Abstract

Objectives: In patients with multiple sclerosis (MS), a relationship between physical disability and pain has been observed. In addition a relationship between physical disability and cognition in MS has been suggested. However, cognitive functions and pain appear not to be correlated in MS patients. Therefore, we examined whether a possible relationship between pain and cognitive functioning may exist, and if so, if such a relationship is mediated by physical disability.
Methods: Forty-five MS patients with chronic pain, and in an advanced stage of the disease were included. Physical disabilities were assessed by the Expanded Disability Status Scale (EDSS). Episodic memory was assessed by means of the Eight Words test, and Face and Picture Recognition. Executive functions (EF) were examined by Digit Span Backward for working memory, and the Rule Shift Cards and Category Fluency test for cognitive flexibility. Pain Intensity and Pain Affect were assessed by means of visual analogue scales and one verbal pain scale and mood (depression, anxiety) by the Beck Depression Inventory and the Symptom Check List (SCL-90). The research questions were analyzed by means of regression analyses and the Sobel test for mediation.
Results: A significant relationship was found between Pain Affect and EF, but that relationship was not mediated by physical disabilities (EDSS). In addition, Pain Intensity and EF showed a significant relationship but only in combination with physical disabilities (EDSS). Finally, mood was related to pain affect.
Discussion: The findings suggest that the lower the EF, exclusively or in combination with more physical disabilities, the more the patient may suffer from pain.
Implications: The more one is cognitively and physically impaired, the more one might suffer from pain, and, the less one is able to communicate pain. The latter could put MS patients at risk for underdiagnosing and undertreatment of pain.

Keywords: anxiety; chronic pain; depression; executive functions; mood; multiple sclerosis; physical disability; regression analyses; visual analogue scales; working memory.

Introduction

Multiple sclerosis (MS) is a progressive neurodegenerative disease of the central nervous system (CNS) [1–3]. Known symptoms of MS include cognitive dysfunction, spasticity, muscle weakness, fatigue, mood disorders, bladder and sexual dysfunction, and pain [2, 4].

Concerning cognitive dysfunction, MS patients may suffer from progressive cognitive impairment during the course of the disease [5, 6]. In most cases, the cognitive impairment consists of a decline in memory, attention, information processing speed, and executive functions [5–7]. Either white or grey matter lesions may cause MS-related cognitive impairment [8–10]. With respect to pain, the prevalence of pain in MS ranges from 29 to 92% [11]. Pain may have a negative influence on the quality of life in MS patients [6]. MS related pain can be differentiated

***Corresponding author: Rogier J. Scherder**, MD, Department of Clinical Neuropsychology, Free University, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands,
E-mail: rogierscherder@hotmail.com
Angela J. Prins, Atlant, Beekbergen, The Netherlands,
E-mail: angela.prins@atlant.nl
Marit J. van Dorp, Tante Louise, Bergen op Zoom, The Netherlands,
E-mail: marit_vandorp@live.nl
Chris van Klaveren and Ilja Cornelisz, Department of Clinical Neuropsychology, Vrije Universiteit, Amsterdam, The Netherlands,
E-mail: c.p.b.j.van.klaveren@vu.nl (C. van Klaveren),
i.cornelisz@vu.nl (I. Cornelisz)
Joep Killestein, Department of Neurology, Amsterdam UMC location VUmc, Amsterdam, The Netherlands, E-mail: J.Killestein@vumc.nl
Henry Weinstein, Department of Neurology, OLVG location West, Amsterdam, The Netherlands, E-mail: h.weinstein@olvg.nl

in neuropathic, nociceptive and mixed pain, the latter implying a combination of the former two [11, 12]. Neuropathic pain is caused by a lesion of the CNS and can result in extremity pain, Lhermitte's sign and trigeminal neuralgia [12], whereas nociceptive pain arises by mechanical, thermal or chemical stimulation of nociceptors, caused by tissue damage [1, 11].

In a previous study, with *another group of MS patients*, we examined whether a relationship exists between cognition dysfunction and chronic pain in MS patients. The inflammatory process, characteristic for MS, supports such a relationship [13]. We hypothesized that cognitive impairment might be correlated either with an increase or a decrease in pain [14]. On the one hand, pain experience may increase during the course of MS following the possible presence of white matter lesions causing deafferentation pain. On the other hand, a decrease in pain experience might also occur, due to grey matter atrophy of e.g. the hippocampus and prefrontal cortex [15]. The results of that study show only a trend between pain intensity and executive functions (verbal fluency) and no further significant relationship between pain and other cognitive function [14]. An explanation might be that MS patients use different brain areas when they were subjected to the neuropsychological tests in comparison to healthy controls. For example, compared to people without MS, MS patients activated additional brain regions during an alertness task [16]. These areas, including e.g. the inferior and superior frontal and temporal cortex, the angular gyrus, and the lateral cerebellum, do not fulfill a specific function in transducing pain signals [14].

Another explanation might be that we did not control for physical disabilities, a limitation of that study [14]. Indeed, spasticity might cause pain in MS [17]. Pain and spasticity are both associated with greater disability [17–19]. The relationship between pain and disability, as measured by the Expanded Disability Status Scale (EDSS), was found in several studies. Patients with chronic pain showed higher scores on the EDSS [20, 21]. It was argued that the higher the EDSS score, the more MS patients suffered from spasticity, paresis and postural abnormalities, resulting in an increase in both neuropathic and nociceptive pain [20, 22]. It is generally known that pain is of great influence on the quality of life [19].

Physical disabilities are also related to cognition in MS. For example, a correlation was found between white matter lesion volume and physical disability, measured by the EDSS, and between white matter lesion volume and working memory, attention, and information processing speed, measured by the Paced Auditory Serial Addition Test-3 (PASAT-3) [8]. The authors ascribe this relationship to white matter lesion volume in particular, whereas cortical lesions (CL) showed only a trend with disability. In another study, compared to the non-CL group, MS patients with CL, showed a significant larger impairment in more difficult neuropsychological tests and showed a higher score on the EDSS score, implying more physical disability [23]. Others describe a negative influence of cognitive impairment on disability and investigated, among other things, a possible correlation between cognitive impairment and disability. They found a significant correlation between the severity of cognitive impairment and EDSS score [24].

In sum, a relationship appears to exist between pain and physical disability, and between physical disability and cognitive functions in MS. A relationship between pain and cognitive functioning in MS has not been demonstrated yet. Therefore, the question arises whether a possible relationship between pain (four pain scales) and cognitive functioning (EF, memory) exists, and if so, if such a relationship is mediated by physical disability (EDSS).

Materials and methods

Design and subjects

Study design: Cross sectional.

Participants: With reference to our previous study [14], the present study included *a new* group of patients, i.e. forty-five patients with advanced multiple sclerosis and chronic pain (17 males, 28 females) (G* Power 3.1.9.7: multiple regression, medium/large effect size: 0.35 (Cohen's f^2), α=0.05, 4 predictors: n=40). The diagnosis was made by an MS-neurologist. The patients were enrolled at Nieuw Unicum, a center for the professional care of patients with physical disabilities in particular, Zandvoort, The Netherlands.

Multiple sclerosis subtypes: The subtype of multiple sclerosis was categorized in: relapsing-remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS), and progressive undetermined.

Global cognitive functioning: We used the Mini Mental State Examination [25] to assess global cognitive functioning (maximum score=30). One speaks of cognitive decline when a score of 25 or less is achieved. For further details see ref. [14].

Education: Level of education of all participants was listed as follows: elementary school not finished (score: 1), elementary school finished (score: 2), more than 6 classes elementary school (score: 3), education but not the level of secondary school (score: 4), secondary school (score: 5), higher secondary school (score: 6), higher vocational training for 18+/university (score: 7) [26].

Intoxications: Percentages of alcohol and cigarette consumption was noted.

Medication: We noted all medicines that were used by the participants, including analgesics, i.e. baclofen, paracetamol, naproxen, ibuprofen, diclofenac, and cannabis.

Comorbidities: We incorporated the chronic comorbidities in the past six months of the participants into eight different categories: cardiovascular diseases, endocrinological and metabolic disorders, neurological disorders, eye disorders, infections, internal disorders, disorders of the musculoskeletal system, and psychiatric disorders other than mood. For a description of the comorbidities that belong to each separate category, see ref. [27]. Each separate comorbidity was scored as follows: 0=absent, 1=present. All scores were added up, providing a Total Comorbidity Score.

Exclusion criteria: Exclusion criteria incorporated a clinically relevant history of central nervous system disorders other than MS, alcoholism, neoplasms, severe and/or recurrent psychiatric illness. Patients with severe vision disturbances and/or cognitive disturbances (MMSE score ≤15) were also excluded.

Informed consent: All participants gave their oral and written informed consent after being informed about the purpose and content of the study. The present study involved human subjects, and consequently, complied with all relevant national regulations, institutional policies, is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the authors' Institutional Review Board (IRB): NL 19801.029.07, 2007.211.

Instruments and procedure

Mood

Since mood, i.e. depression and anxiety, could have a possible negative influence on pain experience [28], mood was assessed with the following questionnaires: the Beck Depression Inventory (BDI: minimum score=0, maximum score=63) [29], the SCL-90 anxiety subscale (minimum score=0, maximum score=40) [30, 31], and the SCL-90 depression subscale (minimum score=0, maximum score=52) [30, 31], scores of these three subscales were converted into z-scores. Factor analysis showed that the three scales could load on one component. Subsequently, we composed a composite domain score for mood (Cronbach's alpha 0.86).

Physical disability

To measure physical disability trained raters applied the Expanded Disability Status Scale (EDSS) [32]. This results in a score from 0 to 10, in which a score of 0 means no disability and 10 means death due to MS [33]. The EDSS focuses mainly on physical disabilities and is a less viable instrument for measuring cognitive functioning [7, 34].

Cognition

Episodic memory

Episodic memory was tested by means of the following tests. *Eight-Words Test* [35]. *Face and Picture Recognition of the Rivermead Behavioural Memory Test* (RBMT-faces) [36]. For further details, please see ref [14].

The scores of the separate tests were converted into *z*-scores. Factor analysis showed that the three tests could load on one component. Subsequently, we composed a composite domain score for memory (Cronbach's alpha 0.82).

Executive functions were assessed by the following tests. *The Digit Span Backwards (DSB) of the Wechsler Memory Test* [37]. *The Rule Shift Cards of the Behavioural Assessment of the Dysexecutive Syndrome (BADS)* [36]. *Category fluency (a subtest of the Dutch Gronginger Intelligence Test)* [38]. Factor analysis showed that a domain 'executive functions' could be composed (Cronbach's Alpha 0.75).

Pain

We used four pain scales to measure pain intensity and pain affect at the time of testing. *Coloured Analogue Scale (CAS)* [39]. This pain scale is used to measure pain intensity and suffering from pain (called: pain affect) (score 0=no pain, score 10=severe pain). *Faces pain scale (FPS)* [40]. The participant is asked to choose a drawn picture of a face with a certain expression, amongst other drawn pictures of faces with different expressions, which matches with the severity of pain they experience (score 0=no pain, score 6=severe pain). This scale measures pain intensity. *Number of Words Chosen-Affective (NWC-A)* [41]. The participant is asked to choose a word out of a group of three words that is an indication of the pain that has been experienced (score 0=no pain, score 15=severe pain). This pain scale is used to measure suffering from pain (pain affect).

For further details about the tests we used to measure pain, see ref. [14].

Procedure

The neuropsychological tests and the EDSS scores were performed by trained raters (MvD and AP). The assessment

of cognitive functions and pain took place during one session. The total administration time was approx. 1–1.5 h. If the patient became too tired to proceed with the testing, the remaining neuropsychological tests were *not* administered at a later moment, to avoid bias. The test session started with the linguistic understanding and subsequently administration of the pain scales. Similar to our former studies, the sequence of administering the tests was: the Eight Words Test (Immediate Recall), Rule Shift Cards, Eight Words Test (Delayed Recall), Eight Words Test (Recognition), Digit Span Backwards, Face Recognition, Picture Recognition, Category Fluency, and, at the end, the Beck Depression Inventory and the SCL-90.

Data-analyses

For data-analyses, we used the SPSS-PC program and STATA 16.0. Chi square tests were applied to analyze data concerning pain medication and comorbidities. The first research question, i.e. is physical disability involved in the relationship between pain and cognition in MS patients, was examined by means of four separate linear regression analyses. The dependent variables were Coloured Analogue Scale (CAS) Affect, Number of Words Chosen – Affective (NWC-A), Coloured Analogue Scale (CAS) Intensity, and the Faces Pain Scale (FPS), respectively. Four models were applied. We started with the domain EF or Memory (Model 1), and added subsequently EDSS (Model 2), interaction cognitive domain x EDSS (Model 3), and finally adding Mood (Model 4). Level of significance was set at $p<0.05$.

In case of a significant relationship between pain (four pain scales) and cognition (EF, memory) in MS, the research question whether such a relationship is mediated by physical disabilities (EDSS), will be examined with mediation analysis; significance of the (partial) mediation effect will be determined by the Sobel test [42, 43]. To determine complete or partial mediation, the following associations will be analyzed. In the first place, a significant association between cognition (EF and memory) and pain (assessed with four different pain scales) will be examined, which represents the overall effect. Next, the association between cognition (EF, memory) and physical disabilities (EDSS) will be examined, and (partial) mediation can only occur if this association is statistically significant. Third, the association between EDSS and pain (four pain scales) should also be statistically significant, adjusting for cognition (EF, memory). Next, controlling path a and path b, should lower the significant association between cognition and pain (path c) in the presence of a mediation effect. The mediation analysis will indicate to what extent the association between pain and cognition is mediated by EDSS, and to what extent the relation is a direct effect. Level of significance was set at $p<0.05$.

Results

Demographics

Age

The mean age of the patients was 56.31 years (SD: 8.49; range 29–71 years). The mean disease duration was 16.87 years (SD: 8.80).

MS subtypes

The results were as follows: RRMS 4.4%, PPMS 44.4%, SPMS 48.9% and progressive undetermined 2.2%.

MMSE (Global cognitive functioning)

The mean score was 27.09 (range 16–30, SD 3.34).

Education

Mean education level: 5.42 (range: 2–7).

Intoxications

17.8% of the participants did smoke, whereas 46.7% used alcohol. Mean number of glasses per week was: 2.48 (SD: 5.05), range: 0–21 per week.

Cognition

The mean scores of the MS patients are lower concerning episodic memory and executive functions (for means and standard deviations, see Table 1) when compared to healthy controls (please see ref. [14] for means and standard deviations of healthy controls). See Table S1.

Pain

For results (*M* and SD) concerning pain intensity and pain affect at time of testing, see Table 2. Compared to the maximum scores on the scales, the mean scores suggest that the MS patients reported a relatively low level of pain. See Table S2.

Table 1: Hierarchical regression analysis predicting scores the CAS affect (dependent variable) with mood, EF domain, memory domain, EDSS, interaction EDSS × EF, and interaction EDSS × memory in a sample of MS patients experiencing pain at the moment of testing.

CAS affect	β (SE)	t	p	F	df	p	R^2_{adj}	R^2	ΔR^2
Model 1				4.75	1.42	0.035	0.08	0.102	0.102
EF	−0.145(0.07)	−2.18	0.035						
Model 2				0.80	1.41	0.38	0.08	0.119	0.017
EF	−0.143(0.07)	−2.15	0.037						
EDSS	0.139(0.16)	0.90	0.38						
Model 3				0.15	1.40	0.70	0.06	0.122	0.003
EF	−0.149(0.07)	−2.17	0.036						
EDSS	0.178(0.19)	0.96	0.35						
EF × EDSS	−0.034(0.09)	−0.39	0.70						
Model 4				0.90	1.39	0.35	0.05	0.142	0.020
EF	−0.173(0.07)	−2.36	0.020						
EDSS	0.166(0.19)	0.89	0.38						
EF × EDSS	−0.033(0.06)	−0.37	0.71						
Mood	0.056(0.06)	0.95	0.35						
Model 1				0.038	1.41	0.85	−0.023	0.001	0.001
Memory	−0.008(0.04)	−0.19	0.85						
Model 2				0.339	1.40	0.56	−0.04	0.009	0.008
Memory	−0.007(0.04)	−0.16	0.88						
EDSS	0.09(0.16)	0.58	0.56						
Model 3				0.869	1.39	0.36	−0.04	0.031	0.022
Memory	−0.013(0.04)	−0.29	0.77						
EDSS	0.068(0.16)	0.41	0.68						
Mem × EDSS	0.035(0.04)	0.93	0.36						
Model 4				0.392	1.38	0.54	−0.06	0.041	0.010
Memory	−0.019(0.04)	−0.43	0.67						
EDSS	0.066(0.17)	0.40	0.69						
Mem × EDSS	0.035(0.04)	0.92	0.36						
Mood	0.039(0.06)	0.63	0.54						

Physical disability

The mean EDSS score of the MS patients was 7.16 (SD=1.08) (range 3.5–9.0).

Mood

Compared to the maximum scores, the mean scores on the various scales for depression and anxiety are relatively low (Table 3). See Table S3.

Pain medication

The percentages of the various analgesics used by MS patients were: Baclofen: 40%, Paracetamol: 42.2%, Diclofenac: 0%, Naproxen: 4.4%, Ibuprofen: 2.2%, and Cannabis: 15.6%.

Comorbidity

Percentages of eight different comorbidity categories are presented in Table S4. The mean total comorbidity was M=2.58, SD=1.69 (max. score: 8).

Relationship between pain, cognition, physical disability, and mood

Pain affect

CAS affect

EF domain

In Model 1, the EF domain, explains 10% of the variance of the scores on CAS Affect (Table 1). The relationship was

Table 2: Hierarchical regression analysis predicting scores the NWC-A (dependent variable) with mood, EF domain, memory domain, EDSS, interaction EDSS × EF, and interaction EDSS × Memory in a sample of MS patients experiencing pain at the moment of testing.

NWC-A	β (SE)	t	p	F	df	p	R^2_{adj}	R^2	ΔR^2
Model 1				0.20	1.42	0.66	−0.02	0.005	0.005
EF	−0.029(0.07)	−0.44	0.66						
Model 2				1.62	1.41	0.21	−0.01	0.04	0.04
EF	−0.027(0.07)	−0.42	0.68						
EDSS	0.193(0.15)	1.27	0.21						
Model 3				0.23	1.40	0.64	−0.02	0.05	0.23
EF	−0.020(0.07)	−0.30	0.77						
EDSS	0.146(0.18)	0.80	0.43						
EF × EDSS	0.041(0.09)	0.48	0.64						
Model 4				8.56	1.39	0.006	0.14	0.22	0.17
EF	−0.085(0.07)	−1.30	0.20						
EDSS	0.112(0.17)	0.67	0.51						
EF × EDSS	0.044(0.08)	0.56	0.58						
Mood	0.156(0.05)	2.93	0.006						
Model 1				0.002	1.41	0.97	−0.02	0.00	0.00
Memory	−0.002(0.04)	−0.04	0.97						
Model 2				0.73	1.40	0.40	−0.03	0.02	0.02
Memory	0.000(0.04)	0.01	0.99						
EDSS	0.129(0.15)	0.86	0.40						
Model 3				1.82	1.38	0.19	−0.01	0.06	0.04
Memory	−0.008(0.04)	−0.19	0.85						
EDSS	0.094(0.15)	0.62	0.54						
Mem × EDSS	0.047(0.04)	1.35	0.19						
Model 4				11.30	1.37	0.002	0.20	0.28	0.22
Memory	−0.035(0.04)	−0.98	0.33						
EDSS	0.086(0.14)	0.64	0.53						
Mem × EDSS	0.046(0.03)	1.48	0.15						
Mood	0.170(0.05)	3.36	0.002						

significant (p=0.035). This relationship remained significant in the other three models.

Memory domain

None of the models showed one or more significant predictors of the scores on CAS Affect.

NWC-A

EF domain

In Model 4 of the EF domain, entering Mood explained significantly 17% more of the variance of the scores on the NWC-A (see Table 2).

Memory domain

In Model 4 of the Memory domain, even 22% of the variance of the scores on the NWC-A were explained by Mood (Table 2). No other models showed one or more significant predictors of the scores on NWC-A.

Pain intensity

CAS intensity

EF domain

The data presented in Table 3, show that no model significantly explained variance of the scores on CAS Intensity.

Memory domain

No model significantly explained variance of the scores on CAS Intensity (Table 3).

FPS

EF domain

Adding the interaction EF × EDSS to Model 3, significantly explained 10% more of the variance of the scores on the FPS. The significant relationship between the interaction EF × EDSS remained after entering Mood as a predictor in

Table 3: Hierarchical regression analysis predicting scores the CAS intensity (dependent variable) with mood, EF domain, memory domain, EDSS, interaction EDSS × EF, and interaction EDSS × memory in a sample of MS patients experiencing pain at the moment of testing.

CAS intensity	β (SE)	t	p	F	df	p	R^2_{adj}	R^2	ΔR^2
Model 1				1.22	1.42	0.28	0.005	0.03	0.03
EF	−0.073(0.07)	−1.11	0.28						
Model 2				0.38	1.41	0.54	−0.01	0.04	0.01
EF	−0.072(0.07)	−1.08	0.29						
EDSS	0.095(0.16)	0.62	0.54						
Model 3				0.05	1.40	0.83	−0.03	0.04	0.00
EF	−0.069(0.07)	−1.0	0.33						
EDSS	0.073(0.19)	0.39	0.70						
EF × EDSS	0.019(0.09)	0.22	0.83						
Model 4				1.29	1.39	0.26	−0.03	0.07	0.03
EF	−0.097(0.07)	−1.33	0.19						
EDSS	0.059(0.19)	0.32	0.75						
EF × EDSS	0.021(0.09)	0.24	0.81						
Mood	0.067(0.06)	1.14	0.26						
Model 1				0.06	1.41	0.81	−0.02	0.001	0.001
Memory	0.010(0.04)	0.25	0.81						
Model 2				0.10	1.40	0.75	−0.05	0.004	0.003
Memory	0.011(0.04)	0.26	0.80						
EDSS	0.050(0.15)	0.32	0.75						
Model 3				1.40	1.39	0.24	−0.04	0.04	0.04
Memory	0.003(0.04)	0.08	0.93						
EDSS	0.018(0.16)	0.12	0.91						
Mem × EDSS	0.042(0.04)	−0.19	0.85						
Model 4				1.43	1.38	0.24	−0.02	0.07	0.04
Memory	−0.008(0.04)	−0.19	0.85						
EDSS	0.015(0.16)	0.10	0.93						
Mem × EDSS	0.042(0.04)	1.18	0.25						
Mood	0.070(0.06)	1.20	0.24						

Model 4. Entering Mood explained an additional 7% of the variance (Table 4).

Memory domain

No model significantly explained variance of the scores on CAS Intensity (see Table 4).

Mediation analysis

As only EF showed a significant negative relationship with pain, in particular assessed by CAS Affect, the question arises whether this relationship was mediated by EDSS. As can be observed in Figure 1, EDSS did not significantly mediate the relationship between EF and CAS Affect.

Discussion

The goal of the present study was to examine if a relationship exists between cognition (EF, memory) and pain, assessed by four different pain scales. The reason why we have chosen for four different pain scales, instead of a more 'general' pain domain is three-fold. In the first place, we tried to make a more refined distinction between pain affect and pain intensity. Such a distinction, although somewhat arbitrary, is based on the functioning of the medial and lateral pain system, respectively [44]. The medial pain system projects to the prefrontal cortex, involved in the motivational-affective processing of pain, whereas the lateral pain system finally projects to the parietal lobe, for its role in processing the sensory-discriminative aspects of pain [44]. Important for this discussion is that the prefrontal-parietal networks are also involved in cognitive functions, e.g. EF [45]. In the second place, each pain scale assesses pain in somewhat different way, visual with and without faces, and verbal. In the third place, we used the same four pain scales in previous studies, not only in MS patients, but also in other groups of cognitively impaired persons, e.g. patients with dementia. By applying the same scales in each study, we are able to compare the various results.

Table 4: Hierarchical regression analysis predicting scores the FPS (dependent variable) with mood, EF domain, memory domain, EDSS, interaction EDSS × EF, and interaction EDSS × memory in a sample of MS patients experiencing pain at the moment of testing.

FPS	β (SE)	t	p	F	df	p	R^2_{adj}	R^2	ΔR^2
Model 1				0.81	1.42	0.38	−0.005	0.019	0.019
EF	−0.06(0.07)	−0.90	0.38						
Model 2				0.02	1.41	0.89	−0.029	0.019	0.000
EF	−0.06(0.07)	−0.88	0.38						
EDSS	0.022(0.16)	0.14	0.89						
Model 3				4.35	1.40	0.04	0.05	0.116	0.096
EF	−0.03(0.07)	−0.44	0.66						
EDSS	−0.18(0.18)	−0.18	0.32						
EF × EDSS	0.18(0.08)	2.09	0.04						
Model 4				3.47	1.39	0.07	0.10	0.188	0.072
EF	−0.073(0.07)	−1.06	0.30						
EDSS	−0.203(0.18)	−1.16	0.25						
EF × EDSS	0.177(0.08)	2.18	0.04						
Mood	0.104(0.06)	1.86	0.07						
Model 1				0.32	1.41	0.57	−0.016	0.008	0.008
Memory	−0.023(0.04)	−0.57	0.57						
Model 2				0.00	1.40	0.99	−0.042	0.008	0.000
Memory	−0.023(0.04)	−0.56	0.58						
EDSS	−0.002(0.16)	−0.010	0.99						
Model 3				2.85	1.39	0.10	0.004	0.075	0.068
Memory	−0.033(0.04)	−0.82	0.42						
EDSS	−0.046(0.15)	−0.30	0.77						
Mem × EDSS	0.059(0.04)	1.69	0.10						
Model 4				3.30	1.38	0.08	0.06	0.15	0.074
Memory	−0.049(0.04)	−1.24	0.22						
EDSS	−0.051(0.15)	−0.34	0.74						
Mem × EDSS	0.059(0.03)	1.72	0.09						
Mood	0.102(0.06)	1.82	0.08						

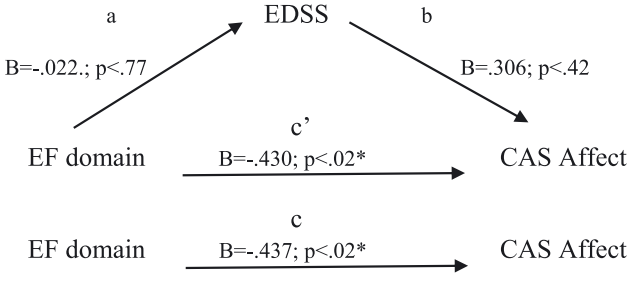

Figure 1: Mediation model between EF domain and CAS affect, by EDSS, controlled for mood. EF, executive functions; CAS, coloured analogue scale; EDSS, expanded disability status scale. *Significant 95% CI level.

First, we will discuss the positive main findings. A significant negative relationship was observed between EF and Pain Affect (CAS Affect), implying that the lower the EF, the more the patient may suffer from pain. In an earlier study, a negative relationship between EF and pain affect was also observed [14]. However, that relationship only concerned Verbal Fluency and was not significant but showed a trend, possibly due to somewhat larger standard deviations [14]. One can only speculate about a neuropathological mechanism underlying such a relationship; since we did not obtain neuroimaging data ourselves in the present study. One such a speculation is that a negative relationship between EF and pain might be related to white matter pathology. This suggestion arises from studies on pain in patients with 'possible' and 'probable' vascular dementia [46, 47]. Similar to MS, the neuropathology of vascular dementia is characterized by, among others, white matter lesions, resulting in de-afferentation pain [47]. De-afferentiation pain might be caused by a disconnection of brain regions, resulting in an increase in pain affect [48]. Indeed, patients with vascular dementia experienced an increase in pain, compared to those without dementia. It is argued that the more the white matter is affected, the higher the increase in pain affect and the larger the impairment in EF. We discussed earlier that an impairment in EF, in combination with an increase in pain affect (medial pain system), might be explained by a deterioration of the prefrontal-parietal networks in MS [45].

Considering the significant relationship between EF and pain affect in the present study, the question arises whether this relationship is mediated by EDSS. The outcome of the Sobel mediation test was however negative (see Figure 1).

Another main finding is that EF shows a negative relationship with pain intensity (measured by the FPS), but only *in combination with* EDSS. This finding implies that in MS patients' pain intensity may be related to a higher level of physical disabilities (higher EDSS scores) and lower scores on tests for EF. The fronto-parietal networks are not only involved in pain, and EF, but also in physical abilities. One study showed a negative relationship between fronto-parietal grey matter volume loss and the scores on the EDSS in MS patients treated with Natalizumab [49]. In addition, as mentioned earlier, the parietal lobe, more precisely the primary and secondary somatosensory regions and the parietal operculum are part of the lateral pain system [44]. The lateral pain system processes the intensity of pain in particular.

In sum, our results suggest that a decrease in cognitive functions (EF) and an increase in physical disabilities (EDSS) may correlate with an increase in pain experience. Within the same line of reasoning, better cognitive and physical functioning implies more intact grey and white matter and, consequently, a better functioning of person's own pain suppressing systems; in other words, less pain experience.

Furthermore, we did also find a significant relationship between mood and pain affect, measured with the NWC-A. It is well known that chronic pain is frequently seen in patients with mood disorders, such as depression and anxiety. One study reports that 70% of patients with mood disorders may experience chronic pain [50]. The study also described that pain could be a predictor of depression and vice versa. One might wonder why a relationship between mood and pain was not found for the other pain scales (CAS intensity, CAS affect and FPS). A possible explanation could be that the MS patients who participated in our study reported relatively low scores on both the pain and mood scales. In sum, concerning the positive main findings, we observed a direct relationship between pain affect (CAS affect) and EF, not mediated by EDSS, a relationship between pain intensity (FPS) and EF, only in combination with physical disabilities (EDSS) and, finally, a relationship between mood and pain affect, when assessed by NWC-A.

Next we discuss the negative findings. CAS Intensity and NWC-A did not show a relationship with EF, the scores on all four pain scales appeared not to be related to memory and three out of the four pain scales were not related to mood; only the NWC-A was related to mood. Although visual analogue scales were found to be reliable pain assessment instruments in MS [51], justifying its use in the present study. In some studies, the FPS is the preferred choice for pain assessment in MS [52, 53]. The FPS preference does also hold for other groups of cognitively (un) impaired people but not for each group. For example, elderly persons from African American origin, with and without cognitive impairment, prefer the FPS, next to the Iowa Pain Thermometer (IPT), which is quite similar to the CAS we used, and the Verbal Descriptor Scale (VDS) [54, 55]; the NWC-A is an example of a verbal descriptor scale. The FPS was also the preferred instrument for adults with Mild Cognitive Impairment (MCI) [56]. Similarly, compared to other pain scales, the FPS could be filled in by the highest percentage of cognitively impaired long-term care patients [57]. However, compared to the FPS, the Philadelphia Pain Intensity Scale (PIS), another type of a verbal descriptor scale, was filled in by a higher percentage of community-dwelling cognitively impaired older persons [58]. In sum, in the majority of the studies, including those with MS patients, multiple (non)verbal pain assessment scales are used, assessment scales that are similar to the scales we applied in the present study. The one pain scale might be more accessible for the patient than the other. For the present and other studies is the variety in accessibility of the pain scales, the main reason for applying more than one pain scale, each one of a somewhat different nature.

An alternative explanation for the negative findings and a limitation of the present study might be that mainly patients with advanced MS with high EDSS scores were included, whereas adding more patients with lower EDSS scores might have rendered more variation in the data. The same holds for pain and mood: our patients showed relative low scores on pain and mood. One explanation might be that our study was underpowered. Our sample consisted of 45 subjects which was based on a power analysis, incorporating a medium/large effect size of 0.35 (Cohen's f^2). The question remains if the choice for a medium/large effect size of 0.35 is justified. On the one hand, there is ample evidence for a reciprocal relationship between chronic pain and cognitive functions [59], justifying a medium/large effect size. On the other hand, the relationship between cognition and pain has not yet been observed in MS patients. We therefore suggest that a replication of the study should take place with a larger number of participants.

Another limitation is that we did include mood and not fatigue as a possible confound to cognition and physical disabilities. Compared to mood, is fatigue a more consistent confounder. A recent study shows a strong association

between fatigue and cognition, social life, and physical disability [60]. Fatigue also shows a close relationship with pain, in the majority of MS patients [61]. According to these authors, the mechanism underlying those relationships is neuroinflammation. Others emphasize that a combination of pain, anxiety, depression, and fatigue seriously complicates a healthy lifestyle and, consequently, quality of life [62]. In contrast to fatigue, the association between mood and physical disabilities, assessed by EDSS, is less studied in MS and results are less consistent. In one study, depression was unrelated to EDSS [63]. In a more recent study it was observed that depression was positively associated with the EDSS-score [64]. However, anxiety appeared to be negatively associated with the EDSS score in that study. The authors argue that by becoming progressively more aware of one's physical disability, one may accept it, lowering the level of anxiety. Because of its inconsistency as a confounder, we included mood instead of fatigue in the present study. However, in a next study, with a larger group of patients, fatigue should be included as a confounder as well. A final limitation is that part of the explanations of the main findings we presented above, are based on neuro-imaging data that were not collected in the present study.

Taking these limitations into consideration, we conclude that our findings should be interpreted with caution. The findings may suggest that a more severe impairment in EF might be related to a higher experience of pain affect, and that a more severe impairment in EF, in combination with a more severe decline in physical abilities, might be related to a higher experience of pain intensity. In other words, the more one is cognitively and physically impaired, the more one might suffer from pain, and the less one is able to communicate pain. The latter could put MS patients at risk for underdiagnosing and undertreatment of pain.

Acknowledgments: The authors are most grateful to all participants and to the team of Nieuw Unicum Zandvoort, The Netherlands.

Research funding: Not applicable.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: The authors report no conflict of interest.

Informed consent: Informed written consent was received from every participant.

Ethical approval: The present study involved human subjects, and consequently, complied with all relevant national regulations, institutional policies, is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the authors' Institutional Review Board (IRB): NL 19801.029.07, 2007.211.

References

1. Drulovic J, Basic-Kes V, Grgic S, Vojinovic S, Dincic E, Toncev G, et al. The prevalence of pain in adults with multiple sclerosis: a multicenter cross-sectional survey. Pain Med 2015;16:1597–602.
2. Huisman E, Papadimitropoulou K, Jarrett J, Bending M, Firth Z, Allen F, et al. Systematic literature review and network meta-analysis in highly active relapsing-remitting multiple sclerosis and rapidly evolving severe multiple sclerosis. BMJ Open 2017;7: e013430.
3. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet 2018;391:1622–36.
4. Crayton HJ, Rossman HS. Managing the symptoms of multiple sclerosis: a multimodal approach. Clin Therapeut 2006;28: 445–60.
5. Jønsson A, Andresen J, Storr L, Tscherning T, Soelberg Sorensen P, Ravnborg M. Cognitive impairment in newly diagnosed multiple sclerosis patients: a 4-year follow-up study. J Neurol Sci 2006;245:77–85.
6. Huijbregts SC, Kalkers NF, de Sonneville LM, de Groot V, Polman CH. Cognitive impairment and decline in different MS subtypes. J Neurol Sci 2006;245:187–94.
7. Wybrecht D, Reuter F, Pariollaud F, Zaaraoui W, Le Troter A, Rico A, et al. New brain lesions with no impact on physical disability can impact cognition in early multiple sclerosis: a ten-year longitudinal study. PloS One 2017;12:e0184650.
8. Papadopoulou A, Müller-Lenke N, Naegelin Y, Kalt G, Bendfeldt K, Kuster P, et al. Contribution of cortical and white matter lesions to cognitive impairment in multiple sclerosis. Mult Scler 2013;19: 1290–6.
9. Fisniku LK, Chard DT, Jackson JS, Anderson VM, Altmann DR, Miszkiel KA, et al. Gray matter atrophy is related to long-term disability in multiple sclerosis. Ann Neurol 2008;64:247–54.
10. Roosendaal SD, Moraal B, Pouwels PJ, Vrenken H, Castelijns JA, Barkhof F, et al. Accumulation of cortical lesions in MS: relation with cognitive impairment. Mult Scler 2009;15:708–14.
11. Ferraro D, Plantone D, Morselli F, Dallari G, Simone AM, Vitetta F, et al. Systematic assessment and characterization of chronic pain in multiple sclerosis patients. Neurol Sci 2018;39:445–53.
12. Heitmann H, Biberacher V, Tiemann L, Buck D, Loleit V, Selter RC, et al. Prevalence of neuropathic pain in early multiple sclerosis. Mult Scler 2016;22:1224–30.
13. Benson C, Kerr BJ. Pain and cognition in multiple sclerosis. Curr Top Behav Neurosci 2014;20:201–15.
14. Scherder R, Kant N, Wolf E, Pijnenburg ACM, Scherder E. Pain and cognition in multiple sclerosis. Pain Med 2017;18:1987–98.
15. Scherder E, Wolters E, Polman C, Sergeant J, Swaab D. Pain in Parkinson's disease and multiple sclerosis: its relation to the medial and lateral pain systems. Neurosci Biobehav Rev 2005; 29:1047–56.
16. Penner IK, Rausch M, Kappos L, Opwis K, Radu EH. Analysis of impairment related functional architecture in MS patients during performance of different attention tasks. J Neurol 2003;250: 461–72.

17. Bethoux F, Marrie RA. A cross-sectional study of the impact of spasticity on daily activities in multiple sclerosis. Patient 2016;9: 537–46.
18. Solaro C, Cella M, Signori A, Martinelli V, Radaelli M, Centonze D, et al. Identifying neuropathic pain in patients with multiple sclerosis: a cross-sectional multicenter study using highly specific criteria. J Neurol 2018;265:828–35.
19. Young J, Amatya B, Galea MP, Khan F. Chronic pain in multiple sclerosis: a 10-year longitudinal study. Scand J Pain 2017;16: 198–203.
20. Grau-López L, Sierra S, Martínez-Cáceres E, Ramo-Tello C. Analysis of the pain in multiple sclerosis patients. Neurologia 2011;26:208–13.
21. O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: systematic review and proposed classification. Pain 2008;137:96–111.
22. Svendsen KB, Sørensen L, Jensen TS, Hansen HJ, Bach FW. MRI of the central nervous system in MS patients with and without pain. Eur J Pain 2011;15:395–401.
23. Matsushita F, Kida H, Tabei KI, Nakano C, Matsuura K, Li Y, et al. Clinical significance of cortical lesions in patients with multiple sclerosis: a neuropsychological and neuroimaging study. Brain Behav 2018;8:e00934.
24. Nelson F, Datta S, Garcia N, Rozario NL, Perez F, Cutter G, et al. Intracortical lesions by 3T magnetic resonance imaging and correlation with cognitive impairment in multiple sclerosis. Mult Scler 2011;17:1122–9.
25. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
26. Verhage F. Intelligentie en leeftijd: bij volwassenen en bejaarden [Intelligence and age: in adults and elderly people]. Assen: Van Gorcum & Comp. N.V.; 1964.
27. Scherder R, Kant N, Wolf ET, Pijnenburg B, Scherder EJ. Psychiatric and physical comorbidities and pain in patients with multiple sclerosis. J Pain Res 2018;11:325–34.
28. Rusu AC, Santos R, Pincus T. Pain-related distress and clinical depression in chronic pain: a comparison between two measures. Scand J Pain 2016;12:62–7.
29. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatr 1961;4:561–71.
30. Arrindell WA, Ettema JHM. SCL-90, Handleiding bij een multidimensionele psychopathologie-indicator. Lisse: Swets & Zeitlinger; 1986.
31. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. Br J Psychiatr 1976; 128:280–9.
32. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33: 1444–52.
33. Collins CD, Ivry B, Bowen JD, Cheng EM, Dobson R, Goodin DS, et al. A comparative analysis of patient-reported expanded disability status scale tools. Mult Scler 2016;22:1349–58.
34. Reynders T, D'haeseleer M, De Keyser J, Nagels G, D'hooghe MB. Definition, prevalence and predictive factors of benign multiple sclerosis. eNeurologicalSci 2017;7:37–43.
35. Lindeboom J, Jonker C. Amsterdamse Dementie Screening (ADS6). Lisse: Swets & Zeitlinger; 1989.
36. Wilson B, Cockburn J, Baddeley A. The rivermead behavioural memory test. Titchfield: Thames Valley Test Company; 1987.
37. Wechsler D. Manual for the Wechsler adult intelligence scale. New York: The Psychological Corporation; 1955.
38. Luteijn F, Ploeg van der FAE. Groninger intelligentie test. Lisse: Swets & Zeitlinger; 1983.
39. McGrath PA, Seifert CE, Speechly KN, Booth JC, Stitt L, Gibson MC. A new analogue scale for assessing children's pain: an initial validation study. Pain 1996;64:435–43.
40. Kim EJ, Buschmann MT. Reliability and validity of the faces pain scale with older adults. Int J Nurs Stud 2006;43:447–56.
41. Kloot van der WA, Oostendorp RAB, Meij van der J, Heuvel van der J. De Nederlandse versie van McGill pain questionnaire: een betrouwbare pijnvragenlijst. Ned Tijdschr Geneeskd 1995;139:669–73.
42. Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. Socio Methodol 1982;13:290–312.
43. Sobel ME. Some new results on indirect effects and their standard errors in covariance structure models. Socio Methodol 1986;16:159–86.
44. Scherder EJ, Sergeant JA, Swaab DF. Pain processing in dementia and its relation to neuropathology. Lancet Neurol 2003;2: 677–86.
45. Cui Z, Stiso J, Baum GL, Kim JZ, Roalf DR, Betzel RF, et al. Optimization of energy state transition trajectory supports the development of executive function during youth. Elife 2020;9: e53060.
46. Scherder EJ, Slaets J, Deijen JB, Gorter Y, Ooms ME, Ribbe M, et al. Pain assessment in patients with possible vascular dementia. Psychiatry 2003;66:133–45.
47. Scherder EJ, Plooij B, Achterberg WP, Pieper M, Wiegersma M, Lobbezoo F, et al. Chronic pain in "probable" vascular dementia: preliminary findings. Pain Med 2015;16:442–50.
48. Scherder E, Oosterman J, Swaab D, Herr K, Ooms M, Ribbe M, et al. Recent developments in pain in dementia. BMJ 2005;330: 461–4.
49. Ciampi E, Pareto D, Sastre-Garriga J, Vidal-Jordana A, Tur C, Rio J, et al. Grey matter atrophy is associated with disability increase in natalizumab-treated patients. Mult Scler 2017;23: 556–66.
50. de Heer EW, Gerrits MM, Beekman AT, Dekker J, van Marwijk HWJ, de Waal MWM, et al. The association of depression and anxiety with pain: a study from NESDA. PloS One 2014;9:e106907.
51. Kos D, Raeymaekers J, Van Remoortel A, D'hooghe MB, Nagels G, D'Haeseleer M, et al. Electronic visual analogue scales for pain, fatigue, anxiety and quality of life in people with multiple sclerosis using smartphone and tablet: a reliability and feasibility study. Clin Rehabil 2017;31:1215–25.
52. Mueller ME, Gruenthal M, Olson WL, Olson WH. Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. Arch Phys Med Rehabil 1997;78:521–4.
53. D'Aleo G, Rifici C, Sessa E, Di Bella P, Bramanti P. R3 nociceptive reflex in multiple sclerosis patients with paroxysmal symptoms treated with gabapentin. Funct Neurol 2000;15:205–59.
54. Taylor LJ, Harris J, Epps CD, Herr K. Psychometric evaluation of selected pain intensity scales for use with cognitively impaired and cognitively intact older adults. Rehabil Nurs 2005;30: 55–61.
55. Ware LJ, Epps CD, Herr K, Packard A. Evaluation of the revised faces pain scale, verbal descriptor scale, numeric rating scale, and Iowa pain thermometer in older minority adults. Pain Manag Nurs 2006;7:117–25.

56. Zhou Y, Petpichetchian W, Kitrungrote L. Psychometric properties of pain intensity scales comparing among postoperative adult patients, elderly patients without and with mild cognitive impairment in China. Int J Nurs Stud 2011;48: 449–57.
57. Wynne CF, Ling SM, Remsburg R. Comparison of pain assessment instruments in cognitively intact and cognitively impaired nursing home residents. Geriatr Nurs 2000;21:20–3.
58. Krulewitch H, London MR, Skakel VJ, Lundstedt GJ, Thomason H, Brummel-Smith K. Assessment of pain in cognitively impaired older adults: a comparison of pain assessment tools and their use by nonprofessional caregivers. J Am Geriatr Soc 2000;48: 1607–11.
59. Higgins DM, Martin AM, Baker DG, Vasterling JJ, Risbrough V. The relationship between chronic pain and neurocognitive function: a systematic review. Clin J Pain 2018;34:262–75.
60. Penner IK, McDougall F, Brown TM, Slota C, Doward L, Julian L, et al. Exploring the impact of fatigue in progressive multiple sclerosis: a mixed-methods analysis. Mult Scler Relat Disord 2020;43:102207.
61. Heitmann H, Andlauer TFM, Korn T, Mühlau M, Henningsen P, Hemmer B, et al. Fatigue, depression, and pain in multiple sclerosis: how neuroinflammation translates into dysfunctional reward processing and anhedonic symptoms. Mult Scler J. 2020. 1352458520972279. https://doi.org/10.1177/1352458520972279.
62. Marck CH, De Livera AM, Weiland TJ, Jelinek PL, Neate SL, Brown CR, et al. Pain in people with multiple sclerosis: associations with modifiable lifestyle factors, fatigue, depression, anxiety, and mental health quality of life. Front Neurol 2017;8:461.
63. Möller A, Wiedemann G, Rohde U, Backmund H, Sonntag A. Correlates of cognitive impairment and depressive mood disorder in multiple sclerosis. Acta Psychiatr Scand 1994;89:117–21.
64. Gill S, Santo J, Blair M, Morrow SA. Depressive symptoms are associated with more negative functional outcomes than anxiety symptoms in persons with multiple sclerosis. J Neuropsychiatry Clin Neurosci 2019;31:37–42.

Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/sjpain-2021-0067).