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Schmerzen bei Multipler Sklerose – Prävalenz und Zusammenhang mit Depression und Fatigue

Zusammenstellung wissenschaftlicher Veröffentlichungen
zur Erlangung der Lehrbefähigung für das Fach

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Für meine Familie

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Abkürzungsverzeichnis

BDI = Beck Depression Inventory II

CFS = Chronisches Fatigue Syndrom

CI = 95% Konfidenzintervall

FSMC = Fatigue Scale for Motor and Cognitive Functions

IASP = International Association for the Study of Pain

IL = Interleukin

PASAT = Paced Auditory Serial Addition Test

PDQ = PainDETECT Fragebogen

PPMS = Multiple Sklerose mit primär-progredienter Verlaufsform

DN4 = Doleur Neuropathique en 4 questions Fragebogen

EDSS = Expanded Disability Status Scale

fMRT = funktionelle Magnetresonanztomographie

MRT = Magnetresonanztomographie

MS = Multiple Sklerose

NIMH = National Institutes of Mental Health

NRS = Numerische Ratings Skala

KIS = Klinisch isoliertes Syndrom

KKNMS = Krankheitsbezogenes Kompetenznetz Multiple Sklerose

RIS = Radiologisch-isoliertes Syndrom

RRMS = Multiple Sklerose mit schubförmig-remittierender Verlaufsform

SPMS = Multiple Sklerose mit sekundär-progredienter Verlaufsform

TNF = Tumor Nekrose Faktor

VAS = Visuelle Analogskala

ZNS = Zentrales Nervensystem

Disclaimer

Zur besseren Lesbarkeit wird in dieser Schrift das generische Maskulinum verwendet. Die verwendeten Personenbezeichnungen beziehen sich – sofern nicht anders kenntlich gemacht – auf alle Geschlechter.

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1. Einleitung und Hintergrund

1.1 Multiple Sklerose

Die Multiple Sklerose (MS) ist eine chronisch-entzündliche Erkrankung des zentralen Nervensystems (ZNS) autoimmuner Genese [1, 2]. Die am ehesten multifaktoriellen Auslöser und Pathomechanismen sind bisher unvollständig verstanden. Zur lokalen Inflammation scheinen sowohl humorale als auch zelluläre Faktoren beizutragen [1]. Entzündliche Läsionen treten sowohl im Gehirn als auch im Rückenmark auf und führen zu Demyelinisierung, axonalen und neuronalen Schäden sowie schlussendlich astrozytischer Gliose und Atrophie (vgl. Abbildung 1) [1, 2]. Der Erkrankungsverlauf ist initial überwiegend schubförmig-remittierend (RRMS), und geht bei ungefähr einem Drittel in einen sekundär-progredienten Verlauf über (SPMS). Bei circa 15% verläuft die Erkrankung primär-progredient (PPMS) [1]. Die Erkrankung betrifft weltweit mehr als zwei Millionen Menschen und hat eine Prävalenz von 50 bis 300 pro 100.000, wobei Frauen deutlich häufiger als Männer erkranken (im Verhältnis 3:1) [1].

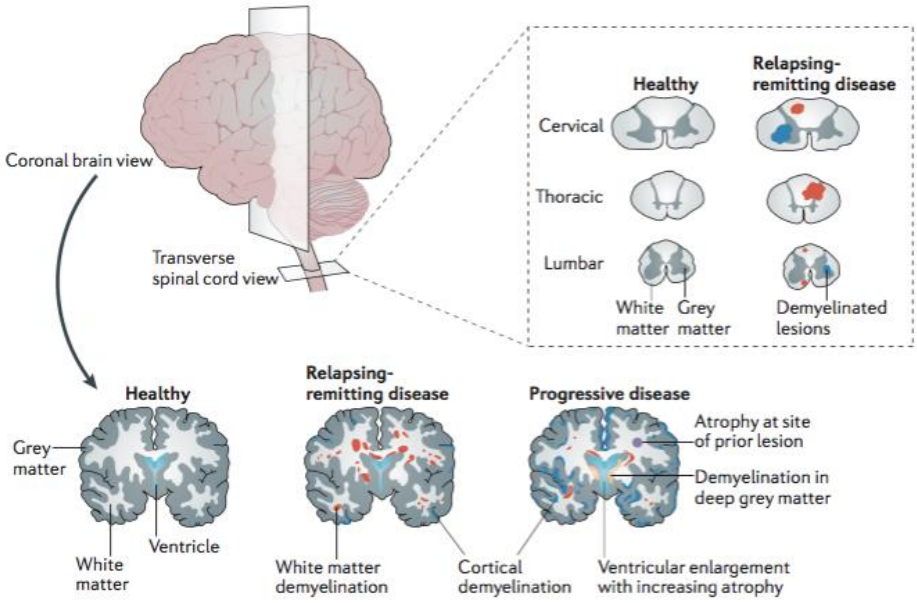


Abbildung 1: Läsionscharakteristika und Verlaufsformen der MS *(modifiziert nach Dendrou et al, 2015).*

Die Diagnosestellung erfolgt nach den sogenannten McDonald-Kriterien, wobei eine räumliche und zeitliche Dissemination der Erkrankung gegeben sein muss [3]. Liegt beim ersten Schubereignis nur eine räumliche Dissemination vor, spricht man von einem Klinisch-isolierten Syndrom (KIS). Inzidentelle MRT-Befunde krankheitstypischer Läsionen, als mögliche präklinische Frühform, werden als Radiologisch-isoliertes Syndrom (RIS) bezeichnet [1].

Die Therapie akuter Schubereignisse erfolgt meist mittels hochdosierter Glukokortikoidgabe. Die Verlaufsmodifikation erfolgt durch eine stetig wachsende Auswahl immun-modulatorischischer Substanzen mit Unterschieden bei Wirkmechanismus und -stärke [4]. Diese reichen von subkutan verabreichten Interferonen und Glatirameroiden über orale Sphingosin-Modulatoren bis zu intravenösen B-Zell-depletierenden Antikörpertherapien [4].

1.2 Schmerzen bei Multipler Sklerose

Schmerzen gelten als häufiges und beeinträchtigendes Symptom bei MS [5, 6]. Patientenseitig wird es als eines der am stärksten belastenden MS-Symptome bewertet [7, 8]. Zusätzlich wurden Schmerzen als schlechter prognostischer Faktor für verschiedene krankheitsbezogene Faktoren wie Lebensqualität, Grad der körperlichen Behinderung und Arbeitsfähigkeit beschrieben [9, 10].

1.2.1 Schmerzarten und -mechanismen

Auch wenn die zugrunde liegenden Pathomechanismen von Schmerzen bei MS nur teilweise bekannt sind, unterscheiden aktuell gängige Klassifikationen verschiedene Schmerzarten unter mechanistischen Gesichtspunkten. Hierbei werden in erster Linie neuropathische, nozizeptive und gemischte Schmerzarten unterschieden [11, 12] (vgl. Abbildung 2).

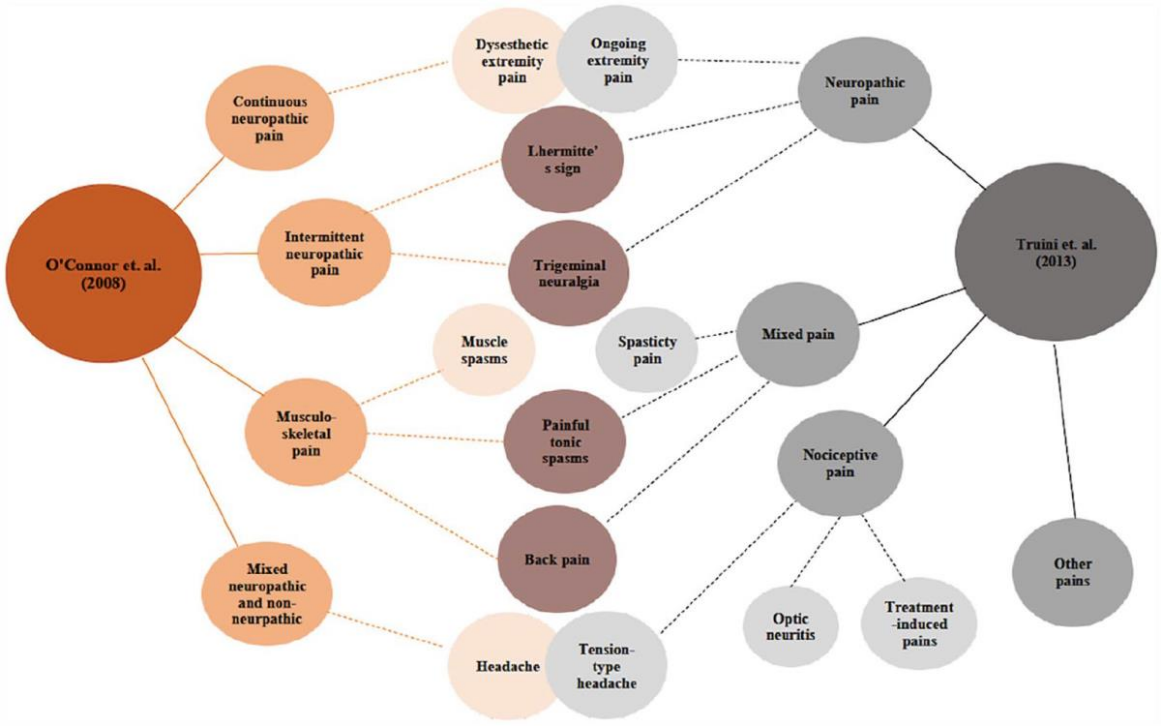


Abbildung 2: Vergleichende Übersicht gängiger Schmerzklassifikationen bei Multipler Sklerose *(modifiziert nach Yilmazer et al, 2020).*

Neuropathische Schmerzen bei MS

Neuropathischen Schmerzen entstehen nach Definition der *International Association for the Study of Pain* (IASP) als direkte Konsequenz von Läsionen oder Krankheiten des somatosensorischen Nervensystems [13]. Entsprechend ist bei dieser Schmerzarzt der Zusammenhang mit der MS als Grunderkrankung, durch das Auftreten von entzündlichen Läsionen im zentralen Nervensystem, am direktesten nachvollziehbar [5, 11]. Neuropathische Schmerzen gehen meist mit unangenehmen Missempfindungen einher und werden von Patienten häufig mit Deskriptoren wie „brennend“ oder „elektrisierend“ beschrieben [13]. Als häufigste Symptomausprägung bei der MS werden hierbei anhaltende neuropathische Schmerzen der Körperextremitäten aufgeführt [5, 11]. Bildgebend wurde dieses Symptom in direkten Zusammenhang mit entzündlichen Läsionen im Bereich des Tractus spinothalamicus des Rückenmarks gesetzt [12, 14]. Weitere neuropathische Schmerzentitäten bei MS, mit jedoch intermittierendem Charakter, sind die Trigeminusneuralgie und das Lhermitte-Zeichen. Bei der Trigeminusneuralgie kommt es zu hochfrequent und blitzartig einschießenden Schmerzen im Bereich des Gesichtes [15]. Bei Patienten mit MS sind diese zumeist auf entzündliche Läsionen im Bereich der Nervenwurzeleintrittszone des N. trigeminus zurückzuführen [14]. Der Ausdruck Lhermitte-Zeichen beschreibt ein elektrisierendes Gefühl entlang der Wirbelsäule, welches bei MS-Patienten zumeist nach Beugung des Nackens oder Rückens auftritt und mit entzündlichen Läsionen im Bereich der Hinterstränge des Rückenmarks in Verbindung gebracht wird [14] (vgl. Abbildung 3).

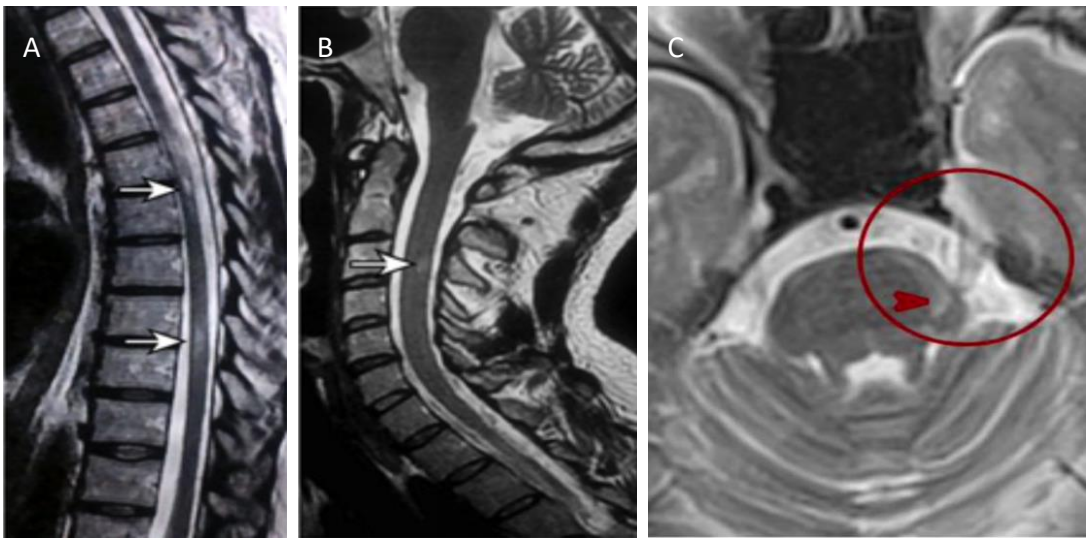


Abbildung 3. Lokalisation entzündlicher Läsionen bei neuropathischen Schmerzen. *A: Spinale Läsionen bei einem Patienten mit anhaltenden Extremitätenschmerzen. B: Hochzervikale Läsion bei einem Patienten mit Lhermitte-Zeichen. C: Pontine Läsion bei einem Patienten mit Trigeminusneuralgie (modifiziert nach Truini et al. 2012 und 2016).*

Neben diesen Korrelaten neuropathischer Schmerzen bei MS in der strukturellen Bildgebung wurden in einer Studie mittels funktioneller Kernspintomographie (fMRT) Störungen in dem Bereich des Gehirns festgestellt, der mit Motivation und Belohnung in Verbindung gebracht wird [16].

Nozizeptive Schmerzen bei MS

Nozizeptive Schmerzen werden per IASP-Definition durch die Aktivierung von Nozizeptoren im Kontext einer tatsächlichen oder potentiellen Schädigung von nicht-neuronalem Gewebe ausgelöst [17]. Bei der MS ist diese Schmerzart unscharf abgegrenzt und meist nicht direkt mit der Grunderkrankung in Verbindung zu bringen [6]. Einige Autoren ordnen zudem Spannungskopfschmerzen als nozizeptiv ein [12]. Teilweise werden auch weitere indirekt mit der Erkrankung zusammenhängende Schmerzen, wie z.B. durch ödematöse Gewebsschwellung in der Orbita bei Neuritiden des N. opticus oder durch subkutane Injektionen oder Grippe-ähnliche Symptome im Kontext von Interferontherapien zur Krankheitsmodulation, dieser Schmerzarzt zugeordnet [12].

Gemischte Schmerzen bei MS

Der Begriff gemischter Schmerz („mixed pain“) beschreibt Entitäten bei denen sowohl neuropathische als auch nozizeptive Schmerzanteile vermutet werden [18]. Bei der MS werden unter diesem Sammelbegriff vor allem verschiedene muskuloskelettale Schmerzsymptome mit indirektem Zusammenhang zur Grunderkrankung zusammengefasst [11, 12]. Von den meisten Autoren werden z.B. Rückenschmerzen, die durch krankheitsbedingte körperliche Einschränkungen und Fehlhaltungen verursacht sein können, zu dieser Kategorie gezählt [11, 12]. Auch durch anhaltende oder einschießende Muskelspasmen verursachte Schmerzen werden in den gängigen Klassifikationen dem gemischten Schmerz zugeordnet [11, 12]. Die meisten Autoren klassifizieren zudem auch Kopfschmerzsymptome bei MS als gemischte Schmerzen [11].

1.2.2 Prävalenz

Die Prävalenzschätzungen von Schmerzen bei MS unterscheiden sich teils stark zwischen verschiedenen Quellen und werden mit Werten zwischen 29 und 83 % angegeben [5, 6, 11]. Im Rahmen einer Metanalyse wurde eine Schmerzprävalenz von 63 % (95 % Konfidenzintervall

[CI] 55-70 %) gefunden [5]. Die großen Unterschiede der Prävalenzschätzungen zwischen den einzelnen Studien sind am ehesten auf die starke Heterogenität der untersuchten Studienpopulationen und der verwendeten Screening-Methoden zurückzuführen [5, 6]. So wurden in den meisten Einzelstudien Patienten in uneinheitlichen, meist fortgeschrittenen, Krankheitsstadien untersucht und häufig nicht zwischen verschiedenen Schmerzarten unterschieden [5, 6, 11].

Durch eine systematische Literaturanalyse und Metaanalyse, gibt es jedoch orientierende Daten zur Prävalenz der häufigsten Schmerzsymptome im Kontext der MS [5].

Für die *neuropathischen* Schmerzentitäten wird eine gepoolte Gesamtprävalenz von 29% (CI 24-34 %) angeben, was deutlich über der in der Normalbevölkerung berichteten Prävalenz von 9% liegt [19]. Die Einzelprävalenz der neuropathischen Beschwerdebilder wird mit 27 % (CI 7-53 %) für den anhaltenden Extremitätenschmerz, 16 % (CI 10-25 %) für das Lhermitte Zeichen und 4 % (CI 2-6 %) für die Trigeminusneuralgie angegeben [5].

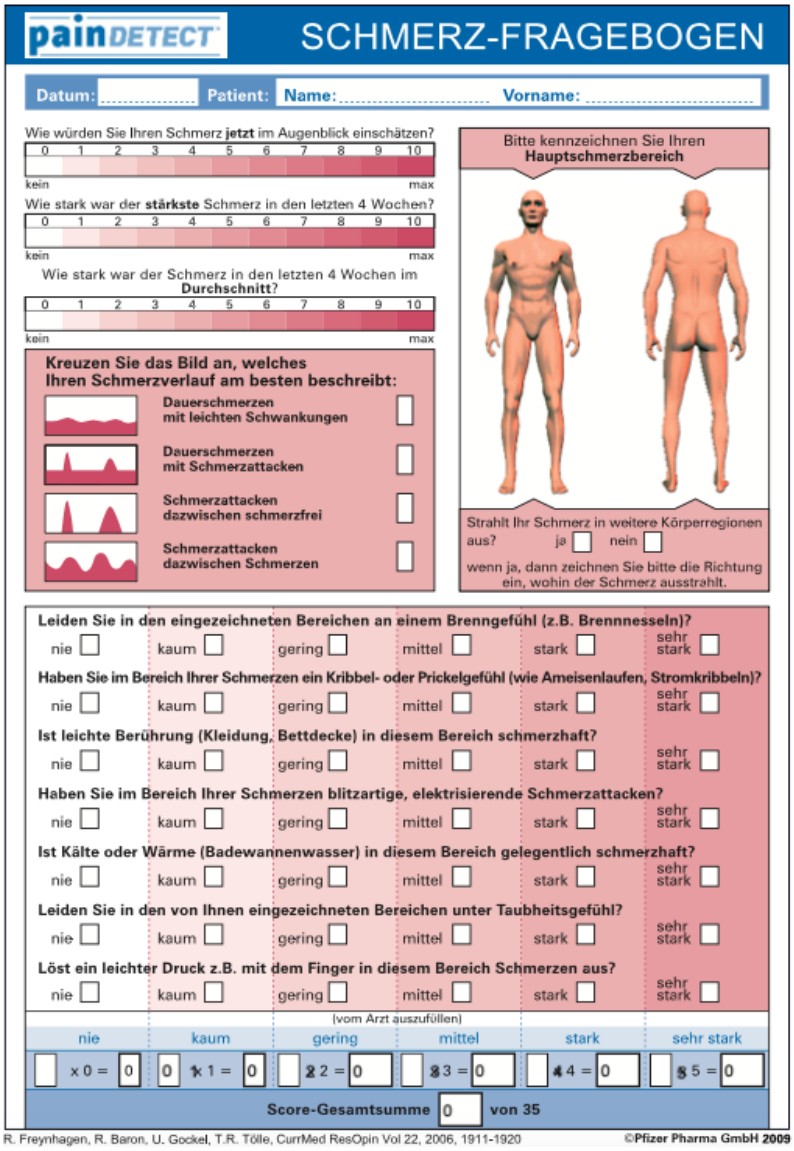
Die gepoolte Gesamtprävalenz *nozizeptiver Schmerzen* wird mit 18 % (CI 14-23 %) angegeben. Bei den *gemischten Schmerzen* haben Kopfschmerzen mit 43% (CI 33-52 %) die höchste Prävalenz, gefolgt von Rückenschmerzen mit 20 % (CI 13-28 %) sowie schmerzhaften Spasmen mit 15 % (CI 9-23 %). Somit ergeben sich für weniger spezifische Schmerzarten wie Rücken- und Kopfschmerz mit der Allgemeinbevölkerung vergleichbare Prävalenzwerte [20, 21].

1.1.3 Screeningmethoden

In den meisten Studien werden Schmerzsymptome durch Selbstauskunft und vorwiegend über Visuelle Analogskalen (VAS) oder Numerische Rating Skalen (NRS) mit einem Minimalwert von „0“ und einem Maximalwert von „10“ erfasst [6]. Um eine mögliche neuropathische Schmerzkomponente und deren Ausprägung zu erfassen liegen verschiedene Screening-Methoden vor, die teilweise Fragebögen und klinische Untersuchungen kombinieren [22]. Bei der MS sind der rein patientenseitig auszufüllende *PainDETECT*-Fragebogen (PDQ) sowie der aus einem Fragebogen- und einem Untersuchungsanteil bestehende *Doleur Neuropathique en 4 questions* (DN4) am weitesten verbreitet [6].

Der PDQ wurde ursprünglich bei Patienten mit Rückenschmerzen etabliert und erfragt in einem ersten Teil die aktuelle sowie die durchschnittliche und maximale Intensität (in den letzten 4 Wochen) von Schmerzen im Allgemeinen auf einer NRS von 0 bis 10. Der zweite Teil untersucht dann spezifisch neuropathische Schmerzen anhand von 7 Deskriptoren

neuropathischer Schmerzcharakteristika wie Brenn- oder Kribbelgefühle, einschießende elektrisierende Schmerzen, Berührungs- oder Druckschmerzempfindlichkeit und Taubheitsgefühle [23]. Die Ausprägung dieser Deskriptoren kann jeweils auf einer Skala von 0 („nie“) bis 5 („sehr stark“) angegeben werden woraus sich ein Gesamtpunktewert ergibt (vgl. Abbildung 4). Zusätzliche Punkte werden vergeben für Schmerzen die als ausstrahlend (+2 Punkte) oder attackenartig (+1 Punkt) auftretend angegeben werden. Somit kann eine Gesamtpunktzahl von 38 Punkten erzielt werden. Bei einem Wert ≥19 Punkten wird von einer wahrscheinlichen neuropathischen Schmerzkomponente ausgegangen, bei einem Wert von 13-18 Punkten gilt dies als unklar und bei einem Wert von 12 oder weniger als unwahrscheinlich [23].


painDETECT SCHMERZ-FRAGEBOGEN

Datum: Patient: Name: Vorname:

Wie würden Sie Ihren Schmerz **jetzt** im Augenblick einschätzen?
0 1 2 3 4 5 6 7 8 9 10
kein max

Wie stark war der **stärkste** Schmerz in den letzten 4 Wochen?
0 1 2 3 4 5 6 7 8 9 10
kein max

Wie stark war der Schmerz in den letzten 4 Wochen im **Durchschnitt**?
0 1 2 3 4 5 6 7 8 9 10
kein max

Kreuzen Sie das Bild an, welches Ihren Schmerzverlauf am besten beschreibt:
- Dauerschmerzen mit leichten Schwankungen
- Dauerschmerzen mit Schmerzattacken
- Schmerzattacken dazwischen schmerzfrei
- Schmerzattacken dazwischen Schmerzen

Bitte kennzeichnen Sie Ihren **Hauptschmerzbereich**

Strahlt Ihr Schmerz in weitere Körperregionen aus? ja nein
wenn ja, dann zeichnen Sie bitte die Richtung ein, wohin der Schmerz ausstrahlt.

Leiden Sie in den eingezeichneten Bereichen an einem Brenngefühl (z.B. Brennnesseln)?
nie kaum gering mittel stark sehr stark

Haben Sie im Bereich Ihrer Schmerzen ein Kribbel- oder Prickelgefühl (wie Ameisenlaufen, Stromkribbeln)?
nie kaum gering mittel stark sehr stark

Ist leichte Berührung (Kleidung, Bettdecke) in diesem Bereich schmerzhaft?
nie kaum gering mittel stark sehr stark

Haben Sie im Bereich Ihrer Schmerzen blitzartige, elektrisierende Schmerzattacken?
nie kaum gering mittel stark sehr stark

Ist Kälte oder Wärme (Badewannenwasser) in diesem Bereich gelegentlich schmerzhaft?
nie kaum gering mittel stark sehr stark

Leiden Sie in den von Ihnen eingezeichneten Bereichen unter Taubheitsgefühl?
nie kaum gering mittel stark sehr stark

Löst ein leichter Druck z.B. mit dem Finger in diesem Bereich Schmerzen aus?
nie kaum gering mittel stark sehr stark

(vom Arzt auszufüllen)

nie	kaum	gering	mittel	stark	sehr stark
x 0 = 0	x 1 = 0	x 2 = 0	x 3 = 0	x 4 = 0	x 5 = 0

Score-Gesamtsumme 0 **von 35**

R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle, CurrMed ResOpin Vol 22, 2006, 1911-1920 ©Pfizer Pharma GmbH 2009

Abbildung 4: PainDETECT Fragebogen zur Untersuchung neuropathischer Schmerzen *(modifiziert nach Freynhagen et al. 2006).*

Beim DN4 werden Patienten ebenfalls anhand von 7 Deskriptoren neuropathischer Schmerzen befragt, wofür bei Vorliegen des jeweiligen Symptoms je ein Punkt vergeben wird. Ergänzt wird dies durch 3 klinische Tests bei denen ein betroffenes Hautareal stimuliert wird. Auffälligkeiten hierbei führen jeweils zu einem weiteren Punkt. Bei einem Maximalwert von 10 Punkten gelten Werte von ≥4 als Hinweis auf neuropathische Schmerzen [24].

1.1.4 Einfluss- und Risikofaktoren

Schmerzen bei MS sind mit einer Vielzahl von soziodemographischen, krankheitsbezogenen und neuropsychiatrischen Faktoren in Verbindung gebracht worden [5, 25].

Bei den *soziodemographischen Faktoren* sind vor allem ein höheres Patientenalter und in einzelnen Studien auch ein niedrigeres Bildungsniveau, ein niedrigerer sozioökonomischer Status und weibliches Geschlecht als potentielle Risikofaktoren beschrieben [26-28]. Ausgeprägte Zusammenhänge zu Häufigkeit und Ausprägung von Schmerzen bei MS wurden vor allem für *krankheitsbezogene Faktoren* wie den krankheitsbedingten Grad körperlicher Behinderung sowie teilweise auch die Krankheitsdauer beschrieben [27]. Als wichtigste *neuropsychiatrische Faktoren* mit wechselseitigen Zusammenhängen zu Schmerzen bei MS gelten komorbide Depressions- oder Fatiguesymptome sowie in geringerem Ausmaß auch Angst- und Schlafstörungen [29-31]. Bei MS-Patienten mit Depressionen wurden zum Beispiel eine höhere Prävalenz sowie eine stärkere Beeinträchtigung durch Schmerzen beschrieben [31, 32]. Auch zwischen Fatiguesymptomen und Schmerzen bei MS wurden Zusammenhänge beschrieben und Fatigue als mögliches Bindeglied zwischen den gehäuft komorbide auftretenden Schmerz- und Depressionssymptomen diskutiert [30].

Longitudinale Studien, die derartige wechselseitige Kausalzusammenhänge zwischen Schmerz und den genannten biopsychosozialen Faktoren im zeitlichen Verlauf untersuchen fehlten jedoch bisher.

1.2 Depressionen bei Multipler Sklerose

Prävalenzschätzungen für Depressionen bei MS liegen zwischen 24-50 % [33-35]. Depressionen bei MS sind mit einer deutlich verschlechterten Lebensqualität, einer stark erhöhten Suizidalität und einer verminderten Adhärenz für die medikamentöse Therapie der Grunderkrankung vergesellschaftet [35-37]. Als bildgebende Korrelate von Depressionen bei MS werden verschiedene strukturelle und funktionelle Auffälligkeiten beschrieben [33, 35].

Strukturell-bildgebend sind dies zumeist Atrophien im Bereich des medialen (prä-)frontalen Kortex, der striatalen Anteile des Belohnungssystems und des limbischen Systems [33, 35]. Funktionell-bildgebend werden ebenfalls vorwiegend Störungen in diesen beiden Systemen beschrieben [33, 35]. Bezüglich der Ätiologie von Depressionen bei MS werden vor allem immunologisch-inflammatorische und psychosoziale Faktoren diskutiert [33, 35]. Immunologisch-inflammatorisch werden vor allem Zusammenhänge der Ausprägung depressiver Symptome mit den Messwerten pro-inflammatorischer Zytokine beobachtet [33, 35, 38]. Als wichtigste psychosoziale Einflussfaktoren auf Depressionen bei MS werden Schmerz und Fatigue sowie in geringerem Ausmaß auch eine kognitive Beeinträchtigung genannt [33, 35].

1.3 Fatigue bei Multipler Sklerose

Fatigue gilt als eines der häufigsten MS-Symptome mit Prävalenzschätzungen von 50-90 % [39, 40]. Wie auch Depression und Schmerz ist Fatigue bei MS mit einer erheblichen Einschränkung der Lebensqualität und der Arbeitsfähigkeit in Verbindung gebracht worden [41, 42]. Als bildgebende Korrelate von Fatigue wurden verschiedene strukturelle als auch funktionelle Veränderungen beschrieben [40, 43]. Ähnlich wie bei der Depression handelt es sich hierbei strukturell-bildgebend vorwiegend um Läsions- und Atrophiemuster im Bereich des (prä-)frontalen Kortex und des Striatums sowie funktionell-bildgebend zumeist um Störungen kortiko-striataler und kortiko-subkortikaler Verbindungen, die ebenfalls Teile des Belohnungssystems sind [43]. Auch die Fatigue bei MS wird als multifaktorielles Symptom angesehen und verschiedene immunlogisch-inflammatorische, kognitive und psychosoziale Einflussfaktoren beschrieben [39, 40]. Wie bei den depressiven Symptomen bei MS wird ein Zusammenhang mit immunologisch-inflammatorischen Prozessen vermutet, da auch die Ausprägung der Fatiguesymptomatik mit Messwerten pro-inflammatorischer Zytokine korreliert [44, 45]. In diesem Kontext wird auch ein hemmender inflammatorischer Einfluss auf den Stoffwechsel des Neurotransmitters Dopamin vermutet, der eine zentrale Rolle im zerebralen Belohnungssystem spielt [40]. Neben diesen pathophysiologisch-orientierten Erklärungsansätzen gibt es auch kognitive Modelle dazu, wie die subjektive Perzeption von Fatigue entstehen könnte [40]. Diese basieren auf einem computationalen Modell der „allostatischen Selbstwirksamkeit“ [46]. Dieses postuliert, dass in einem „metakognitiven“ Prozess ein ständiger Abgleich zwischen den interozeptiven Körperwahrnehmungen und der subjektiven Fähigkeit, die eigenen Körperfunktionen zu kontrollieren stattfindet [46]. Hierbei

entstehen z.B. im Kontext einer Dysregulation durch eine entsprechende Grunderkrankung Vorhersagefehler („prediction error“). Das Symptom der Fatigue wird als eine mögliche Reaktion des Körpers hierauf interpretiert, um diesen davon abzuhalten, weiter übermäßig Energie zur Selbstregulation aufzuwenden [40]. Als wichtigste psychosoziale Einflussfaktoren auf Fatigue bei MS werden aufgrund häufiger Komorbidität Depressionen und Schmerzen genannt, weshalb manche Autoren sogar von einem „Symptomcluster“ sprechen [30, 35].

1.4 Fragestellungen

Mit Blick auf den geschilderten Stand der Literatur ergeben sich vor allem Fragestellungen bezüglich der Prävalenz und Determinanten von Schmerzen bei Multipler Sklerose, welche die Grundlage für die im folgenden Abschnitt vorgestellten eigenen Untersuchungen darstellen.

Um die Prävalenz und Relevanz von verschiedenen Schmerzarten bei MS in frühen Krankheitsstadien beurteilen zu können, wurden daher entsprechende Untersuchungen an einer einheitlichen Studienpopulation unter Einsatz etablierter Screening-Werkzeuge durchgeführt. Zur Untersuchung möglicher kausaler Zusammenhänge zwischen Schmerzen und biopsychosozialen Einflussfaktoren bei MS erfolgte zudem eine longitudinale Untersuchung. Aufgrund der hohen Komorbiditätsraten von Schmerz, Depression und Fatigue wurde dem Zusammenhang zwischen diesen Symptomen hierbei besondere Aufmerksamkeit geschenkt.

2. Präsentation ausgewählter Originalarbeiten

2.1 Prävalenz neuropathischer Schmerzen in frühen Krankheitsstadien Multipler Sklerose

Dieses Kapitel bezieht sich auf folgende Originalarbeit:

Heitmann H, Biberacher V, Tiemann L, Buck D, Loleit V, Selter RC, Knier B, Tölle TR, Mühlau M, Berthele A, Hemmer B and Ploner M. *Prevalence of neuropathic pain in early Multiple Sclerosis*. Multiple Sclerosis Journal. 2016 Aug;22(9):1224-30.

Die Schätzungen zur Prävalenz neuropathischer Schmerzen bei MS variieren stark und vor allem in frühen Krankheitsstadien liegen keine belastbaren Untersuchungen diesbezüglich vor. Bisherige Studien untersuchten überwiegend heterogene Studienpopulationen in fortgeschrittenen Krankheitsstadien [5, 26, 47]. Auch ist weitgehend unklar, welche demographischen, krankheitsbezogenen und neuropsychiatrischen Faktoren mit dem Auftreten neuropathischer Schmerzen in frühen Krankheitsstadien der MS vergesellschaftet sind.

Daher erfolgte eine Auswertung von schmerzbezogenen Daten der prospektiven TUM-MS Kohortenstudie der Klinik und Poliklinik für Neurologie der TU München. Insgesamt konnten Daten von 377 Patienten (252 weiblich und 125 männlich, Durchschnittsalter 36 ±10 Jahre) aus den Jahren 2008 bis 2014 ausgewertet werden. Von allen Patienten wurden die Daten des ersten Studienbesuchs nach Diagnosestellung einer MS entsprechend der bei Einschluss gültigen McDonald-Kriterien eingeschlossen [48]. Bei 96.8 % lag ein schubförmig-remittierender, bei 2.4 % ein sekundär-progredienter und bei 0.8 % ein primär-progredienter Krankheitsverlauf vor. Der durchschnittliche Wert zur Einschätzung der krankheitsbezogenen körperlichen Behinderung auf der Expanded Disability Status Scale (EDSS) betrug 1.6 ±1.3 Punkte. Die durchschnittliche Krankheitsdauer seit der Erstmanifestation der Erkrankung waren 4.2 ±5.6 Jahre. Eingeschlossene Patienten waren therapienaiv bezüglich immunmodulatorischer Medikation.

Neuropathische Schmerzsymptome wurden anhand des PainDETECT-Fragebogens (PDQ) erhoben [23]. Zusätzlich wurden depressive Symptome anhand des Beck Depression Inventory II (BDI) [49] und Fatigue anhand der Fatigue Scale for Motor and Cognitive Functions (FSMC) [50] sowie kognitive Fähigkeiten anhand des Paced Auditory Serial Addition Test (PASAT) [51] untersucht.

Bei 16 der 377 Patienten (4.2 %) fand sich ein PDQ-Wert von 19 Punkten oder mehr, indikativ für eine signifikante neuropathische Schmerzkomponente. Bei weiteren 9.5 % lag mit einem Wert von 13 bis 18 Punkten ein unklares Ergebnis vor. Der überwiegende Teil der Betroffenen litt unter Extremitätenschmerzen (vgl. Abbildung 5).

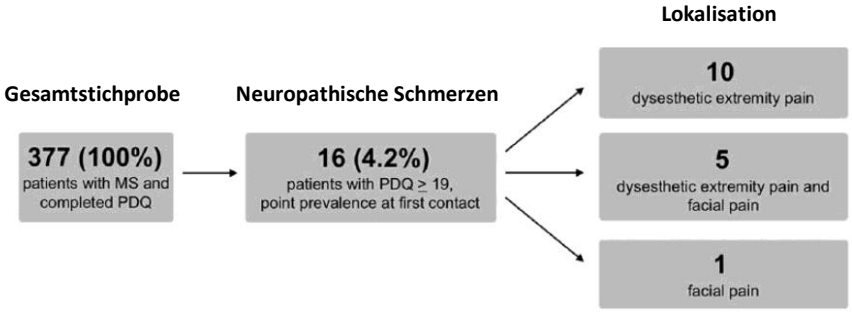
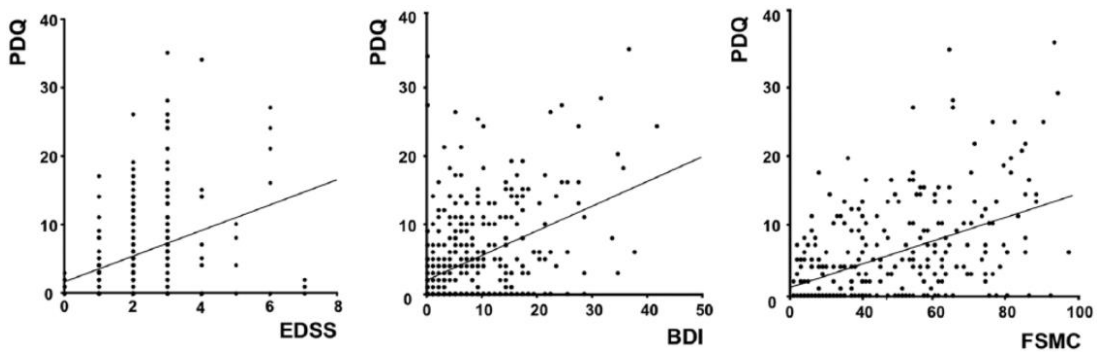


Abbildung 5: Prävalenz und Lokalisation neuropathischer Schmerzen in der TUM-MS Studienkohorte. *PDQ = PainDETECT-Fragebogen (modifiziert nach Heitmann et al., 2016).*

Mittels t-Statistiken wurden die Patientengruppen ober- und unterhalb des PDQ-Grenzwertes von 19 Punkten miteinander verglichen. Patienten mit neuropathischen Schmerzen zeigten signifikant höhere Ausprägungen von körperlicher Behinderung (EDSS 3.3 vs. 1.5, $t=4.2$, $p<0.001$), Depression (BDI 17.5 vs. 7.3, $t=5.3$, $p<0.0001$) und Fatigue (FSMC 74.3 vs. 43.0, $t=6.9$, $p<0.0001$) auf. Keine Gruppenunterschiede fanden sich hingegen bezüglich Alter (36.4 vs. 36.0 Jahre, $t=0.2$, $p=0.87$), Krankheitsdauer (6.2 vs.4.1 Jahre, $t=1.1$, $p=0.26$) und kognitiven Fähigkeiten (PASAT 42.3 vs. 45.1, $t=0.1$, $p=0.34$).

Korrelationsanalysen ergaben entsprechende signifikante positive Zusammenhänge zwischen den PDQ-Punktewerten und der Ausprägung von körperlicher Behinderung (EDSS $r=0.41$, $p<0.0001$), Depression (BDI $r=0.43$, $p<0.0001$) und Fatigue (FSMC $r=0.50$, $p<0.0001$). Zusätzlich fanden sich schwächere positive Korrelationen mit den Faktoren Alter ($r=0.17$, $p<0.001$) und Krankheitsdauer ($r=0.18$, $p<0.001$). Ein Zusammenhang mit kognitiver Beeinträchtigung fand sich hingegen nicht (PASAT $r=-0.07$, $p=0.18$) (vgl. Abbildung 6).



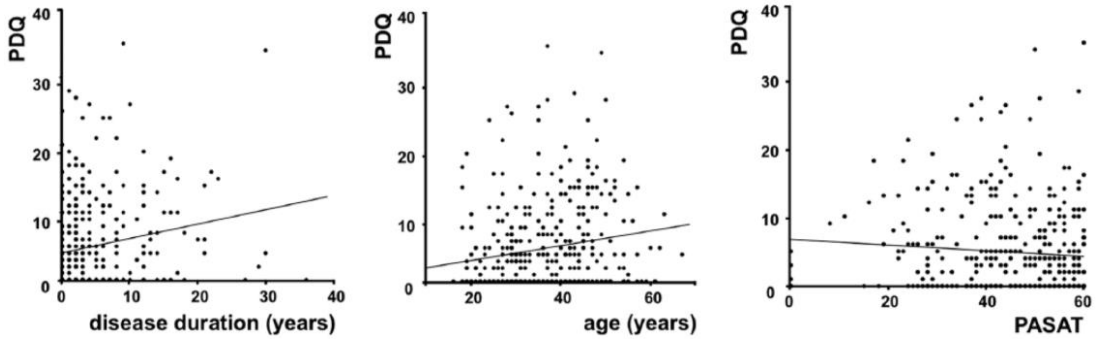


Abbildung 6: Korrelationsanalysen mit neuropathischen Schmerzen in frühen Krankheitsstadien der MS*. PDQ=PainDETECT-Fragebogen, EDSS=Expanded Disability Status Scale, BDI=Beck Depression Inventory II, FSMC=Fatigue Scale for Motor and Cognitive Functions, PASAT=Paced Auditory Serial Addition Task (modifiziert nach Heitmann et al., 2016).*

Multiple Regressionsanalysen erbrachten körperliche Behinderung (EDSS ß=0.25, t=4.4, p<0.0001), Depression (BDI ß=0.24, t=3.8, p<0.0001) und Fatigue (FSMC ß=0.22, t=3.1, p=0.002) als die drei stärksten Prädiktoren für PDQ-Werte (vgl. Abbildung 7). Das finale Modell unter Berücksichtigung der EDSS, BDI und FSMC-Werte erklärte 33% der Varianz in den PDQ-Werten. Keinen zusätzlichen signifikanten erklärenden Wert hatten hingegen die Parameter Alter, Krankheitsdauer und kognitive Leistungsfähigkeit (PASAT).

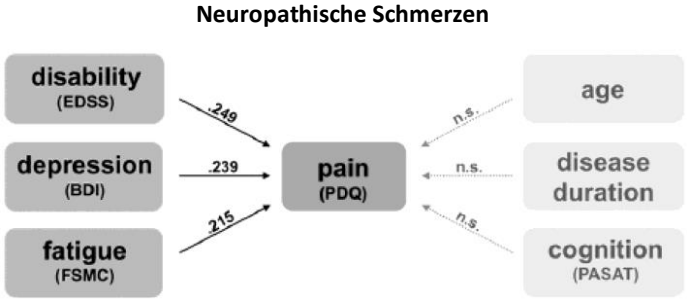


Abbildung 7: Lineares Regressionsmodell mit neuropathischen Schmerzen in frühen Krankheitsstadien der MS. *PDQ-Werte fungierten als abhängige Variable und die Werte der sonstigen Parameter als unabhängige Variablen. PDQ=PainDETECT-Fragebogen, EDSS=Expanded Disability Status Scale, BDI=Beck Depression Inventory II, FSMC=Fatigue Scale for Motor and Cognitive Functions, PASAT=Paced Auditory Serial Addition Task. (modifiziert nach Heitmann et al., 2016).*

Zusammenfassend zeigte sich in dieser Studie eine niedrige Prävalenz neuropathischer Schmerzen in frühen Krankheitsstadien. Der vorbeschriebene Zusammenhang mit körperlicher Behinderung und vor allem Depression und Fatigue konnte jedoch bereits in diesem frühen Krankheitsstadium in starker Ausprägung nachgewiesen werden.

2.2 Longitudinale Prävalenz und Determinanten von Schmerzen bei Multipler Sklerose

Dieses Kapitel bezieht sich auf folgende Originalarbeit:

Heitmann H, Haller B, Tiemann L, Mühlau M, Berthele A, Tölle TR, Salmen A, Ambrosius B, Bayas A, Asseyer S, Hartung HP, Heesen C, Stangel M, Wildemann B, Haars S, Groppa S, Luessi F, Kümpfel T, Nischwitz S, Meuth SG, Klotz L, Linker RA, Zettl UK, Ziemann U, Tumani H, Tackenberg B, Zipp F, Wiendl H, Gold R, Hemmer B, Ploner M. *Longitudinal Prevalence and Determinants of Pain in Multiple Sclerosis - Results from the German National MS Cohort Study*. PAIN. 2020 Apr;161(4):787-796.

Mit Blick auf die stark schwankenden Prävalenzschätzungen verschiedener Schmerzarten bei MS und die unklaren kausalen Zusammenhänge mit biopsychosozialen Einflussfaktoren wurde eine longitudinale Auswertung von Daten der nationalen MS-Kohortenstudie („Nation MS“) des Krankheitsbezogenen Kompetenznetz Multiple Sklerose (KKNMS) durchgeführt.

Insgesamt konnte eine Studienpopulation von 410 Patienten mit der Diagnose einer MS entsprechend der zum Einschlusszeitpunkt gültigen McDonald-Kriterien [48] mit Erstmanifestation innerhalb der letzten 24 Monate oder eines KIS in den letzten 6 Monaten in die Analysen eingeschlossen werden (275 weiblich, 135 männlich). Hierbei wurden Daten zum Zeitpunkt des Einschlusses in die Kohortenstudie (T0) sowie der Folgeuntersuchung vier Jahre (±120 Tage) später (T4) ausgewertet. Patienten bei denen es zu einem der genannten Untersuchungszeitpunkte Hinweise auf ein aktuelles Schubereignis gab oder für die keine schmerzspezifischen Untersuchungsdaten vorlagen wurden ausgeschlossen (vgl. Abbildung 8).

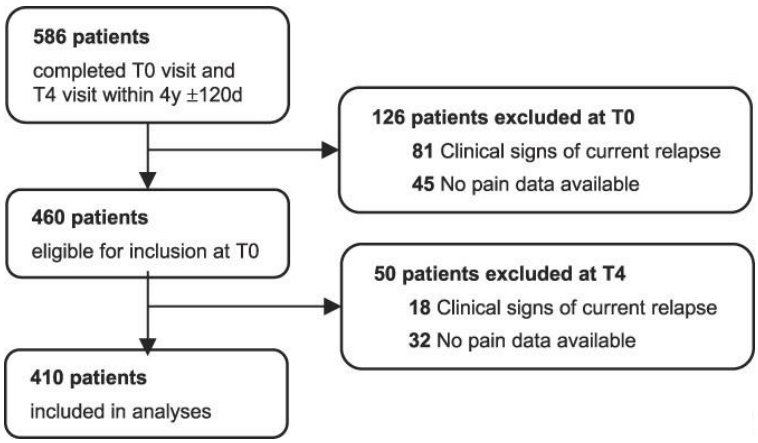


Abbildung 8: Flussdiagramm zur Auswahl der Studienstichprobe in der KKNMS-Kohorte. *T0=Einschlussuntersuchung („Baseline“), T4=Vierjahres-Folgeuntersuchung („Year four“), d = Tage, y = Jahre (modifiziert nach Heitmann et al., 2020).*

Für eine ausführliche Darstellung der Charakteristika der Studienstichprobe siehe Tabelle 1. Das durchschnittliche Alter bei Studieneinschluss lag bei 34 (±10) Jahren, die Krankheitsdauer bei 7 (±7) Monaten. Der Krankheitsverlauf wurde bei Studieneinschluss (T0) bei 46 % als KIS und bei 54% als RRMS klassifiziert. Zum Zeitpunkt T4 hatten 11 % die Diagnose eines KIS, 88 % einer RRMS sowie 1 % einer MS mit sekundär-progredienter Verlaufsform (SPMS). Der durchschnittliche EDSS-Punktewert betrug 1.4 (±1.0) zum Zeitpunkt T0 und 1.5 (±1.2) zum Zeitpunkt T4.

***Tabelle 1*: Stichprobencharakteristika KKNMS-Kohorte**

	Baseline (T0)	Year 4 (T4)	*P*
Gender (female/male)	67/33%	n.a.	n.a.
Age ± SD	34 ±10 y	n.a.	n.a.
Duration ± SD	7 ±7 m	n.a.	n.a.
Course (CIS/RRMS/SPMS)	46/54/0%	11/88/1%	n.a.
Disability (mean EDSS ±SD)	1.39 ± 0.98	1.46 ± 1.18	0.155 (t = −1.4)
Fatigue (mean FSMC ± SD)	38.6 ± 18.1	44.4 ± 21.5	<0.001 (t = −6.5)
Depression (mean BDI ±SD)	7.0 ± 7.5	6.9 ±7.6	0.697 (t = 0.4)
Cognition (mean PASAT ±SD)	46.5 ± 10.6	51.1 ±9.1	<0.001 (t = −8.4)
Education (Univ. degree)	32.0%	39.5%	<0.001
Employment (curr. employed)	91.0%	86.3%	0.018
Treatment (IMT/INF)	n.a.	80.0/25.9%	n.a.

Der statistische Vergleich der Parameter zu den Zeitpunkten T0 („Baseline") und T4 („Year four") erfolgte mittels t-test für abhängige Stichproben für metrische Variablen und mittels McNemar-Bowker Test für kategoriale Variablen. BDI=Beck Depression Inventory II, CIS=KIS=Klinisch isoliertes Syndrom, EDSS=Expanded Disability Status Scale, FSMC=Fatigue Scale for Motor and Cognitive Functions, IMT=Immunomodulatorische Therapie (inklusive Interferone), INF=Interferone, n.a.=nicht anwendbar, PASAT=Paced Auditory Serial Addition Task, RRMS=MS mit schubförmig-remittierender Verlaufsform, SPMS=MS mit sekundär-progredienter Verlaufsform (modifiziert nach Heitmann et al., 2020).

Die Datenextraktion aus der Kohortenstudiendatenbank umfasste neben den genannten soziodemographischen und krankheitsbezogenen Daten auch die detaillierten Fragebogen- und Testergebnisse zu Schmerzen (PDQ), Depression (BDI), Fatigue (FSMC) und Kognition (PASAT).

Zuerst wurde die Prävalenz von allgemeinen Schmerzsymptomen zu den beiden Untersuchungszeitpunkten anhand der NRS-Werte auf dem PDQ ermittelt. Die Klassifikation von allgemeinen Schmerzsymptomen in die Ausprägungsgrade „leicht" (NRS 1-2), „moderat" (NRS 3-5) und „stark" (NRS ≥6) wurde entsprechend der für MS vorgeschlagenen Empfehlungen vorgenommen [52] (vgl. Abbildung 9).

Zusätzlich wurde die Prävalenz „wahrscheinlicher" (PDQ ≥19) und „unklarer" (PDQ 13-18) neuropathischer Schmerzen untersucht (vgl. Abbildung 9). Mögliche Unterschiede zwischen den beiden Zeitpunkten wurden mittels McNemar-Bowker Test untersucht, wobei sich jedoch kein Hinweis für eine signifikante Veränderung im zeitlichen Verlauf ergab.

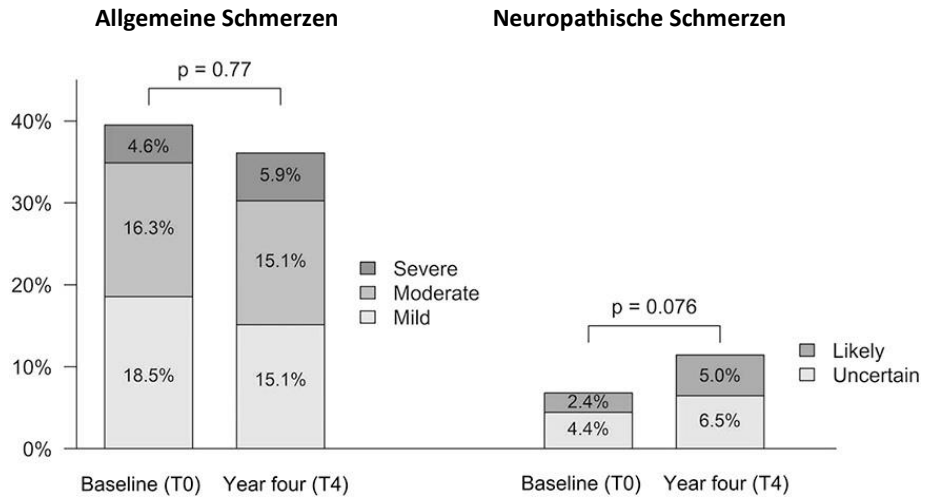


Abbildung 9: Longitudinale Prävalenz allgemeiner und neuropathischer Schmerzsymptome in der KKNMS-Kohorte. *Gezeigt wird die Prävalenz allgemeiner („unspecified pain", UP) und neuropathischer („neuropathic pain", NP) Schmerzsymptome zu den Untersuchungszeitpunkten T0 („Baseline") und T4 („Year four"). Bei den allgemeinen Schmerzen erfolgt die Eingruppierung in leichte („mild", NRS 1-2), moderate („moderate" NRS 3-5) und starke (NRS ≥6) Beschwerden. Bei den neuropathischen Schmerzen in „wahrscheinlich" („likely", PDQ≥19) sowie „unklar" („uncertain", PDQ 13-18). Der statistische Vergleich der jeweiligen Prävalenz zu den beiden Zeitpunkten T0 und T4 erfolgte mittels McNemar-Bowker Test (modifiziert nach Heitmann et al., 2020).*

Anschließend wurden die möglichen biopsychosozialen Determinanten allgemeiner und neuropathischer Schmerzen mittels verschiedener linearer Regressionsanalysen untersucht. Hierfür wurden die NRS- und PDQ-Werte als abhängige Variablen und die sonstigen soziodemographischen, krankheitsbezogenen und neuropsychiatrischen als unabhängige Variablen verwendet.

In einem ersten Schritt wurden, im Sinne einer Querschnittsstudie, einfache Regressionsanalysen zu den Zeitpunkten T0 und T4 durchgeführt. Hier wurden für allgemeine und neuropathische Schmerzen jeweils die Zusammenhänge mit den einzelnen anderen Faktoren analysiert (vgl. Abbildung 10).

Hierbei fanden sich für beide Schmerzarten die jeweils stärksten Zusammenhänge mit der Ausprägung von Fatigue, Depressionen und dem Grad der körperlichen Behinderung. Diese Zusammenhänge waren stärker bei neuropathischen als bei allgemeinen Schmerzen ausgeprägt und nochmals deutlich stärker zum Zeitpunkt T4 verglichen mit dem Zeitpunkt T0. So erklärte alleine die Fatigue-Symptomatik zum Zeitpunkt T4 ganze 34 % beziehungsweise 41 % der Varianz in den Werten für allgemeine beziehungsweise neuropathische Schmerzen. Bei der depressiven Symptomatik waren die entsprechenden Werte zum Zeitpunkt T4 22 % und 32 % sowie für den Grad der körperlichen Einschränkung 21 % und 22 %, respektive für allgemeine und neuropathische Schmerzen.

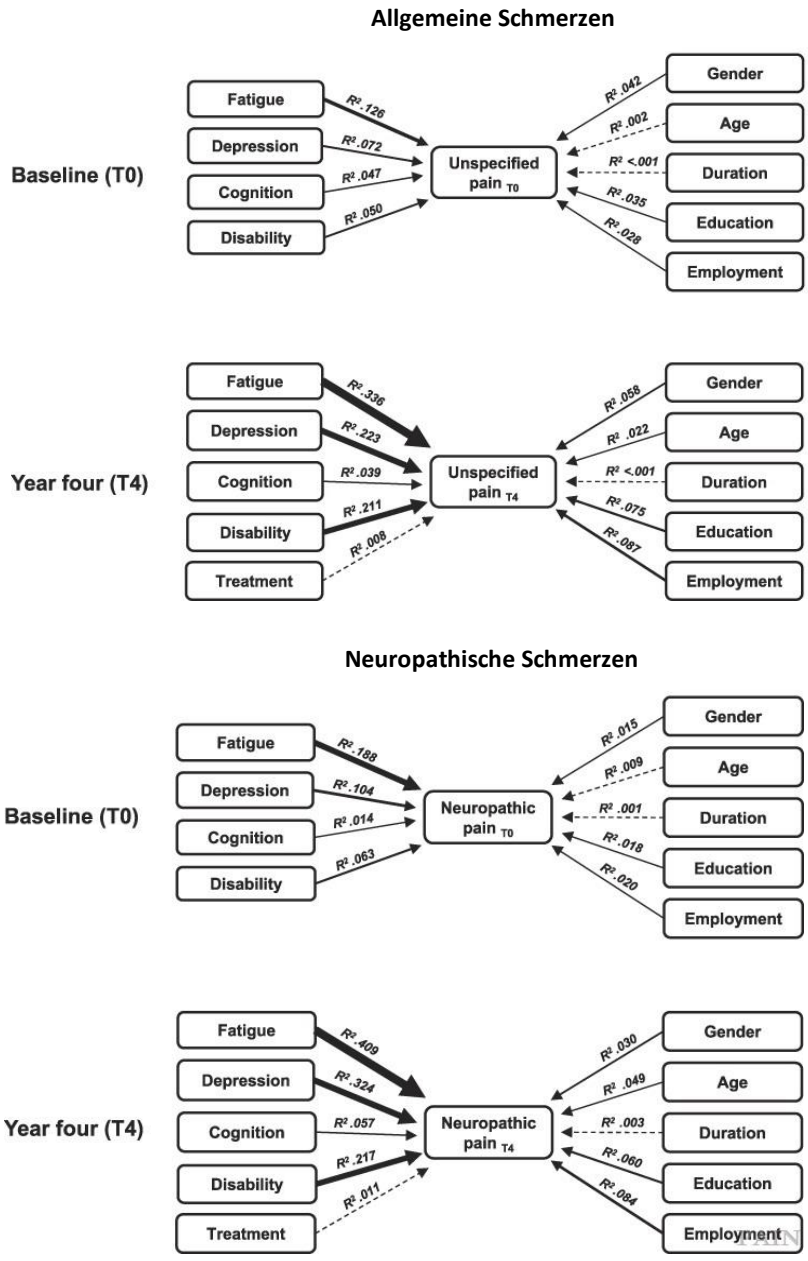


Abbildung 10: Querschnittsuntersuchung von Determinanten allgemeiner und neuropathischer Schmerzen mittels einfacher linearer Regressionsanalysen. *Gezeigt werden die R^2-Werte zu den Zeitpunkten T0 und T4 zwischen allgemeinen („unspecified pain", NRS-Werte) beziehungsweise neuropathischen („neuropathic pain", PDQ-Werte) Schmerzen mit Geschlecht, Alter, Krankheitsdauer, Bildungs- und Beschäftigungsstatus, Grad der körperlichen Behinderung (EDSS-Werte) und Behandlungsstatus (nur zu T4) sowie Depression (BDI-Werte), Fatigue (FSMC-Werte) und kognitiven Testergebnissen (PASAT-Werte). Gepunktete Linien markieren nicht-signifikante Ergebnisse. PDQ=PainDETECT-Fragebogen, EDSS=Expanded Disability Status Scale, BDI=Beck Depression Inventory II, FSMC=Fatigue Scale for Motor and Cognitive Functions, PASAT=Paced Auditory Serial Addition Task (modifiziert nach Heitmann et al., 2020).*

Anschließend wurden für die Querschnittsdaten zu den Zeitpunkten T0 und T4 multiple lineare Regressionsmodelle mit allgemeinen und neuropathischen Schmerzen als abhängigen und allen potentiellen biopsychosozialen Determinanten als unabhängigen Variablen aufgestellt (vgl. Tabelle 2). Auch hier zeigte sich erneut die Fatigue als stärkster Prädiktor für beide Schmerzarten. Hinweise für einen Einfluss von Medikation fanden sich nicht.

Tabelle 2: **Querschnittsuntersuchung von Determinanten allgemeiner und neuropathischer Schmerzen mittels multipler linearer Regressionsanalysen**

Allgemeine Schmerzen

	Unspecified pain							
	Baseline (T0)				Year 4 (T4)			
	r_{part}	B (SE)	β	*P*	r_{part}	B (SE)	β	*P*
Gender (f)	0.121	0.472 (0.198)	0.114	0.018	0.131	0.429 (0.171)	0.107	0.013
Age (y)	−0.004	−0.001 (0.010)	−0.003	0.943	−0.045	−0.008 (0.009)	−0.039	0.391
Duration (m)	−0.024	−0.006 (0.013)	−0.022	0.634	−0.066	−0.014 (0.011)	−0.052	0.212
Disability	0.099	0.192 (0.099)	0.098	0.053	0.157	0.261 (0.086)	0.164	0.003
Fatigue	0.169	0.024 (0.007)	0.223	0.001	0.265	0.031 (0.006)	0.337	<0.001
Depression	0.030	0.010 (0.016)	0.037	0.556	0.093	0.027 (0.015)	0.107	0.077
Cognition	−0.130	−0.022 (0.009)	−0.124	0.011	−0.004	−0.001 (0.009)	−0.004	0.936
Education (Univ. degree)	−0.108	−0.422 (0.200)	−0.102	0.035	−0.144	−0.465 (0.168)	−0.119	0.006
Employment (curr. employed)	−0.079	−0.493 (0.320)	−0.074	0.124	−0.146	−0.701 (0.250)	−0.121	0.005
Treatment (curr. on IMT)	n.a.	n.a.	n.a.	n.a.	0.092	0.365 (0.208)	0.076	0.081
Treatment (curr. on INF)	n.a.	n.a.	n.a.	n.a.	−0.002	−0.007 (0.187)	−0.002	0.969

Neuropathische Schmerzen

	Neuropathic pain							
	Baseline (T0)				Year 4 (T4)			
	r_{part}	B (SE)	β	*P*	r_{part}	B (SE)	β	*P*
Gender (f)	0.043	0.444 (0.575)	0.040	0.441	0.007	0.071 (0.572)	0.006	0.902
Age (y)	0.012	0.006 (0.036)	0.011	0.838	0.039	0.020 (0.030)	0.032	0.505
Duration (m)	−0.009	−0.006 (0.036)	−0.008	0.876	−0.023	−0.015 (0.038)	−0.018	0.686
Disability	0.097	0.471 (0.283)	0.092	0.097	0.079	0.407 (0.297)	0.081	0.172
Fatigue	0.244	0.092 (0.020)	0.323	<0.001	0.301	0.106 (0.019)	0.381	<0.001
Depression	0.055	0.046 (0.047)	0.067	0.331	0.169	0.146 (0.049)	0.197	0.003
Cognition	−0.036	−0.016 (0.025)	−0.034	0.521	−0.040	−0.021 (0.031)	−0.033	0.488
Education (Univ. degree)	−0.060	−0.619 (0.577)	−0.057	0.285	−0.072	−0.700 (0.562)	−0.058	0.213
Employment (curr. employed)	−0.042	−0.672 (0.902)	−0.039	0.457	−0.096	−1.358 (0.816)	−0.078	0.097
Treatment (curr. on IMT)	n.a.	n.a.	n.a.	n.a.	0.090	1.097 (0.702)	0.074	0.119
Treatment (curr. on INF)	n.a.	n.a.	n.a.	n.a.	0.011	0.123 (0.627)	0.009	0.845

Multiple lineare Regressionsanalyse mit NRS („unspecified pain“) beziehungsweise PDQ-Werten („neuropathic pain“) als abhängigen und den sonstigen biopsychosozialen Parametern als unabhängigen Variablen. Für die Zeitpunkte T0 („Baseline) und T4 („Year 4“) wurden separate Regressionsmodelle erstellt. f=female, y=years, m=months, n.a.=nicht anwendbar, IMT=Immunomodulatorische Therapie, INF=Interferon, r_{part}=partieller Regressionskoeffizient, B=Regressionskoeffizient, SE=Standardfehler, ß=standardisierter Regressionskoeffizient, Depression (BDI-Werte), Fatigue (FSMC-Werte) und kognitiven Testergebnissen (PASAT-Werte). PDQ=PainDETECT-Fragebogen, EDSS=Expanded Disability Status Scale, BDI=Beck Depression Inventory II, FSMC=Fatigue Scale for Motor and Cognitive Functions, PASAT=Paced Auditory Serial Addition Task (modifiziert nach Heitmann et al., 2020).

In einem zweiten Schritt wurden als Längsschnittstudie Prädiktoren für die Veränderung von Schmerz über den untersuchten Vierjahreszeitraum analysiert. Als mögliche Prädiktoren wurden die Ausgangswerte (T0) sowie die Änderungswerte (T4-T0) der einzelnen Parameter verwendet. Mit diesen wurden, wie auch schon bei den Querschnittsuntersuchungen, einfache und multiple lineare Regressionsmodelle erstellt (vgl. Abbildung 11 und Tabelle 3).

Die einfachen linearen Regressionsanalysen erbrachten keinen prädiktiven Wert der Ausgangswerte der verschiedenen biopsychosozialen Faktoren. Jedoch erklärten die Veränderungen von Fatigue, Depression und körperlicher Behinderung einen signifikanten Anteil der Veränderungen sowohl allgemeiner als auch neuropathischer Schmerzen im Beobachtungszeitraum.

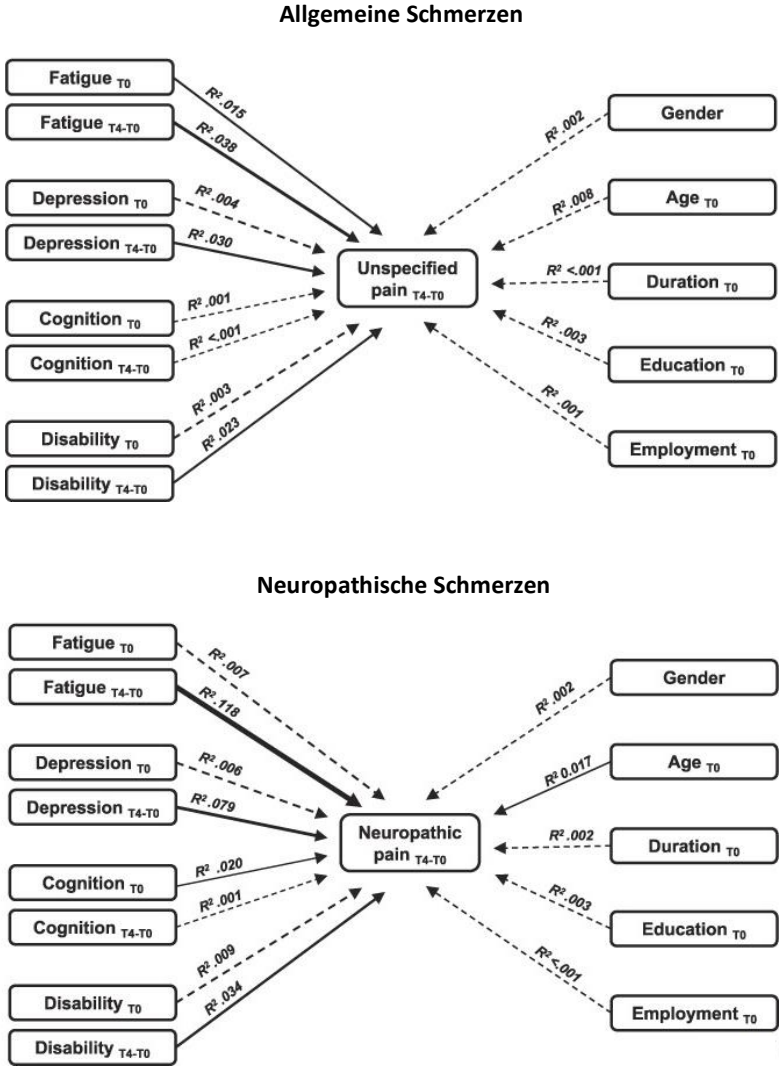


Abbildung 11. Längsschnittuntersuchung von Determinanten allgemeiner und neuropathischer Schmerzen mittels einfacher linearer Regressionsanalysen. *Gezeigt werden die R^2-Werte der Ausgangswerte (T0) Änderungswerte (T4-T0) zwischen allgemeinen („unspecified pain", NRS-Werte) beziehungsweise neuropathischen („neuropathic pain", PDQ-Werte) Schmerzen mit Geschlecht, Alter, Krankheitsdauer, Bildungs- und Beschäftigungsstatus, Grad der körperlichen Behinderung (EDSS-Werte) sowie Depression (BDI-Werte), Fatigue (FSMC-Werte) und kognitiven Testergebnissen (PASAT-Werte). Gepunktete Linien markieren nicht-signifikante Ergebnisse. PDQ=PainDETECT-Fragebogen, EDSS=Expanded Disability Status Scale, BDI=Beck Depression Inventory II, FSMC=Fatigue Scale for Motor and Cognitive Functions, PASAT=Paced Auditory Serial Addition Task (modifiziert nach Heitmann et al., 2020).*

Zusätzlich wurden auch zwei multiple lineare Regressionsmodelle erstellt. In das erste Modell wurden die Werte aller biopsychosozialen Parameter zum Zeitpunkt T0 eingeschlossen, um hiermit die Veränderung (T4-T0) allgemeiner und neuropathischer Schmerzen im Untersuchungszeitraum vorherzusagen. Hierbei fanden sich für keinen der Parameter signifikante prädiktive Werte (vgl. Tabelle 3). Das zweite Modell untersuchte den prädiktiven Wert der Veränderungen (T4-T0) von Fatigue, Depression und Grad der körperlichen Behinderung für die Veränderung allgemeiner und neuropathischer Schmerzen. Hierbei ergaben sich lediglich für Fatigue signifikante Werte (vgl. Tabelle 3).

Tabelle 3. Längsschnittuntersuchung von Determinanten allgemeiner und neuropathischer Schmerzen mittels multipler linearer Regressionsanalysen

	Allgemeine Schmerzen				**Neuropathische Schmerzen**			
	Change in unspecified pain				**Change in neuropathic pain**			
	r_{part}	B (SE)	β	*P*	r_{part}	B (SE)	β	*P*
Gender (f)	0.021	0.093 (0.230)	0.021	0.686	0.052	0.701 (0.814)	0.053	0.390
Age (y) T0	0.068	0.015 (0.011)	0.071	0.187	0.112	0.080 (0.043)	0.117	0.064
Duration (m) T0	−0.024	−0.007 (0.015)	−0.024	0.644	0.036	0.031 (0.053)	0.035	0.555
Disability T0	0.002	0.004 (0.114)	0.002	0.973	0.053	0.357 (0.408)	0.056	0.382
Fatigue T0	0.083	0.013 (0.008)	0.119	0.104	0.007	0.003 (0.030)	0.010	0.910
Depression T0	−0.009	−0.003 (0.019)	−0.012	0.866	0.023	0.025 (0.066)	0.031	0.699
Cognition T0	−0.009	−0.002 (0.010)	−0.009	0.862	−0.108	−0.063 (0.035)	−0.111	0.073
Education T0 (Univ. degree)	−0.054	−0.242 (0.231)	−0.055	0.296	−0.044	−0.602 (0.821)	−0.046	0.464
Employment T0 (curr. employed)	0.075	0.546 (0.370)	0.077	0.141	0.033	−0.721 (1.331)	0.033	0.589
Disability T4-T0	0.110	0.211 (0.101)	0.112	0.038	0.085	0.443 (0.328)	0.082	0.178
Fatigue T4-T0	0.087	0.012 (0.007)	0.104	0.098	0.221	0.080 (0.022)	0.256	<0.001
Depression T4-T0	0.068	0.023 (0.017)	0.080	0.196	0.094	0.079 (0.053)	0.105	0.135
Cognition T4-T0	0.016	0.003 (0.011)	0.015	0.768	0.047	0.027 (0.036)	0.044	0.453

Multiple lineare Regressionsanalyse mit Veränderung (T4-T0) von NRS („unspecified pain") beziehungsweise PDQ-Werten („neuropathic pain") als abhängigen und den Ausgangswerten (T0) beziehungsweise Veränderungen (T4-T0) der sonstigen biopsychosozialen Parametern als unabhängigen Variablen. f=female, y=years, m=months, r_{part}=partieller Regressionskoeffizient, B=Regressionskoeffizient, SE=Standardfehler, ß=standardisierter Regressionskoeffizient, Depression (BDI-Werte), Fatigue (FSMC-Werte) und kognitive Testergebnissen (PASAT-Werte). PDQ=PainDETECT-Fragebogen, EDSS=Expanded Disability Status Scale, BDI=Beck Depression Inventory II, FSMC=Fatigue Scale for Motor and Cognitive Functions, PASAT=Paced Auditory Serial Addition Task (modifiziert nach Heitmann et al., 2020).

Zusammenfassend fand sich eine hohe Prävalenz allgemeiner, aber nicht neuropathischer Schmerzen in frühen Krankheitsstadien der MS. Zudem wurde ein bereits bei Studieneinschluss starker Zusammenhang von Schmerzen mit Fatigue, Depression und dem Grad der körperlichen Behinderung gefunden, welcher im Krankheitsverlauf weiter zunahm. Das Symptomcluster aus Schmerz, Depression und Fatigue scheint sich hierbei im Gleichschritt zu entwickeln, ohne dass die Ausprägung eines der Faktoren bei Erkrankungsbeginn die spätere Entwicklung der anderen im Krankheitsverlauf voraussagt.

3. Diskussion

3.1 Prävalenz von Schmerzsymptomen in frühen Krankheitsstadien Multipler Sklerose

Die Feststellung, dass allgemeine Schmerzsymptome bereits in frühen Krankheitsstadien der MS eine Prävalenz von fast 40 % aufweisen, deckt sich mit Studien, die Patientenkollektive mit ähnlicher Krankheitsdauer und vergleichbarer körperlicher Einschränkung untersucht haben. Diese Studien nennen eine Prävalenz von 30-70 % [53-55]. In einer großen Populations-basierten Studie wurde jedoch auch eine vergleichbar hohe Prävalenz allgemeiner Schmerzen in der sonstigen Bevölkerung berichtet, was die Frage nach dem kausalen Zusammenhang zwischen derartigen Schmerzsymptomen und der MS aufwirft [20]. Die Konstanz, beziehungsweise sogar leichte Abnahme dieser Schmerzsymptome im Rahmen der longitudinalen Studie, könnte als Hinweis in die gleiche Richtung interpretiert werden. Allerdings werden allgemeine Schmerzsymptome in retrospektiven Studien auch als häufiges prodromales Symptom der MS, welches schon Jahre vor Diagnosestellung auftritt, berichtet [56, 57].

In Übereinstimmung zeigen beide aufgeführten Originalarbeiten eine eher niedrige Prävalenz neuropathischer Schmerzen in frühen Krankheitsstadien der MS von unter 5 %. Die jeweilige Prävalenz ist jedoch deutlich niedriger als die in anderen Studien zu neuropathischen Schmerzen bei Patienten in frühen Krankheitsstadien der MS, die mit zirka 14 % angegeben wird [54, 55]. Diese Unterschiede sind höchstwahrscheinlich auf die bereits erwähnte methodische Heterogenität inklusive unterschiedlicher Screening-Instrumente zurückzuführen [5, 11]. Hierzu passt auch, dass eine Hinzunahme der Patienten mit PDQ-Ergebnissen, die auf eine unklare neuropathische Komponente hindeuten, eine Prävalenz von 13,7 % in der Querschnittsstudie [58] und 6,8 % (T0) beziehungsweise 11,5 % (T4) in der Längsschnittstudie [59] ergeben würde. Der gefundene Trend für einer Zunahme der Prävalenz neuropathischer Schmerzen in der Längsschnittstudie passt zu Daten aus anderen Studien, die eine höhere Prävalenz neuropathischer Schmerzen in fortgeschrittenen Krankheitsstadien berichten [26, 47, 54]. Dies kann im Sinne des Kausalitätszusammenhangs zwischen neuropathischen Schmerzen und MS bei im Krankheitsverlauf akkumulierender Last struktureller Läsionen des ZNS interpretiert werden [55, 60, 61]. In diesem Kontext sind auch rezente Änderungen der Diagnosekriterien, hin zu einer früheren Diagnosestellung, und große Therapiefortschritte in der medikamentösen Krankheitsmodulation zu nennen. Hierdurch sind die in den beiden aktuellen Originalarbeiten untersuchten Patientenkohorten vermutlich

früher diagnostiziert worden und weisen sehr wahrscheinlich benignere Krankheitsverläufe auf als die in älteren Studien. Hierfür spricht auch, dass es in der Längsschnittstudie im Untersuchungsintervall zu keiner signifikanten Zunahme der krankheitsbedingten körperlichen Behinderung in der Gesamtkohorte kam.

3.2 Determinanten von Schmerzen bei Multipler Sklerose

Sowohl für allgemeine als auch neuropathische Schmerzen waren in der Querschnittsstudie und in der Längsschnittstudie Fatigue, Depression und körperliche Behinderung die wichtigsten Einflussfaktoren. Dies ist im Einklang mit der bestehenden Literatur [11, 26, 27, 30, 33]. Zusätzlich konnte in der longitudinalen Studie eine Zunahme dieser Zusammenhänge im Krankheitsverlauf nachgewiesen werden. Mit Blick auf die körperliche Behinderung ist dies im Kontext der Zunahme MS-bedingter struktureller Läsionen zu diskutieren, was sich auch mit den Berichten über eine synchrone Zunahme von Schmerz und körperlicher Behinderung in kleineren longitudinalen Studien deckt [53, 62-64]. Bei Fatigue und Depression wirft der beobachtete starke wechselseitige Einfluss die Frage nach möglichen überlappenden Kausalzusammenhängen mit Schmerzsymptomen bei MS auf. Interessant hierbei ist, dass die jeweiligen Ausgangswerte von Fatigue und Depression zum Zeitpunkt T0 einen ungleich kleineren prädiktiven Wert für die Veränderung (T4-T0) allgemeiner und neuropathischer Schmerzsymptome hatten als die Veränderung (T4-T0) dieser beiden Symptome im zeitlichen Verlauf. Diese Symptome scheinen also nicht die Entwicklung des jeweils anderen zu verursachen, sondern sich vielmehr „im Gleichschritt“ zu entwickeln. Hierfür spricht auch, dass alle drei Symptome bereits gehäuft in der Prodromalphase noch vor Diagnose einer MS beobachtet wurden [56, 57]. Dies kann als Hinweis auf eine mögliche gemeinsame Pathophysiologie interpretiert werden, welche im folgenden Abschnitt diskutiert werden soll.

3.3 Zusammenhang zwischen Schmerz, Depression und Fatigue bei Multipler Sklerose

Dieses Kapitel bezieht sich auf folgende Übersichtsarbeit:

Heitmann H, Andlauer TFM, Korn T, Mühlau M, Henningsen P, Hemmer B and Ploner M. *Fatigue, Depression and Pain in Multiple Sclerosis – how neuroinflammation translates into reward deficiency and anhedonic symptoms* Multiple Sclerosis Journal. 2022 Jun;28(7):1020-1027.

Schmerz, Depression und Fatigue betreffen zusammen mehr als die Hälfte der Patienten mit MS. Das häufige gemeinsame Auftreten und die starken wechselseitigen Zusammenhänge haben dazu geführt, dass einige Autoren sogar von einem „Symptomcluster“ sprechen [35, 65]. Da jedes der genannten Symptome für sich bereits eine erhebliche Einschränkung der Lebensqualität und Arbeitsfähigkeit bedingt, ist von einer hohen individuellen und gesellschaftlichen Belastung durch dieses Cluster auszugehen [29]. Leider ist die Effektivität der bestehenden Therapieansätze für diese Symptome jedoch sehr begrenzt [5, 33, 35, 39]. Die Identifikation möglicher gemeinsamer Pathomechanismen hätte somit großes Potential zur Erschließung neuer Therapieansätze.

Gemeinsame *klinische Merkmale* dieser Symptome sind eine geringe Motivation und das Fehlen von positivem Affekt [33, 39, 66]. Dies entspricht dem klinischen Bild des Symptoms der Anhedonie, welche als reduzierte Fähigkeit, nach Freude zu streben und diese zu erleben definiert ist [67-69]. Die Anhedonie ist ein Kernsymptom verschiedener neuropsychiatrischer Erkrankungen wie der Depression [67, 68], des Chronischen Fatigue Syndroms (CFS) [67] und auch chronischer Schmerzen [66]. Zudem ist es als negativer Prädiktionsfaktor für das therapeutische Ansprechen und Behandlungserfolge beschrieben [68]. Dies ist nicht verwunderlich, da die hedonische Valenz nicht nur ein zentraler Bestandteil emotionaler Reaktionen ist, sondern auch ein starker Motivator mit Auswirkung auf unser Verhalten und Lernen [69, 70]. Von Seiten der Neurobiologie wurde eine Dysfunktion des cerebralen Belohnungssystems als mögliche Ursache für Anhedonie identifiziert [67, 69, 71]. Die wichtigsten Neurotransmitter des Valenz- und Belohnungssystems im menschlichen Gehirn sind die Monoamine Dopamin und Serotonin mit ihren meso-cortico-limbischen Signalwegen, die sich vom Mittelhirn über die Basalganglien und das limbische System bis in den Präfrontalen Kortex erstrecken (vgl. Abbildung 12).

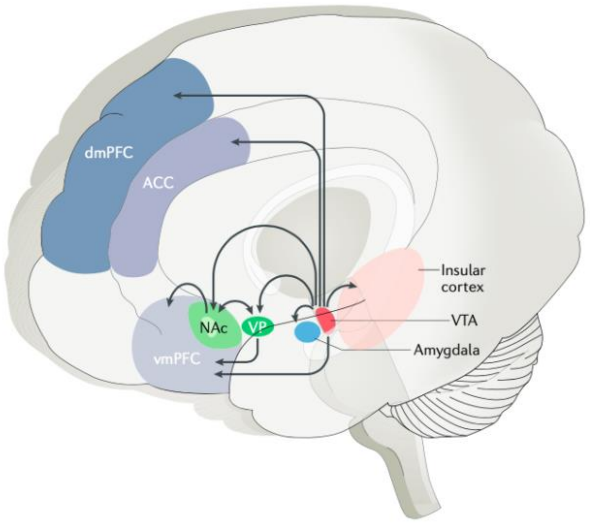


Abbildung 12. Das cerebrale Motivations- und Belohnungssystem.
Die Abbildung zeigt Hirnregionen und Verbindungen des meso-cortico-limbischen Systems inklusive dopaminerger Projektionen vom ventralen Tegmentum (VTA) zum ventralen Striatum, welches aus dem Nucleus accumbens (NAc) und dem ventralen Pallidum (VP) besteht. Die striatalen Anteile projizieren, über den Thalamus, zu verschiedenen Regionen des medialen präfrontalen Kortex wie dem ventromedialen präfrontalen Kortex (vmPFC), den dorsomedialen präfrontalen Kortex (dmPFC) und den anterioren cingulären Kortex (ACC) (modifiziert nach Husain und Roiser, 2018).

Passenderweise zeigen *Neurobildgebungs-Studien* überlappende strukturelle und funktionelle Veränderungen dieser Regionen und Signalwege bei MS Patienten die unter Schmerzen [16], Fatigue [39, 72] und Depressionen [33, 35] leiden. Diese Studien weisen auf überlappende Atrophiemuster von Strukturen grauer Hirnsubstanz sowie eine verminderte funktionelle Konnektivität im Bereich des präfrontalen Kortex, des Striatums und des limbischen Systems hin [14, 16, 33, 35, 39, 72, 73].

Neuroimmunologisch wurden alle drei Symptome mit einer Dysfunktion monoaminerger Neurotransmission im Kontext von inflammatorischen Prozessen im zentralen Nervensystem (ZNS) gebracht [35, 39, 40, 74, 75]. Als exemplarisch für diese Zusammenhänge gilt das sogenannte „sickness behavior" Modell, welches von einer Verursachung der Symptome durch inflammatorische Botenstoffe wie Zytokine ausgeht [38, 44, 74, 76]. Hierbei handelt es sich um einen anhedonischen Zustand, charakterisiert durch eine verringerte Motivation, erhöhte Schmerzsensibilität, ausgeprägte Fatigue und gedrückte Stimmung, wie er zum Beispiel durch die inflammatorische Antwort des Körpers im Rahmen von akuten Infektionen auftritt [74-76]. Zytokine spielen vermutlich auch eine wichtige, jedoch bisher nur partiell verstandene Rolle in der Pathogenese der MS [77]. Zudem wurden erhöhte Konzentrationen der pro-inflammatorischen Zytokine Tumor-Nekrose-Faktor alpha (TNF-alpha), Interferon gamma (IFN-gamma) und Interleukin-6 (IL-6) in Serum und/oder Liquor cerebrospinalis in direkten Zusammenhang mit dem Auftreten von Depression und Fatigue bei MS gebracht [38, 44, 78, 79]. Als Pathomechanismus hierfür wird eine direkte Störung der Synthese und Freisetzung der Neurotransmitter Dopamin und Serotonin mit entsprechender Affektion meso-kortiko-striataler Signalwege durch pro-inflammatorische Zytokine propagiert [40, 73, 80-82]. Eine Schlüsselrolle für inflammatorische Prozesse bei der MS [83, 84] und auch für die inflammatorisch-vermittelte Dysfunktion des cerebralen Belohnungssystems spielen sehr wahrscheinlich auch Microglia-Zellen [75, 76]. Diese setzen Zytokine und neurotoxische Metaboliten frei, die über eine Erhöhung der Glutamat-Konzentration zu Exzitotixizität und schlussendlich Neurodegeneration beitragen [83, 85]. Dies erklärt möglicherweise auch die beobachteten Atrophiemuster meso-cortico-limbischer Strukturen im Kontext von Schmerz, Depression und Fatigue bei Patienten mit MS [73]. Auch wenn die Bedeutung inflammatorischer Prozesse bei der Schmerzentstehung, vor allem bei rheumatischen Erkrankungen, breit diskutiert wird [74, 86-91] fehlt bisher jedoch der Nachweis eines direkten Zusammenhangs zwischen Zytokinen und Schmerzen bei MS [73].

In Zusammenfassung dieser *klinischen, neurobildgebenden und neuroimmunologischen* Evidenz kann ein translationales Modell zur Entstehung der „anhedonischen Trias“ aus Schmerz, Depression und Fatigue bei MS propagiert werden.

In diesem Modell entstehen diese Symptome durch eine Zytokin-induzierte Störung monoaminger Neurotransmission im ZNS, die in einer Funktionsstörung des cerebralen Belohnungssystems resultiert. Im Verlauf kommt es zudem im Kontext der anhaltenden Neuroinflammation zu einer durch Microglia-Zellen vermittelten exzitotoxisch-glutamatergen Schädigung und Atrophie meso-cortico-limbischer Hirnstrukturen. Hieraus ergeben sich die beobachteten funktionellen und strukturellen Bildgebungsauffälligkeiten. Aus der Dysfunktion des cerebralen Belohnungssystems resultiert eine Unfähigkeit, Situationen und Aktionen eine hedonische Valenz zuzuschreiben. Betroffene können somit ein mögliches Belohnungserleben weder antizipieren noch verspüren, was wiederum das beobachtete klinische Leitmotiv der Anhedonie unterhält (vgl. Abbildung 13).

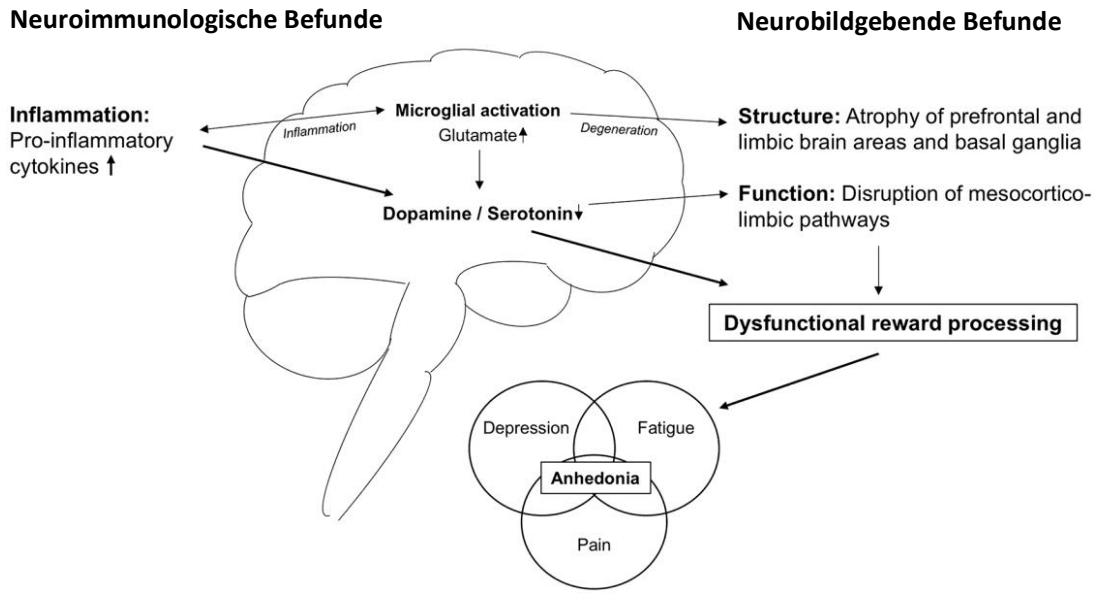


Abbildung 13. Translationales Modell für neuroinflammationsinduzierte Dysfunktion des cerebralen Belohnungssystems. (modifiziert nach Heitmann et al. 2022).

Aus einem solchen Modell ergeben sich auch potentielle pharmakologische und nicht-pharmakologische *therapeutische Implikationen* [73, 82].

Pharmakologische Ansätze zur Unterstützung des Dopamin- und Serotoninstoffwechsels werden bereits in der Therapie dieser Symptome eingesetzt, mit jedoch gemischtem Erfolg [73, 82]. Da von einer inflammations-bedingten Störung der monoaminergen Neurotransmission ausgegangen wird, ergeben sich zudem immunologische

Behandlungsansätze [68, 73, 82]. Antikörper gegen pro-inflammatorische Ziele wie den IL-6-Rezeptor und das Zytokin TNF-Alpha zeigen eine positive Wirkung auf anhedonische Symptome bei verschiedenen Autoimmunerkrankungen wie rheumatoider Arthritis, ankylosierender Spondylitis, Psoriasis und Morbus Crohn [68, 91]. Leider gibt es jedoch Berichte über gehäufte Schubereignisse unter diesen Therapien bei Patienten mit MS [77]. Ein vielversprechender Ansatz könnte jedoch der Einsatz von Substanzen wie Minocyclin sein, die eine Funktionsstabilisierung von Mikroglia-Zellen bewirken und in ersten Studien auch positive Effekte auf die Krankheitsprogression bei MS zeigen [82, 92]. Auch erklärt das genannte Modell mögliche Nebeneffekte breit eingesetzter immunmodulatorischer Therapien bei MS wie von Interferonen, unter denen eine Häufung grippeähnlicher Symptome im Sinne eines „sickness behavior“ beschrieben ist [93].

Nicht-pharmakologisch propagiert ein solches Modell den Einsatz (kognitiv-) behavioraler und (multimodaler) bio-psycho-sozialer Therapieansätze, um den affektiven und motivationalen Einschränkungen im Zuge der Anhedonie entgegenzuwirken [94]. Multimodale Therapiekonzepte werden z.B. bereits erfolgreich in der Therapie chronischer Schmerzen und komorbider Affektstörungen eingesetzt und korrelieren mit Veränderungen der Hirnfunktion auf Netzwerkebene [95]. Eine weitere Behandlungsoption mit direkter Auswirkung auf die Funktion von mit Anhedonie assoziierten Netzwerken und Signalwegen im Gehirn ist die nicht-invasive Hirnstimulation (NIBS) [96]. Diese wird bereits mit Erfolg in kleineren Studien auch bei Patienten mit MS eingesetzt und soll unter anderem auch positive Effekte auf inflammationsbedingte Einschränkungen von Neurotransmission haben [97-99].

4. Ausblick

Die vorliegende Arbeit zeigt, dass allgemeine Schmerzen ein wichtiges Symptom bei MS und eng mit Depressionen und Fatigue verknüpft sind. Neben den diskutierten Implikationen für neue therapeutische Ansätze, sollte dieses Symptomverständnis auch in die entsprechenden Klassifikationen, Konzeptualisierungen und zukünftige Forschungsansätze Eingang finden.

Aktuelle Klassifikationen unterscheiden lediglich nozizeptive, neuropathische und gemischte Schmerzen [6], was jedoch den verschiedenen Phänotypen von Schmerz bei MS nur unzureichend gerecht wird. Um komplexere Schmerzsymptome ohne strukturelles Korrelat einzuordnen wurde durch die IASP rezent ein dritter Schmerzdeskriptor, der noziplastische

Schmerz, etabliert [100]. Dieser beschreibt Schmerzen, die aus einer Funktionsstörung des peripheren somatosensorischen Systems verbunden mit einer erhöhten Sensitivität im zentralen Nervensystem resultieren [100]. Teil der klinischen Charakteristika des noziplastischen Schmerzes ist auch eine ausgeprägte Komorbidität mit affektiven Störungen und anderen körperlichen Symptomen [100]. In einer ersten Studie, die bei Patienten mit MS neben neuropathischen, nozizeptiven und gemischt nozizeptiv-neuropathischen auch noziplastische Schmerzsymptome erfasste, wurde deren Prävalenz mit 23 % angegeben [101]. Entsprechend wäre eine erweiterte Klassifikation von Schmerzen bei MS unter Berücksichtigung noziplastischer Schmerzsymptome erstrebenswert.

Zu einem besseren Verständnis der Komorbidität von Schmerz, Depression und Fatigue bei MS könnten auch neue computationale Modellierungen aus dem Bereich des predictive coding beitragen [40, 67]. Diese konzeptualisieren persistierende körperliche Symptome als Resultat einer konstanten Diskrepanz zwischen den eigenen Erwartungen und dem tatsächlichen sensorischen input [40, 102]. Wie hieraus resultierende negative motivationale und behaviorale Einflüsse zur Symptomentstehung bei MS beitragen und welche Rolle Anhedonie hierbei spielt, sollte in zukünftigen Studien untersucht werden [40]. Auch gibt es bisher keine systematischen translationalen Untersuchungen der Zusammenhänge zwischen Neuroinflammation, der Dysfunktion des meso-cortico-limbischen Systems und Anhedonie als möglichem Bindeglied der Trias aus Schmerz, Depression und Fatigue bei MS.

Derartige transdiagnostische Forschungsansätze, wie sie auch die Research Domain Criteria Initiative der amerikanischen National Institutes of Mental Health (NIMH) propagiert, hätten erhebliches Potential, diese belastende Komorbidität besser zu verstehen. Mögliche daraus resultierende Behandlungsansätze wären von hoher Relevanz auch für andere Erkrankungen und Syndrome mit einem ähnlichen Komorbiditätsspektrum wie zum Beispiel Fibromyalgie, Chronische Fatigue und Long COVID.

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Anhang / Ausgewählte Original- und Übersichtsarbeiten

In der Zusammenstellung beschriebene Original- und Übersichtsarbeiten in chronologischer Reihenfolge nach Erwähnung im Text:

Heitmann H, Biberacher V, Tiemann L, Buck D, Loleit V, Selter RC, Knier B, Tölle TR, Mühlau M, Berthele A, Hemmer B and Ploner M. *Prevalence of neuropathic pain in early Multiple Sclerosis*. Multiple Sclerosis Journal. 2016 Aug;22(9):1224-30.

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Original Research Paper

Prevalence of neuropathic pain in early multiple sclerosis

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Abstract

Background: Pain is considered a frequent symptom in multiple sclerosis. Neuropathic pain is the type of pain most closely related to the pathology of multiple sclerosis and its prevalence estimates vary largely.
Objective: We prospectively assessed the prevalence of neuropathic pain in patients with early multiple sclerosis and investigated the association of neuropathic pain with other clinical parameters.
Methods: A total of 377 outpatients with multiple sclerosis at an early disease stage were included in this prospective study. Mean disease duration was 4.2 years, mean Expanded Disability Status Scale (EDSS) score was 1.6, 96.8% of patients were classified as having relapsing–remitting multiple sclerosis. Neuropathic pain was assessed using the PainDETECT questionnaire (PDQ). Depression, fatigue and cognition were assessed using the Beck Depression Inventory (BDI), the Fatigue Scale for Motor and Cognitive Functions (FSMC) and the Paced Auditory Serial Addition Test.
Results: PDQ scores indicative of neuropathic pain were found in 4.2% of patients. Regression analysis revealed EDSS, BDI and FMSC scores as strongest predictors of PDQ scores.
Conclusions: Neuropathic pain appears to be less frequent in early multiple sclerosis than expected and is significantly associated with disability, depression and fatigue. The assessment and therapy of pain in multiple sclerosis should thus take into account neuropsychiatric symptoms already at early disease stages.

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Introduction

Pain is considered a frequent symptom in multiple sclerosis (MS) with prevalence estimates varying between 29% and 83%[1] and a meta-analysis reporting a prevalence of 63%.[2] Classifications of pain in MS distinguish between neuropathic pain, nociceptive pain and mixed pain including headache.[1,3] Neuropathic pain is most directly related to the pathology of MS and its prevalence has been estimated to be 29% in a meta-analysis.[2] Previous studies on the prevalence of neuropathic pain in early stages of MS found a point prevalence of 14%[4,5] and a lifetime prevalence of 28%.[4] Neuropathic pain particularly comprises neuropathic extremity pain, trigeminal neuralgia and Lhermitte sign. Prevalence is estimated at 12–28% for neuropathic extremity pain, 2–5% for trigeminal neuralgia and 15% for Lhermitte sign.[3] These three forms of neuropathic pain have been directly related to demyelination of spinothalamic pathways, the trigeminal nerve root entry zone and the posterior columns of the cervical spinal cord, respectively.[1,3,6,7]

Pain in MS has been associated with a wide range of demographic, disease-related and emotional factors.[1] Demographic associations include age,[8,9] disease duration and in some studies female sex.[10] Furthermore, disease-related disability is associated with the prevalence and severity of pain.[1,8–11] Emotional factors associated with pain in MS include depression and fatigue. Depression is frequent in MS, with an estimated prevalence of 24%.[12] MS patients

with depression are more likely to have pain,[11,13,14] and a positive relationship between severity and interference of painful symptoms with the severity of depression has been reported.[15] Fatigue is one of the most frequent symptoms in MS, with prevalence estimates ranging from 60% to 95%.[16–18] Fatigue has a strong impact on quality of life in patients with MS,[19] and pain has been described as a potentially influential factor on fatigue.[17,20] Depression and fatigue have been proposed to form a cluster of interdependent symptoms in MS that persists throughout the course of the disease.[16,18,21] A recent study added pain to this cluster and proposed fatigue as the mediating factor between pain and depression in MS.[20] However, the influence of demographic, disease-related and emotional factors on neuropathic pain in early MS has not been investigated so far.

In the present prospective study, we therefore reassessed the prevalence of neuropathic pain in a cohort with early MS using a screening tool specific for neuropathic pain. We further assessed associations of neuropathic pain in MS with demographic, disease-related and emotional factors.

Methods

Patients

A total of 377 patients (252 women and 125 men) with MS were included in the study between August 2008 and November 2014. All patients were outpatients participating in a prospective observational study of our department, which has been performed in accordance with the Declaration of Helsinki and has been approved by the ethics committee of the School of Medicine of the Technische Universität München. The purpose of the study is the establishment of prognostic markers for a rational and targeted treatment of MS. Inclusion criteria were a confirmed diagnosis of MS or related disorders, for example, clinically isolated syndrome or neuromyelitis optica, and the ability to provide consent. Each MS patient visiting our outpatient MS clinic for the first time and fulfilling the inclusion criteria has been asked to participate. However, not all patients were willing to participate and we did not systematically assess the number of patients who refused to participate and their reasons for doing so. Data from the first outpatient visit of each patient to our MS clinic with the confirmed diagnosis of MS according to the McDonald criteria were chosen for analysis. The full dataset from all 377 patients was complete at the first visit. Inpatients were included when they were followed up in the outpatient clinic. The mean age of the patients was 36 (±10.2) years, mean duration of disease was 4.2 (±5.6) years and mean Expanded Disability Status Scale (EDSS) score was 1.6 (±1.3). The disease course was relapsing–remitting in 96.8%, secondary progressive in 2.4% and primary progressive in 0.8% of patients.

Questionnaires

Neuropathic pain was assessed using the PainDETECT questionnaire (PDQ), which is a well-established screening tool specific for neuropathic pain.[22] The questionnaire was completed during the first visit to the MS outpatient clinic. The PDQ comprises three main components. The first part is a 'gradation of pain'. This core component comprises seven descriptive items asking for neuropathic pain qualities on a 6-point rating scale ranging from 0 ('never') to 5 ('very strongly'). Neuropathic pain qualities covered are 'burning', 'tingling/prickling', 'electric shock-like attacks', 'numbness', 'sensitivity to touch', 'sensitivity to heat/cold' and 'pain triggered by light pressure'. The second part refers to the 'pain course pattern'. Patients can choose between four graphically illustrated patterns entitled 'persistent pain with slight fluctuations', 'persistent pain with attacks', 'pain attacks without pain between them' and 'pain attacks with pain between them'. For the two latter patterns an extra point is added to the score, whereas for persistent pain with slight fluctuations no point is added, and for persistent pain with pain attacks one point is subtracted from the score. The third part is a simple yes or no question asking for 'radiating pain'. In the case of pain radiating to other regions of the body two points are added to the overall score. Adding up the three parts, a maximum score of 38 points can be obtained. Scores of 19 or greater are highly indicative of a neuropathic pain component (>90% likely). For a score of 12 or less a neuropathic pain component is considered unlikely (<15% likely), whereas for scores between from 13 to 18 points the result is uncertain.[22]

Depressive symptoms were assessed using the Beck Depression Inventory II (BDI).[23] Fatigue was assessed using the Fatigue Scale for Motor and Cognitive Functions (FSMC)[24] and cognitive function was assessed using the Paced Auditory Serial Addition Test (PASAT).[25]

Statistical analysis

Means for demographic and clinical data as well as for questionnaire scores were compared between patients with and without PDQ scores indicative of neuropathic pain using *t* tests for independent samples after equality of variances had been assessed by using

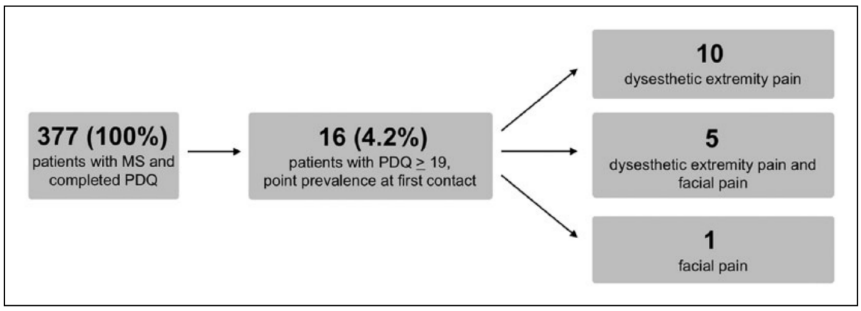

Figure 1. Prevalence and classification of neuropathic pain in the study cohort. MS: multiple sclerosis; PDQ: PainDETECT questionnaire.

Levene's test. Associations between neuropathic pain and demographic and clinical variables were assessed by correlation analyses using Pearson's correlation coefficient. To explore further the contribution of demographic, disease-related and emotional parameters to neuropathic pain in MS patients, multiple regression analysis was performed. The PDQ score served as a dependent variable. EDSS, BDI, FSMC and PASAT scores as well as age and duration of disease were chosen as independent variables. Statistical analyses were performed using SPSS (IBM SPSS for Windows, version 23.0, Armonk, NY, USA).

Results

The prevalence of PDQ scores indicative of neuropathic pain (⩾19) was 4.2% (16/377) (Figure 1). The disease course of the 16 patients was relapsing–remitting. Painful dysesthesia of the extremities was the most prevalent form of neuropathic pain (n=15/16), occurring isolated (n=6/16) as well as in combination with facial (n=5/16) or back pain (n=4/16). One patient suffered from isolated facial pain, namely trigeminal neuralgia. PDQ scores in which a neuropathic pain component was uncertain (13–18) were found in 9.5% (36/377) of patients.

Patients with PDQ scores indicative of neuropathic pain (⩾19) differed significantly from patients with scores below the cut-off (<19) with regard to disability (EDSS 3.3 vs. 1.5, t=4.2, P<0.001), depression (BDI 17.5 vs. 7.25, t=5.3, P<0.0001) and fatigue (FSMC 74.3 vs. 43, t=6.9, P<0.0001) scores. However, no significant difference between groups was found for age (36.4 vs. 36 years, t=0.2, P=0.87), duration of disease (6.2 vs. 4.1 years, t=1.13, P=0.26) and cognitive performance (PASAT 42.3 vs. 45.1, t=0.1, P=0.34).

PDQ scores correlated positively with levels of disability (EDSS r=0.410, P<0.0001), depression (BDI r=0.428, P<0.0001) and fatigue (FSMC r=0.503, P<0.0001) (Figure 2). In addition, positive correlations were found for age (r=0.174, P<0.001) and duration of disease (r=0.183, P<0.001). However, no significant correlation was found between PDQ and PASAT scores (r=−0.07, P=0.18).

Multiple regression analysis revealed disability (EDSS β=0.249, t=4.4, P<0.0001), depression (BDI β=0.239, t=3.8, P<0.0001) and fatigue (FSMC β=0.215, t=3.1, P=0.002) as the three most powerful predictors of PDQ scores (Figure 3). For all three predictors positive regression coefficients were obtained, indicating that higher individual scores in each domain predicted higher PDQ scores. The results show that the final model including EDSS, BDI and FSMC scores explains 33% of variation in PDQ scores. Parameters without significant explanatory contribution to variance in PDQ scores were age (β=0.001, t=0.24, P=0.98), duration of disease (β=0.085, t=1.60, P=0.11) and PASAT scores (β=0.028, t=0.58, P=0.56).

Discussion

In the present prospective study, we assessed the prevalence of neuropathic pain in early MS. Our results revealed a prevalence of 4%, indicating that neuropathic pain is not very frequent in early MS. We further found that disability, depression and fatigue but not cognitive deficits are significantly associated with neuropathic pain in early MS.

Prevalence of neuropathic pain in early MS

Previous studies on the prevalence of pain in MS reported largely different rates ranging from 29% to 83%, with an average prevalence in a recent meta-analysis of 63%.[2] The more specific assessment of neuropathic pain in MS yielded a meta-analytical prevalence of 29%.[2] This large variability in the

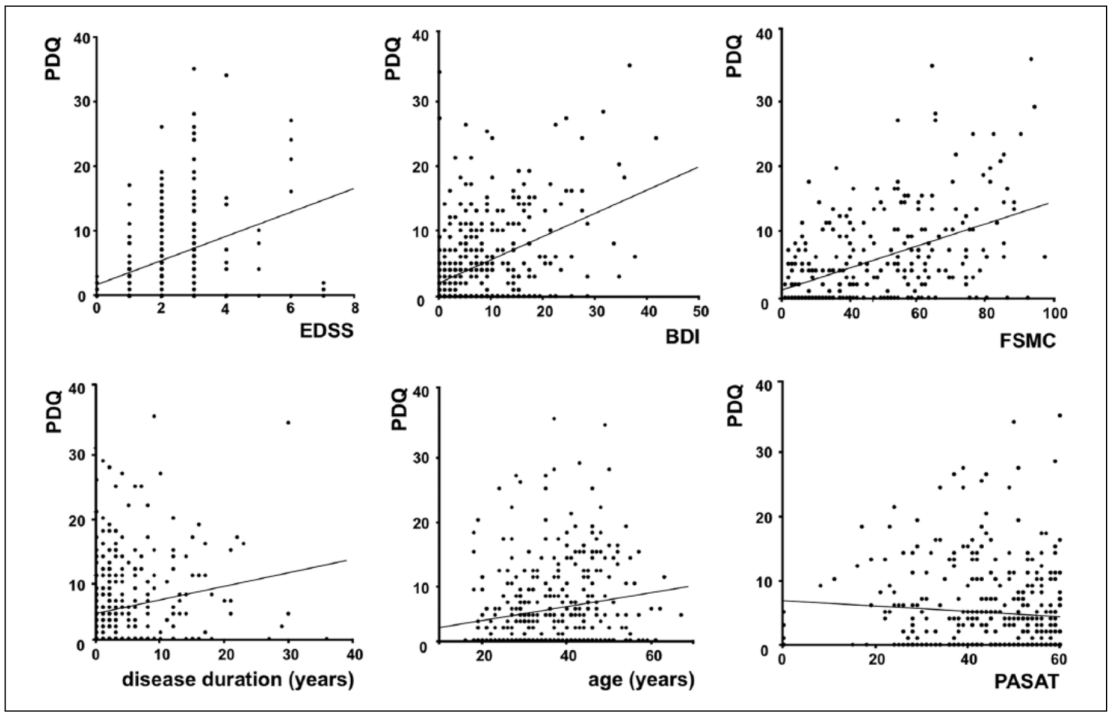

Figure 2. Correlations between neuropathic pain scores and disability, depression and fatigue. PDQ: PainDETECT questionnaire; EDSS: Expanded Disability Status Scale; BDI: Beck Depression Inventory; FSMC: Fatigue Scale for Motor and Cognitive Functions; PASAT: Paced Auditory Serial Addition Test.

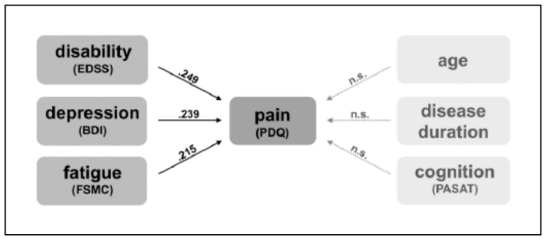

Figure 3. Regression analysis with neuropathic pain as a dependent variable and disability, depression, fatigue, age, time and cognitive function as independent variables. PDQ: PainDETECT questionnaire; EDSS: Expanded Disability Status Scale; BDI: Beck Depression Inventory; FSMC: Fatigue Scale for Motor and Cognitive Functions; PASAT: Paced Auditory Serial Addition Test.

prevalence rates of pain in MS in previous studies is most likely due to methodological differences.[1,2,5] First, the stage of disease differs widely across study cohorts, with a tendency towards advanced disease stages. Second, the frequently used mailing questionnaires might be prone to selection bias, with patients suffering from pain having higher response rates. Third, a wide variety of screening tools for painful symptoms has been used, which, particularly in older studies, include non-specific and non-standardised tools. However, the present observation of a prevalence of neuropathic pain in MS of 4% is significantly lower than all previous findings. This might be due to the characteristics of the present study cohort, which includes outpatients at an early disease stage with an average disease duration of 4 years and an average EDSS score of 1.6. Two previous studies[4,5] specifically addressed neuropathic pain in early MS, and found a point prevalence of 14% in patients with a median EDSS of 2, which is still significantly higher than the prevalence observed in the present study. This discrepancy might be due to differences in study design and the patient population. In the present study, we used a validated questionnaire, which selectively assesses neuropathic pain,[22] whereas in one of the previous studies[4] a questionnaire was used that might not only detect neuropathic pain but also capture other forms of pain observed in MS.[1–3] In the other study,[5] another neuropathic pain questionnaire was used and the sensitivity and specificity of different screening tools for neuropathic pain in multiple sclerosis is unknown. Moreover, the study included patients with a significantly longer disease duration of 8 years than the 4.2 years of the present study.

Neuropathic pain in MS is presumed to relate directly to lesions within the sensory system and is therefore considered the pain type that is most closely related to the pathology of MS.[26] This concept is supported by studies in patients with more advanced disease, which reported an increase in the prevalence of neuropathic pain with disease progression.[4,5,8,27] The low prevalence of neuropathic pain found in our patient sample with early MS lends further support to this concept of a direct causal relationship between disease progression and the prevalence of neuropathic pain.[26] In contrast, the prevalence of pain of any type is high in early[4,5,28] as well as in more advanced stages of MS.[8,29–31] Considering the high prevalence of pain in the general population,[32] the evaluation of pain of any type might therefore only partially reflect pain directly attributed to MS.[26] This notion is supported by a study which found that the prevalence of pain of any type did not significantly differ between MS patients and a control population.[33]

Influence of depression, fatigue and disability on pain in early MS

To our knowledge this is the first prospective study to examine the influence of depression, fatigue and disease-related disability on neuropathic pain in early MS. We found that patients with neuropathic pain showed significantly higher levels of depression, fatigue and disability, and regression analysis revealed these three factors as the most important predictors of neuropathic pain. Furthermore, PDQ scores significantly correlated with scores for depression and fatigue as well as disability, age and duration of disease. This suggests that neuropathic pain in MS is influenced by parameters related to the progression of the disease on the one hand and emotional factors on the other hand. The relevance of disease progression for neuropathic pain is underlined by disability being the strongest predictor for neuropathic pain and a positive correlation of age and disease duration with neuropathic pain. These results confirm previous findings[10,30] and extend it to early disease stages.

A close relationship of fatigue, depression and general[20,21] and neuropathic[34] pain in MS has been described. Our results show that this close relationship already applies to very early disease stages. It is, however, important to note that the observed relationships do not allow us to infer the causal relationship between depression, fatigue and neuropathic pain in MS. It does, however, indicate that already at early disease stages the assessment and therapy of pain in MS should not only take into account somatic factors but also neuropsychiatric symptoms. In contrast, cognitive performance assessed by the PASAT was not related to neuropathic pain. Thus emotional rather than cognitive factors appear to be relevant for neuropathic pain in MS.

Limitations

Several limitations apply to this study. First, results from single-centre studies are not necessarily generalisable to a broader population. Second, we assessed neuropathic pain but not nociceptive and mixed pain syndromes, which are, from a patient perspective, equally important. However, the relationship of the latter pain types to the pathology of MS is less obvious than for neuropathic pain. Furthermore, due to its paroxysmal nature the Lhermitte sign that is commonly subsumed under neuropathic pain was possibly not adequately detected by the questionnaire used. However, the Lhermitte sign is considered the least burdensome and therefore clinically least relevant form of neuropathic pain in MS.[3] Third, in 9.5% of patients with PDQ scores from 13 to 18 a neuropathic pain component remains uncertain. However, correlation analyses were performed using overall PDQ scores and even when adding the 9.5% of patients with uncertain PDQ scores the prevalence of neuropathic pain in our patient sample still remains low compared to previously published results. Fourth, the assessment of neuropathic pain was exclusively based on questionnaires without objective information on lesion location provided by magnetic resonance imaging. Fifth, psychosocial factors with a potential influence on painful symptoms in MS that have previously been described, such as anxiety and sleeping quality, were not evaluated. Moreover, the assessment of depression and fatigue using the BDI and the FSMC might have been confounded by somatic factors. Future studies might use other scales, which are less sensitive to these confounds; for example, the Hospital Anxiety and Depression Scale or the BDI-fast screen for depression. Finally, we cannot rule out that refusal of patients to participate in our study has introduced a selection bias. There is, however, no obvious reason to assume that patients willing to participate in a longitudinal observational study are less affected by neuropathic pain than patients not willing to participate.

Conclusions

Taken together, our results suggest that the prevalence of neuropathic pain as the type of pain most directly related to the pathology of MS is low in early MS. The high prevalence of pain of any type in early MS shown in previous studies might therefore partially reflect pain not directly linked to the disease. Depression and

fatigue are crucial co-factors of neuropathic pain already in early MS. As these two factors have an interdependent relationship with pain in MS and are potentially modifiable,[35] a multimodal therapeutic approach should be used for pain therapy already in early MS.

Conflict of interest

VB has received research support from Merck Serono. DB has received compensation for activities with Bayer HealthCare, BiogenIdec, MerckSerono and Novartis; she is supported by the Abirisk Consortium. TRT has received honoraria for lecturing from and/or serves on the advisory board for Pfizer, Lilly, Grünenthal, Mundipharma, Astellas und Hexal. MM has received research support from Merck Serono and Novartis; he has received travel expenses for attending meetings from Bayer and Merck Serono; he has received honoraria for lecturing from Merck Serono; he has received investigator fees for a phase III clinical study from Biogen Idec. BH has served on scientific advisory boards for Roche, Novartis, Bayer Schering, Merck Serono, Biogen Idec, GSK, Chugai Pharmaceuticals, Micromet, Genentech and Genzyme Corporation; he serves on the international advisory board of *Archives of Neurology*, *Multiple Sclerosis Journal* and *Experimental Neurology*; he has received speaker honoraria from Bayer Schering, Novartis, Biogen Idec, Merck Serono, Roche and Teva Pharmaceutical Industries Ltd.; and he has received research support from Biogen Idec, Bayer Schering, Merck Serono, Five prime, Metanomics, Chugai Pharmaceuticals and Novartis; he serves as a DMC for the Tone (DFG sponsored) and the PQBirch204 trial (Bencard Allergy); he has filed a patent for the detection of antibodies and T cells against KIR4.1 in a subpopulation of MS patients and genetic determinants of neutralising antibodies to interferon-beta. The other authors declare that there is no conflict of interest.

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Research Paper

PAIN

Longitudinal prevalence and determinants of pain in multiple sclerosis: results from the German National Multiple Sclerosis Cohort study

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Abstract

Pain is frequent in multiple sclerosis (MS) and includes different types, with neuropathic pain (NP) being most closely related to MS pathology. However, prevalence estimates vary largely, and causal relationships between pain and biopsychosocial factors in MS are largely unknown. Longitudinal studies might help to clarify the prevalence and determinants of pain in MS. To this end, we analyzed data from 410 patients with newly diagnosed clinically isolated syndrome or relapsing-remitting MS participating in the prospective multicenter German National MS Cohort Study (NationMS) at baseline and after 4 years. Pain was assessed by self-report using the PainDETECT Questionnaire. Neuropsychiatric assessment included tests for fatigue, depression, and cognition. In addition, sociodemographic and clinical data were obtained. Prevalence of pain of any type was 40% and 36% at baseline and after 4 years, respectively, whereas prevalence of NP was 2% and 5%. Pain of any type and NP were both strongly linked to fatigue, depression, and disability. This link was even stronger after 4 years than at baseline. Moreover, changes in pain, depression, and fatigue were highly correlated without any of these symptoms preceding the others. Taken together, pain of any type seems to be much more frequent than NP in early nonprogressive MS. Moreover, the close relationship between pain, fatigue, and depression in MS should be considered for treatment decisions and future research on a possible common pathophysiology.

Keywords: Multiple sclerosis, Neuropathic pain, Epidemiology, Depression, Fatigue

1. Introduction

Pain is considered a frequent symptom in multiple sclerosis (MS), but prevalence estimates vary largely between 29% and 83%.[24] Differences in prevalence estimates are likely due to heterogeneities of patient cohorts, screening tools, and pain classification schemes.[10,24,41] Classifications usually differentiate between neuropathic pain (NP), which is supposed to directly relate to structural MS pathology, and other pain types including nociceptive pain with a less clear causal relationship.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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For NP, a prevalence of 29% has been reported in a meta-analysis,[10] but a lower prevalence of 15% was found when more specific diagnostic criteria were used.[36] Pathophysiologically, NP has been attributed to demyelinating lesions in somatosensory pathways[22,33] such as the spinothalamic tract[25,26,42] and the cranial nerves,[43] causing dysesthetic extremity pain and neuralgias, eg, of the trigeminal and glossopharyngeal nerve, respectively. Other pain types in MS including musculoskeletal complaints are mostly subsumed under nociceptive pain, which has been reported with a meta-analytic prevalence of 18%.[10] However, apart from spasticity-related pain, the causal relationship with MS remains less clear. Pharmacological treatments of pain in MS mainly comprise antineuropathic drugs of antidepressant or antiepileptic type and antispastic drugs. In addition, nonsteroidal anti-inflammatory drugs are widely used to alleviate musculoskeletal pain and flu-like side effects of interferon treatment in MS.

Importantly, pain in MS has been associated with various sociodemographic, disease-related, and neuropsychiatric factors.[19,24] In particular, pain has been related to higher disability, depression, and fatigue.[13,19,21,24,35,39] Depression and fatigue are frequent and highly comorbid in MS.[37,40] Prevalence of depression in MS is 24% to 50%,[9,20] and most patients suffering from depression also report pain.[9,37] Fatigue is even more frequent in MS patients with prevalence estimates of 60% to 95% [29,40] and is believed to be influenced by pain.[40] In addition, fatigue has been proposed as the mediating factor between pain and depression in MS.[3] These frequently co-occurring symptoms impose a large burden on patients with MS and society. Pain, depression, and fatigue have been associated with impaired quality of life in patients with MS.[2,13,19] Furthermore, strong associations with work absenteeism, unemployment, and increased use of health care resources have been described.[8,13,32,34]

Longitudinal studies investigating pain and its relation to biological, psychological, and social factors in patients with MS are lacking. Such longitudinal studies might help to clarify the prevalence and biopsychosocial determinants of pain in patients with MS. To this end, we here analyzed data from the ongoing prospective multicenter German National MS cohort study (NationMS).

2. Materials and methods

2.1. Patients

Data were derived from the ongoing German National MS cohort study (NationMS) conducted by the German Competence Network Multiple Sclerosis (KKNMS). To date, the 22 study centres across Germany have included more than 1000 patients with a diagnosis of clinically isolated syndrome in the previous 6 months or a diagnosis of relapsing–remitting MS according to the 2005 McDonald criteria[31] with first demyelinating attack within the previous 24 months. Exclusion criteria of NationMS comprise previous disease-modifying treatment, contraindications to study procedures including regular magnetic resonance imaging scans, and primary progressive MS or any other progressive debilitating neurologic disease apart from MS. Patients are regularly followed up according to a standardized protocol for a period of at least 10 years.[44] Informed consent was provided by all participants, and the study protocols were approved by the local ethics committee of each study centre.

For this study, a sample of 410 patients (275 women and 135 men) who participated in NationMS between August 2010 and June 2018 was selected according to the following inclusion and exclusion criteria. All patients with a completed 4-year follow-up period and a year 4 follow-up visit performed within a time window of 4 years ±120 days after baseline visit were included. Patients with clinical signs indicative of an ongoing relapse as defined by new or worsened pre-existing neurological deficits or missing pain data at either the baseline or year 4 follow-up visit were excluded (**Fig. 1**).

For characteristics of the patient sample included, see also **Table 1**. The baseline (T0) mean (±SD) age was 34 (±10) years, and the mean (±SD) disease duration defined as time since the first demyelinating attack was 7 (±7) months. The disease course was classified as clinically isolated syndrome in 46% and 11%, and as relapsing–remitting MS in 54% and 88% at the baseline (T0) and year 4 follow-up visit (T4), respectively. In addition, 1% of patients had developed secondary progressive MS at T4. The mean (±SD) Expanded Disability Status Scale (EDSS) score was 1.4 (±1.0) at T0 and 1.5 (±1.2) at T4.

2.2. Assessment of sociodemographic and clinical data

All data used for the present analyses were obtained through standardized study report forms completed at T0 and T4. Pain symptoms were assessed using the PainDETECT Questionnaire (PDQ).[11] Pain of any type (unspecified pain [UP]) was screened for using 3 Visual Analogue Scales (VASs) on the PDQ asking patients to rate their respective "current" as well as "worst" and "average" pain during the last 4 weeks on a scale from 0 ("no pain") to 10 ("maximum pain"). Visual Analogue Scale ratings ≥1/10 for average pain during the last 4 weeks were taken as an indicator for the presence of UP. Visual Analogue Scale ratings of 1 to 2/10, 3 to 5/10, and ≥6/10 for average pain during the last 4 weeks were taken as indicators for the presence of "mild," "moderate," and "severe" UP, respectively.[1] Neuropathic pain was screened for using the 3 other core parts of the PDQ. Here, a maximum score of 38 points can be obtained. Scores ≥19 are highly indicative of an NP component (>90% likely). For a score ≤12, an NP component is considered unlikely (<15% likely), whereas for scores between 13 and 18, an NP component is considered uncertain.[11] In case of incomplete PDQ data in the 3 NP screening parts, the following procedures were applied. In cases where all 3 VAS scores were rated 0 and NP screening parts were not filled in by patients, a PDQ total score of 0 was manually imputed because the absence of UP contradicts the presence of an NP component (T0: n = 176, T4: n = 206). In case of missing answers

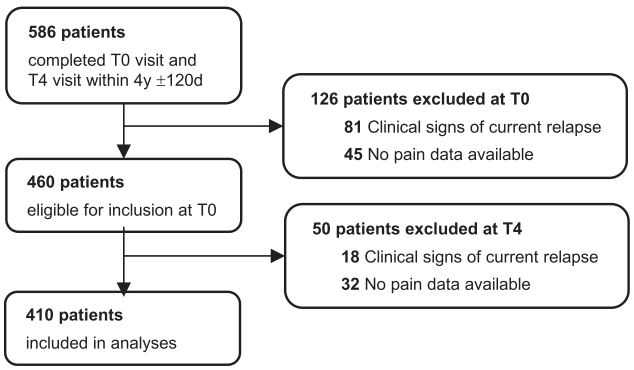

Figure 1. Patient sample selection. The initial patient sample comprised 586 patients with a completed year 4 follow-up visit (T4) within 4 years ±120 days after baseline visit (T0). A total of 176 patients were excluded from analyses due to clinical signs of a current relapse or unavailability of pain data. y, years; d, days; T0, baseline visit; T4, year 4 follow-up visit.

Table 1

Patient cohort demographics and characteristics.

	Baseline (T0)	Year 4 (T4)	*P*
Gender (female/male)	67/33%	n.a.	n.a.
Age ± SD	34 ±10 y	n.a.	n.a.
Duration ± SD	7 ±7 m	n.a.	n.a.
Course (CIS/RRMS/SPMS)	46/54/0%	11/88/1%	n.a.
Disability (mean EDSS ±SD)	1.39 ± 0.98	1.46 ± 1.18	0.155 (t = −1.4)
Fatigue (mean FSMC ± SD)	38.6 ± 18.1	44.4 ± 21.5	<0.001 (t = −6.5)
Depression (mean BDI ±SD)	7.0 ± 7.5	6.9 ±7.6	0.697 (t = 0.4)
Cognition (mean PASAT ±SD)	46.5 ± 10.6	51.1 ±9.1	<0.001 (t = −8.4)
Education (Univ. degree)	32.0%	39.5%	<0.001
Employment (curr. employed)	91.0%	86.3%	0.018
Treatment (IMT/INF)	n.a.	80.0/25.9%	n.a.

Parameters at baseline (T0) and year 4 follow-up (T4) were compared using *t*-tests for dependent samples for metrical and the McNemar test for categorical parameters, respectively.
BDI, Beck Depression Inventory II; CIS, clinically isolated syndrome; curr., currently; EDSS, Expanded Disability Status Scale; FSMC, Fatigue Scale For Motor And Cognitive Function; IMT, immunomodulatory therapy (including interferon medication); INF, interferon; n.a., not applicable; PASAT, Paced Auditory Serial Addition Test; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; Univ., university.

to items in either of the 3 NP screening parts, multiple imputation was performed to predict PDQ total scores (T0: n = 72; T4: n = 69).[18,27] To this end, the multiple imputation tool implemented in SPSS (Version 25.0; IBM SPSS, Armonk, NY) was used, and the scores from all available answers to other NP screening items on the PDQ were used as predictors. Further analyses using total PDQ scores were calculated on the original data set (T0: n = 338; T4: n = 341; T0; and T4 available: n = 291) and 5 imputed data sets (n = 410) leading to a pooled multiply imputed estimate of results.[27] Patient data sets with scores ≥1 in 1 of the 3 VAS ratings and completely missing answers in all 3 NP screening parts were excluded from analyses (T0: n = 4; T4: n = 0).

Neuropsychiatric symptoms were evaluated using the Fatigue Scale Motor and Cognitive Function[30] for fatigue, the Beck Depression Inventory II[16] for depression, and the Paced Auditory Serial Addition Test[12] for cognition. Moreover, disability was assessed using the EDSS.[17] Additional sociodemographic as well as clinical data derived from study report forms included gender, age, education, employment, disease duration, and immunomodulatory therapy (IMT).

2.3. Statistical analyses

Prevalence of VAS scores indicative of "mild," "moderate," and "severe" UP as well as PDQ scores indicative of "likely" and "uncertain" NP was compared between T0 and T4 using the McNemar–Bowker test. In addition, mean VAS scores at T0 and T4 were compared using *t*-tests for dependent samples. Likewise, group characteristics at T0 and T4 were compared using the McNemar test for categorical variables and *t*-tests for dependent samples for metrical variables.

To further explore associations between biological, psychological, and social factors and pain symptoms, regression analyses were performed in a two-step approach. First, cross-sectional associations of pain were evaluated by performing simple and multiple regression analyses for T0 and T4 visits separately. To this end, linear regression was performed using VAS scores (for UP) and PDQ scores (for NP) as dependent variables, respectively. Independent variables were EDSS (for disability), Beck Depression Inventory II (for depression), Fatigue Scale Motor and Cognitive (for fatigue), and Paced Auditory Serial Addition Test (for cognition) scores as well as gender, age, disease duration, education, and employment status. Because patients were treatment naïve upon inclusion, effects of IMT and especially interferon (INF) treatment, which may cause pain as a common side effect,[24] were evaluated at T4 only. Second, longitudinal relationships of changes in pain were evaluated. "Change" was defined as scores at T4 minus scores at T0, eg, $VAS_{T4} - VAS_{T0}$ (for UP) and $PDQ_{T4} - PDQ_{T0}$ (for NP). Independent variables were similar to cross-sectional analyses. All regression analyses were first performed separately for each of the independent variables listed above and then second, considering all the parameters in a multivariate model using backward selection. Statistical analyses were performed using SPSS (Version 25.0; IBM SPSS) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Effect sizes of regression analyses were estimated with R^2 cutoffs of 0.01, 0.09, and 0.25 for small, medium, and large effect sizes, respectively.[5]

3. Results

3.1. Prevalence of pain in multiple sclerosis

Prevalence of pain at the baseline (T0) and year 4 follow-up visit (T4) is shown in **Figure 2**.

The prevalence of UP of any (VAS ≥ 1) intensity was 39.5% and 36.1%, at T0 and T4, respectively. The prevalence of mild (VAS 1-2), moderate (VAS 3-5), and severe (VAS ≥ 6) UP was 18.5% and 15.1%, 16.3% and 15.1%, and 4.6% and 5.9% at T0 and T4, respectively. The mean (±SD) VAS score was 1.2 (±1.9) at T0 and 1.2 (±2.0) at T4. Neither prevalence of UP of any intensity ($P = 0.77$, $\chi^2 = 3.34$, $df = 6$) nor mean VAS scores (t = 0.024, $P = 0.98$) differed between T0 and T4.

The prevalence of likely NP (PDQ ≥ 19) was 2.4% vs 5.0% in the original data and 2.1% vs 4.6% in the multiply imputed data at T0 and T4, respectively. An uncertain NP component (PDQ 13-18) was found in 4.4% (multiply imputed data: 4.9%) at T0 and 6.5% (multiply imputed data: 5.8%) at T4. The McNemar–Bowker test showed a trend for an increase in the proportion of patients with uncertain and likely NP in the original ($P = 0.076$, $\chi^2 = 6.87$, $df = 3$) and multiply imputed data ($P = 0.072$, $F_{1,\ 23395} = 3.23$).

3.2. Determinants of pain in multiple sclerosis

3.2.1. Cross-sectional

First, simple linear regression analyses were performed to identify potential cross-sectional biopsychosocial associations of pain at T0

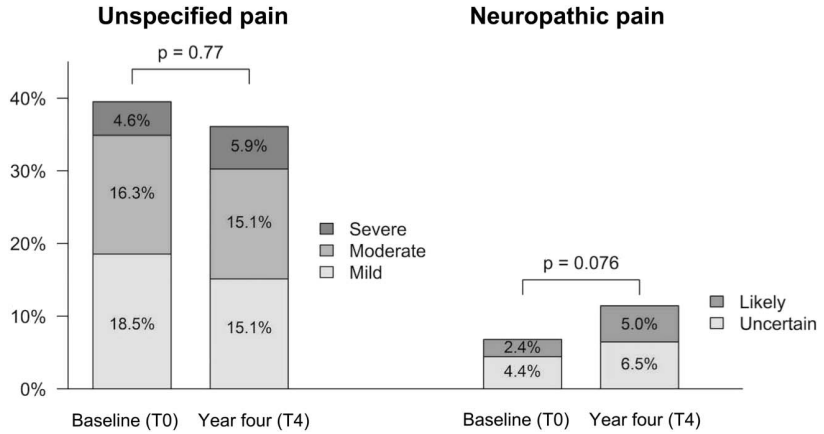

Figure 2. Prevalence of unspecified pain (UP) and neuropathic pain (NP) at baseline (T0) and year 4 follow-up (T4). Prevalence at T0 and T4 was compared using McNemar–Bowker tests and the corresponding *P*-values are shown. For UP, mild, moderate, and severe pain were defined as VAS 1 to 2, 3 to 5, and ≥6, respectively. Likely and uncertain NP were defined as PDQ ≥19 and 13 to 18, respectively. For NP, results of original data (cases with available information) are shown. PDQ, PainDETECT Questionnaire; VAS, Visual Analogue Scale.

and T4 separately. To this end, UP (VAS scores) and NP (PDQ scores) at T0 and T4 served as dependent variables. **Figure 3** shows individual R^2 values that were taken as an indicator of the variance of pain explained by each independent variable. These analyses identified strong positive associations of fatigue, depression, and disability with UP and NP at T0 and T4. All associations had small to medium effect sizes at T0, explaining between 5.0% and 18.8% of variance, and medium to large effect sizes at T4, explaining between 21.1% and 40.9% of variance. No significant effects of MS treatment on pain, neither of IMT in general nor of INF, were found (for bivariate statistics and plots, please see Supplementary Information, available at http://links.lww.com/PAIN/A923).

Next, multiple regression models including all potential biopsychosocial determinants were fitted to the data (**Table 2**). Then, backward selection was applied to identify which determinants were most strongly associated with UP and NP at T0 and T4, respectively. Baseline UP showed the strongest associations with higher fatigue and disability as well as impaired cognition, female gender, and lower educational status, together explaining 18.2% of variance. At T4, higher levels of fatigue, disability, and depression as well as female gender, lower educational status, unemployment, and current IMT treatment showed the strongest associations with UP, together explaining 40.6% of variance. For baseline NP, the strongest associations were found with fatigue and disability, together explaining 19.1% of variance. Neuropathic pain at T4 was most strongly associated with fatigue, depression, and disability, together explaining 41.9% of variance.

Thus, UP and NP were most strongly associated with higher levels of fatigue, depression, and disability, showing increasing

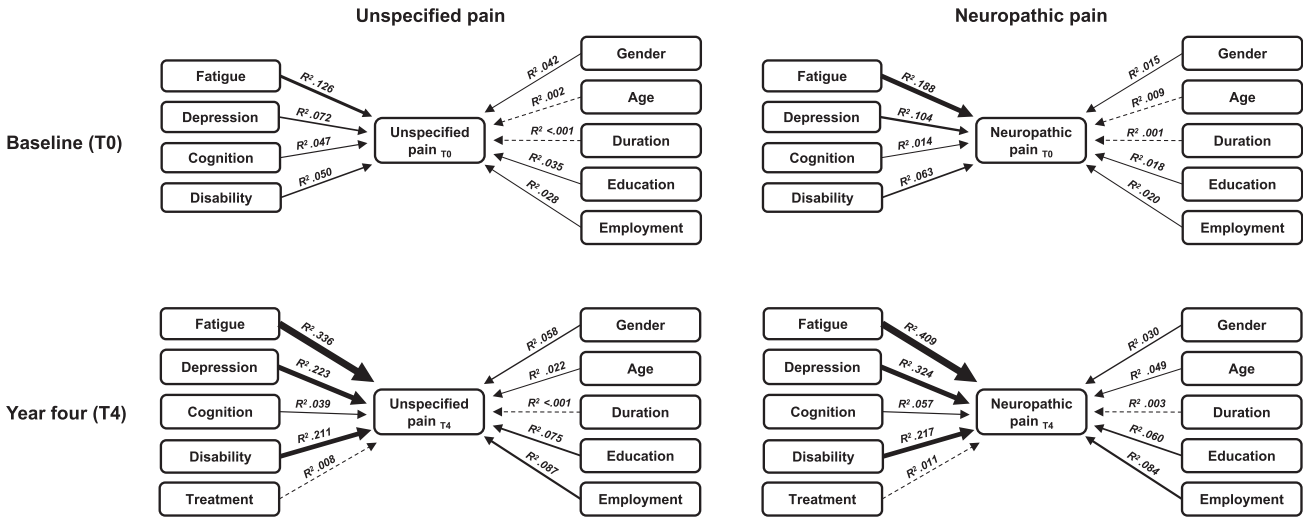

Figure 3. Cross-sectional determinants of pain assessed by simple regression analysis. Plots show R^2 values for simple regression analyses with VAS (for unspecified pain [UP]) and PDQ scores (for neuropathic pain [NP]) at baseline (T0) and year 4 follow-up visits (T4) as dependent variables and FSMC (for fatigue), BDI (for depression), EDSS (for disability), and PASAT (for cognition) scores as well as gender, age, disease duration, education, employment, and treatment (IMT) status as independent variables. Thickness of arrows represents strength of effects measured by R^2, with dotted lines representing nonsignificant effects. For NP, results of original data (pairwise complete observations) are shown. BDI, Beck Depression Inventory II; EDSS, Expanded Disability Status Scale; FSMC, Fatigue Scale for Motor and Cognitive Function; IMT, immunomodulatory therapy; PASAT, Paced Auditory Serial Addition Test; PDQ, PainDETECT Questionnaire; VAS, Visual Analogue Scale.

Table 2

Cross-sectional determinants of pain assessed by multiple regression analysis.

	Unspecified pain								Neuropathic pain							
	Baseline (T0)				Year 4 (T4)				Baseline (T0)				Year 4 (T4)			
	r_{part}	B (SE)	β	*P*	r_{part}	B (SE)	β	*P*	r_{part}	B (SE)	β	*P*	r_{part}	B (SE)	β	*P*
Gender (f)	0.121	0.472 (0.198)	0.114	0.018	0.131	0.429 (0.171)	0.107	0.013	0.043	0.444 (0.575)	0.040	0.441	0.007	0.071 (0.572)	0.006	0.902
Age (y)	−0.004	−0.001 (0.010)	−0.003	0.943	−0.045	−0.008 (0.009)	−0.039	0.391	0.012	0.006 (0.036)	0.011	0.838	0.039	0.020 (0.030)	0.032	0.505
Duration (m)	−0.024	−0.006 (0.013)	−0.022	0.634	−0.066	−0.014 (0.011)	−0.052	0.212	−0.009	−0.006 (0.036)	−0.008	0.876	−0.023	−0.015 (0.038)	−0.018	0.686
Disability	0.099	0.192 (0.099)	0.098	0.053	0.157	0.261 (0.086)	0.164	0.003	0.097	0.471 (0.283)	0.092	0.097	0.079	0.407 (0.297)	0.081	0.172
Fatigue	0.169	0.024 (0.007)	0.223	0.001	0.265	0.031 (0.006)	0.337	<0.001	0.244	0.092 (0.020)	0.323	<0.001	0.301	0.106 (0.019)	0.381	<0.001
Depression	0.030	0.010 (0.016)	0.037	0.556	0.093	0.027 (0.015)	0.107	0.077	0.055	0.046 (0.047)	0.067	0.331	0.169	0.146 (0.049)	0.197	0.003
Cognition	−0.130	−0.022 (0.009)	−0.124	0.011	−0.004	−0.001 (0.009)	−0.004	0.936	−0.036	−0.016 (0.025)	−0.034	0.521	−0.040	−0.021 (0.031)	−0.033	0.488
Education (Univ. degree)	−0.108	−0.422 (0.200)	−0.102	0.035	−0.144	−0.465 (0.168)	−0.119	0.006	−0.060	−0.619 (0.577)	−0.057	0.285	−0.072	−0.700 (0.562)	−0.058	0.213
Employment (curr. employed)	−0.079	−0.493 (0.320)	−0.074	0.124	−0.146	−0.701 (0.250)	−0.121	0.005	−0.042	−0.672 (0.902)	−0.039	0.457	−0.096	−1.358 (0.816)	−0.078	0.097
Treatment (curr. on IMT)	n.a.	n.a.	n.a.	n.a.	0.092	0.365 (0.208)	0.076	0.081	n.a.	n.a.	n.a.	n.a.	0.090	1.097 (0.702)	0.074	0.119
Treatment (curr. on INF)	n.a.	n.a.	n.a.	n.a.	−0.002	−0.007 (0.187)	−0.002	0.969	n.a.	n.a.	n.a.	n.a.	0.011	0.123 (0.627)	0.009	0.845

Multiple linear regression analyses with UP (VAS) and NP (PDQ) as dependent variables and biopsychosocial parameters and treatment status as independent variables were performed separately at baseline (T0) and year 4 follow-up (T4). For NP, results of original data (pairwise complete observations) are shown.
f, female; y, years; m, months; n.a., not applicable; Fatigue (FSMC, Fatigue Scale for Motor and Cognitive Function); Depression (BDI, Beck Depression Inventory II); Disability (EDSS, Expanded Disability Status Scale); Cognition (PASAT, Paced Auditory Serial Addition Test); Univ., university; curr., currently; IMT, immunomodulatory therapy; INF, interferon; UP, unspecified pain (VAS, Visual Analogue Scale); NP, neuropathic pain (PDQ, PainDETECT Questionnaire); r_{part}, partial regression coefficient; B, regression coefficient; SE, standard error; β, standardized regression coefficient.

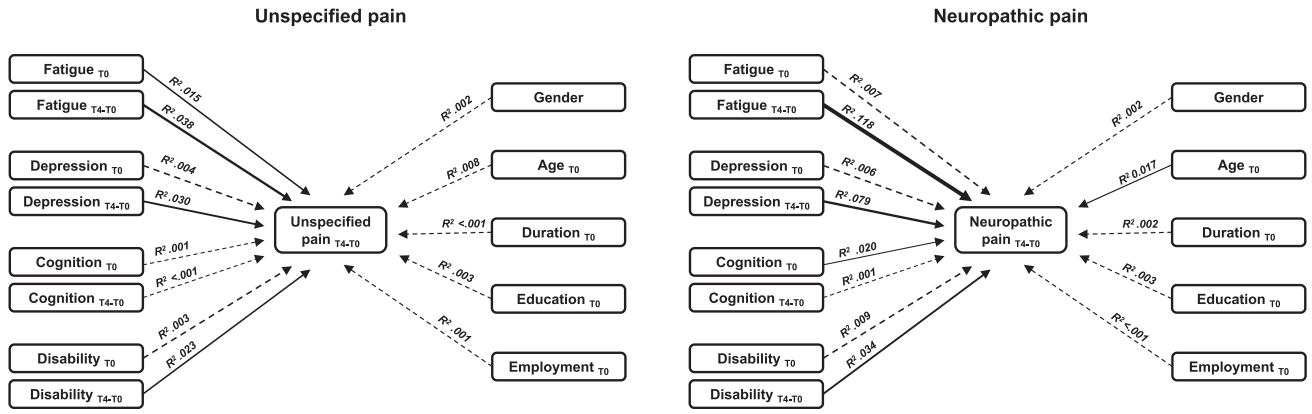

Figure 4. Longitudinal determinants of pain assessed by simple regression analysis. Plots show R^2 values for simple regression analyses with change in VAS scores (for unspecified pain [UP]) and change in PDQ scores (for neuropathic pain [NP]) from baseline (T0) to year 4 follow-up (T4) as dependent variables and FSMC (for fatigue), BDI (for depression), EDSS (for disability), and PASAT (for cognition) scores as well as gender, age, disease duration, education, and employment status as independent variables. Thickness of arrows represents strength of effects measured by R^2, with dotted lines representing nonsignificant effects. For NP, results of original data (pairwise complete observations) are shown. BDI, Beck Depression Inventory II; EDSS, Expanded Disability Status Scale; FSMC, Fatigue Scale for Motor and Cognitive Function; PASAT, Paced Auditory Serial Addition Test; PDQ, PainDETECT Questionnaire; VAS, Visual Analogue Scale.

associations in simple and multiple regression analyses from T0 to T4 with overall medium to large effect sizes.

3.2.2. Longitudinal

To analyze longitudinal associations of pain, we again performed simple linear regression analyses with changes of UP and changes of NP as dependent variables. Independent variables were baseline values (T0) and changes (T4-T0) of biopsychosocial parameters. R^2 values in **Figure 4** illustrate the variance of change in UP and NP explained by each independent variable. For both change in UP and NP, changes in fatigue and depression had the strongest associations, with small to medium effect sizes, explaining between 3.0% and 11.6% of variance. Associations were positive with higher levels of pain being associated with higher levels of fatigue and depression. Moreover, baseline fatigue as well as baseline age and cognition were associated with changes in UP and NP, respectively. These relationships showed small effect sizes, explaining between 1.5% and 2.0% of variance (for bivariate statistics and plots, please see Supplementary Information, available at http://links.lww.com/PAIN/A923).

Next, multiple regression analysis of potential biopsychosocial determinants was used to create regression models analyzing baseline and change values in 2 separate models as shown in **Table 3**. Again, backward selection was applied to identify which parameters are most strongly related to changes in UP and NP. Associations of baseline parameters with change in UP was low with fatigue at T0 being the only significant parameter explaining 1.5% of variance. However, changes in fatigue, depression, and disability from T0 to T4 explained 4.9% in variance of change in UP. Similarly, for change in NP, baseline cognition and age together explained only 3.5% of variance, whereas changes in fatigue, depression, and disability from T0 to T4 together explained 12.7% of variance.

Thus, changes in fatigue, depression, and disability rather than their respective baseline values showed strong positive associations with changes in pain, with overall small to medium effect sizes.

Table 3

Longitudinal determinants of pain assessed by multiple regression analysis.

	Change in unspecified pain				Change in neuropathic pain			
	r_{part}	B (SE)	β	*P*	r_{part}	B (SE)	β	*P*
Gender (f)	0.021	0.093 (0.230)	0.021	0.686	0.052	0.701 (0.814)	0.053	0.390
Age (y) T0	0.068	0.015 (0.011)	0.071	0.187	0.112	0.080 (0.043)	0.117	0.064
Duration (m) T0	−0.024	−0.007 (0.015)	−0.024	0.644	0.036	0.031 (0.053)	0.035	0.555
Disability T0	0.002	0.004 (0.114)	0.002	0.973	0.053	0.357 (0.408)	0.056	0.382
Fatigue T0	0.083	0.013 (0.008)	0.119	0.104	0.007	0.003 (0.030)	0.010	0.910
Depression T0	−0.009	−0.003 (0.019)	−0.012	0.866	0.023	0.025 (0.066)	0.031	0.699
Cognition T0	−0.009	−0.002 (0.010)	−0.009	0.862	−0.108	−0.063 (0.035)	−0.111	0.073
Education T0 (Univ. degree)	−0.054	−0.242 (0.231)	−0.055	0.296	−0.044	−0.602 (0.821)	−0.046	0.464
Employment T0 (curr. employed)	0.075	0.546 (0.370)	0.077	0.141	0.033	−0.721 (1.331)	0.033	0.589
Disability T4-T0	0.110	0.211 (0.101)	0.112	0.038	0.085	0.443 (0.328)	0.082	0.178
Fatigue T4-T0	0.087	0.012 (0.007)	0.104	0.098	0.221	0.080 (0.022)	0.256	<0.001
Depression T4-T0	0.068	0.023 (0.017)	0.080	0.196	0.094	0.079 (0.053)	0.105	0.135
Cognition T4-T0	0.016	0.003 (0.011)	0.015	0.768	0.047	0.027 (0.036)	0.044	0.453

Multiple linear regression analyses with change in UP (VAS) and NP (PDQ) as dependent variables and baseline values as well as change in biopsychosocial parameters as independent variables were performed. Change was defined as respective parameter values at T4-T0. For NP, results of original data (pairwise complete observations) are shown.

f, female; y, years; m, months; Fatigue (FSMC, Fatigue Scale for Motor and Cognitive Function); Depression (BDI, Beck Depression Inventory II); Disability (EDSS, Expanded Disability Status Scale); Cognition (PASAT, Paced Auditory Serial Addition Test); Univ., university; curr., currently; UP, unspecified pain (VAS, Visual Analogue Scale); NP, neuropathic pain (PDQ, PainDETECT Questionnaire); r_{part}, partial regression coefficient; B, regression coefficient; SE, standard error; β, standardized regression coefficient.

4. Discussion

This study assessed the longitudinal prevalence of pain in MS and its relation to biological, psychological, and social factors over a 4-year period. To the best of our knowledge, this is the first longitudinal multicenter study analyzing the prevalence and potential biopsychosocial determinants of pain of any type (UP) and neuropathic pain (NP) in a large cohort of patients with early MS. Our results show that UP but not NP is frequent in early MS. In addition, both UP and NP are strongly and over time increasingly related to fatigue, depression, and disability.

4.1. Prevalence of pain in multiple sclerosis

Our finding of a fairly high and rather constant prevalence of UP in early MS is in line with previous studies that reported a prevalence between 30% and 74% in patient cohorts with a median EDSS of about 2.0.[4,21,42] Considering reports of a similarly high prevalence of pain in a non-MS control population,[39] it remains unclear how UP relates to MS. However, UP has been, among other symptoms, recently identified as a frequent prodromal symptom, years before diagnosis of MS.[7]

Our finding of a fairly low prevalence of NP in early MS confirms previous results using the same screening tool in a related cohort with early MS.[14] However, prevalence of NP is considerably lower than in other studies in early MS reporting a prevalence of 14%.[21,42] Heterogeneity in prevalence estimates of pain in MS is most likely due to methodological differences including different NP screening tools and larger proportions of patients with progressive MS in previous studies. Moreover, because of changes in the diagnostic criteria leading to earlier diagnosis and advances in IMT, more benign disease courses might have been observed in this study. This is further reflected by the lack of an increase in disability throughout the study period. However, the trend towards an increasing prevalence of NP (but not UP) in the present longitudinal data together with previous studies reporting a higher prevalence of NP in more advanced disease stages[21,35,36,42] suggest a causal relation between accumulating structural central nervous system pathology in MS and NP.[25,26,42]

4.2. Determinants of pain in multiple sclerosis

We found fatigue, depression, and disability to be most strongly interrelated with UP and NP at baseline (T0) and even more so at year 4 follow-up (T4). These findings are in accordance with previous studies indicating close relationships of pain in MS with fatigue, depression, and disability.[3,9,13,24,28,29,36,37,42] Moreover, our results show that these relationships become stronger over time as reflected by an increase from medium to large effect sizes in simple and multiple regression analyses from T0 to T4.

We found a generally very low explanatory value of biopsychosocial parameters at baseline for changes in pain over a 4-year period. By contrast, changes in disability and particularly in depression and fatigue had a considerably stronger association with changes in UP and even more so with changes in NP. An association between increases of pain and disability over time is in accordance with previous smaller longitudinal studies.[4,15,38,45] However, to the best of our knowledge, this is the first study to investigate the relationship of pain, depression, and fatigue in MS in a longitudinal fashion. Our finding that changes in pain are much stronger associated with changes in depression and fatigue than with their respective baseline values suggests that these 3 highly comorbid conditions rather concur than cause each other in MS. This points towards a common underlying pathophysiology. This notion is further supported by the present and previous findings that pain, fatigue, and depression occur frequently comorbid already in early MS[14] and even as prodromal symptoms years before diagnosis.[7] Because fatigue and depression have already been directly related to inflammation in MS,[9,29,37] investigating the relationship between inflammatory processes and pain might foster our understanding of these frequently comorbid conditions in MS.

4.3. Limitations

Several limitations should be considered when interpreting the present results. First, patients in this study had early and predominantly nonprogressive MS with rather low and stable disability. Thus, results do not necessarily generalize to more advanced and progressive MS. Second, NP was not assessed clinically but by a self-report questionnaire not specifically designed for patients with MS.[36] Moreover, NP screening parts of the PDQ were partially or completely missing in some patients. However, state-of-the-art multiple imputation procedures were used to account for missing data.[18] Third, the assessment of biopsychosocial factors was incomplete. For instance, other important factors such as anxiety and sleeping quality[3] have not been assessed. Fourth, our multivariate regression analyses suggest multicollinearity between depression and fatigue, which reflects an overlap of clinical symptoms. This substantial overlap highlights the need for a better understanding of potential common underlying pathomechanisms.

4.4. Implications and outlook

The present findings suggest that pain should be assessed early in MS and in conjunction with its frequent neuropsychiatric comorbidities, namely fatigue and depression. Moreover, treatment approaches for pain in MS should take into account these close relationships, eg, by applying multimodal biopsychosocial treatment approaches[6] including targeted pharmacotherapy. Furthermore, future research should aim to disentangle the cluster of pain, fatigue, and depression in MS, eg, by applying mediation analyses and exploring possible common pathophysiological mechanisms. We believe that understanding the relationship between these symptoms and early immunological processes in MS will be key in this context. Moreover, because the common clinical hallmark of the 3 conditions is their high "anhedonic" value as reflected by negative effect and decreased motivation,[9,23,28] the brain's reward system might be another promising research target.

5. Conclusions

Our results suggest that pain of any type but not NP is frequent in early MS, and that pain in MS is strongly interrelated with fatigue, depression, and disability. Because pain, fatigue, and depression in MS are already highly prevalent upon diagnosis, they should be assessed regularly, and their comorbidity should be taken into account for treatment decisions. In addition, future research should aim to identify possible common underlying pathophysiological mechanisms and targets to alleviate this frequent and burdensome combination of symptoms in MS.

Conflict of interest statement

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Topical Review

Fatigue, depression, and pain in multiple sclerosis: How neuroinflammation translates into dysfunctional reward processing and anhedonic symptoms

Henrik Heitmann, Till F M Andlauer, Thomas Korn, Mark Mühlau, Peter Henningsen, Bernhard Hemmer and Markus Ploner

Abstract: Fatigue, depression, and pain affect the majority of multiple sclerosis (MS) patients, which causes a substantial burden to patients and society. The pathophysiology of these symptoms is not entirely clear, and current treatments are only partially effective. Clinically, these symptoms share signs of anhedonia, such as reduced motivation and a lack of positive affect. In the brain, they are associated with overlapping structural and functional alterations in areas involved in reward processing. Moreover, neuroinflammation has been shown to directly impede monoaminergic neurotransmission that plays a key role in reward processing. Here, we review recent neuroimaging and neuroimmunological findings, which indicate that dysfunctional reward processing might represent a shared functional mechanism fostering the symptom cluster of fatigue, depression, and pain in MS. We propose a framework that integrates these findings with a focus on monoaminergic neurotransmission and discuss its therapeutic implications, limitations, and perspectives.

Keywords: Reward, anhedonia, cytokines, depression, fatigue, pain

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Introduction

Fatigue, depression, and pain are highly prevalent in multiple sclerosis (MS), jointly affecting more than half of MS patients.[1–4] Depending on the study cohort and screening method between 60% and 90% of patients suffer from fatigue,[1] 25% and 50% from depressive symptoms,[2,4] and 55% and 70% from pain[3] in the course of the disease. Moreover, these symptoms often co-occur and show strong associations[5,6] and have therefore been conceptualized as a symptom cluster.[4,7] However, current treatments are only partially effective.[1–4] Thus, fatigue, depression, and pain cause a substantial individual and societal burden by affecting the quality of life and the ability to work in patients suffering from MS.[6]

The frequent co-occurrence of fatigue, depression, and pain already in the prodromal phase[8] and in early MS as well as their parallel development over time suggest a common etiology.[5] Moreover, these symptoms share decreased motivation and a lack of positive affect,[1,2,9] which are essential signs of anhedonia.[10,11] Anhedonia is the reduced ability to strive for and to experience pleasure,[10,11] and has been attributed to deficits in reward processing.[12] Importantly, it is a core feature of many neuropsychiatric disorders, including chronic fatigue syndrome,[10] major depression,[10,11] and chronic pain,[9] and has been associated with poor long-term outcomes and treatment responses.[11] This finding is not surprising since hedonic valence is not only a central component of emotional responses but also a powerful motivator in guiding behavior and learning.[10,13,14] From a neurobiological standpoint, dysfunction of the brain's reward system plays an important role in anhedonia.[12,14] The key neurotransmitters involved in valence and reward processing are the monoamines dopamine and serotonin with their mesocorticolimbic pathways from the midbrain to the basal ganglia, the limbic system, and the prefrontal cortex.[11,12,14] Interestingly, MS patients show impaired reward responsiveness, especially when suffering from fatigue.[15] Moreover, neuroimaging studies have shown overlapping structural and functional alterations of mesocorticolimbic pathways in MS patients

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suffering from fatigue,[1,16] depression,[2,4] and pain.[17] Furthermore, all three symptoms have been linked to dysfunction of monoaminergic neurotransmission in central nervous system (CNS) inflammation.[1,4,18–20]

In the present review, we summarize neuroimaging and neuroimmunological findings that indicate that dysfunction of mesocorticolimbic reward pathways might represent a shared mechanism fostering the anhedonic symptom triad of fatigue, depression, and pain in MS. In particular, we will discuss how neuroinflammation might disturb monoaminergic neurotransmission, which leads to dysfunctional reward processing as a possible common pathophysiology underlying anhedonic symptoms in MS. Moreover, we will discuss the potential therapeutic implications and limitations of such a framework.[11,18,19,21,22]

Neuroimaging findings

Fatigue, depression, and pain are associated with several structural and functional changes of the brain in MS[1,2,4,16,17] and beyond.[1,23,24] Such changes have been most consistently observed in the prefrontal cortex, the basal ganglia, and the limbic system.[1,2,4,16,17,23,24]

Structural neuroimaging findings

In MS patients suffering from fatigue and depression, a higher lesion load and more severe cortical atrophy, particularly in the prefrontal cortex, have been observed.[25–27] Similarly, prefrontal gray matter alterations have been frequently reported in chronic pain patients (for a review, see Kang et al.[24]) but have thus far not been assessed in MS. Moreover, gray matter atrophy in the basal ganglia, predominantly the striatum, and the limbic system was described for MS patients suffering from fatigue,[25,28,29] depression,[30] and pain.[17] In addition, diffusion tensor imaging (DTI) studies have shown white matter tract abnormalities in fronto-striatal and fronto-limbic pathways of MS patients with fatigue[31,32] and depression.[30,33] Similar studies in MS patients suffering from pain are lacking.

Functional neuroimaging findings

In line with these structural findings, functional neuroimaging studies have shown alterations of fronto-striatal and fronto-limbic function and connectivity in MS patients with fatigue, depression, and pain.[2,16,17] In fatigued MS patients, a positron emission tomography (PET) study reported decreased glucose metabolism in the basal ganglia and the prefrontal cortex.[34] More recent functional magnetic resonance imaging (fMRI) studies reported decreased functional connectivity between the ventral striatum and the prefrontal cortex that scaled with the severity of fatigue.[35,36] Correspondingly, activation of the fronto-striatal network was associated with an improvement of fatigue.[37] In depressed MS patients, single photon emission tomography (SPECT) indicated a disconnection of cortical and subcortical areas of the limbic system.[38] This notion is supported by a more recent fMRI study showing decreased connectivity between the prefrontal cortex and the amygdala in MS patients suffering from depression.[39] In MS patients with chronic pain, fMRI has shown a decreased connectivity of the caudate and accumbens nuclei.[17]

Summary

Neuroimaging studies in MS patients with fatigue, depression, and pain have indicated gray matter atrophy and decreased functional connectivity in the prefrontal cortex, the basal ganglia, and the limbic system. These structures are core areas of the mesocorticolimbic system, a key structure in valence and reward processing that strongly depends on monoaminergic neurotransmission. Thus, fatigue, depression, and pain in MS are associated with functional disruption and, ultimately, degeneration of mesocorticolimbic pathways.

Neuroimmunological findings

There is mounting evidence that neuroinflammation can disturb neural function, which may eventually result in fatigue, depression, and pain in MS[1,2,4,22] and other contexts.[18,19,40] The model of cytokine-induced sickness behavior has provided insights into these mechanisms. In this model, cytokine-induced disruption of monoaminergic neurotransmission has been proposed as a key mechanism leading to dysfunctional reward processing, and eventually to fatigue, depression, and pain.[18–21]

Cytokines and sickness behavior in MS

Cytokines play an important yet only partially understood role in the pathogenesis of MS[41] and have been directly linked to fatigue and depression in MS and beyond.[1,2,4,20,42] Pro-inflammatory cytokines are well-known to directly act on the brain to induce sickness behavior, an anhedonic state characterized by decreased motivation, heightened pain sensitivity, prominent fatigability, and depressed mood.[18–20] In MS, increased serum levels of the pro-inflammatory cytokines Tumor necrosis factor alpha (TNF-α) and Interferon gamma (IFN-γ), as well as higher

frequencies of CD8+ T cells producing them have been related to fatigue and depression.[43,44] Moreover, fatigue and depression in MS were found to be associated with higher serum and cerebrospinal fluid (CSF) levels of the pro-inflammatory cytokine Interleukin-6 (IL-6).[42,45] Unfortunately, these results are confined by rather small sample and effect sizes. In addition, a prominent role of inflammatory processes in the pathophysiology of chronic pain has been discussed in MS and beyond.[22] However, the relationship between cytokine levels and pain symptoms in MS remains to be elucidated.[22]

From cytokine-induced monoaminergic disruption to dysfunctional reward processing

Sickness behavior resembles the leitmotif of anhedonia observed in fatigue, depression, and pain that has been attributed to dysfunctional reward processing.[11,12,18,19] Importantly, reward processing crucially depends on monoaminergic neurotransmission that is particularly sensitive to inflammation in the periphery and in the CNS.[18,19,21] Specifically, pro-inflammatory cytokines impede monoamine synthesis by reducing the availability of precursor amino acids in the periphery and synaptic availability in the CNS by hampering the release and inducing the reuptake of monoamines.[18,19,21] In the case of the monoamine neurotransmitter serotonin, which plays a key role in the regulation of affect, cytokines increase the metabolism of the precursor tryptophan via the alternative kynurenine pathway by inducing indoleamine 2,3 dioxygenase (IDO).[46] For the key motivational and reward neurotransmitter dopamine, cytokines decrease the availability of the co-factor tetrahydrobiopterin (BH4), thereby limiting the turnover of the precursors phenylalanine and tyrosine.[47] In addition, the synaptic availability of serotonin and dopamine is reduced by decreased presynaptic vesicular release and increased activity of the corresponding reuptake transporters through pro-inflammatory cytokines such as TNF-α and Interleukin-1β (IL-1β), released by brain-resident microglia.[48–50] Correspondingly, altered serotonin transporter (SERT) availability in the brain was shown in MS patients using PET imaging, which scaled with symptoms of depression and fatigue.[51]

The role of microglia

Microglia most likely play an important role not only in MS pathology[52,53] but also in inflammation-induced dysfunction of valence and reward processing associated with fatigue, depression, and pain.[19,21,22,54] This hypothesis is supported by recent PET studies using radioligand binding to the translocator protein (TSPO) that signals microglial activation. In MS patients, increased TSPO signaling in the hippocampus is associated with impaired functional connectivity in corticolimbic structures and depressive symptoms.[55] Beyond MS, increased TSPO signaling in mesocorticolimbic structures was observed in chronic fatigue syndrome[56] and has been related to negative affect in chronic pain conditions, including fibromyalgia.[57,58] Interestingly, fibromyalgia is characterized not only by chronic widespread pain but also by fatigue and depression and has been connected to altered cytokine signaling[59] and monoamine dysregulation.[60]

Importantly, microglia do not only release cytokines that hamper monoaminergic neurotransmission but can also contribute to neurodegeneration.[52] In this context, the previously mentioned kynurenine pathway and the concept of excitotoxicity play an important role.[21] Deviation along the kynurenine pathway by cytokine-mediated induction of IDO leads to microglial production of neurotoxic metabolites such as quinolonic acid that maintains inflammation and fosters neurodegeneration through excitotoxicity.[46] Excitotoxicity is caused by excess extracellular glutamate levels in the CNS, leading to overstimulation of glutamate receptors and, ultimately, neuronal and glial damage.[61,62] Quinolonic acid exerts its excitotoxic effects by stimulating release and inhibiting reuptake of glutamate from astrocytes as well as direct agonist binding to glutamate (N-methyl-D aspartate (NMDA)) receptors.[63] Importantly, stimulation of extrasynaptic NMDA receptors by excess extracellular glutamate levels was reported to be associated with decreased expression of brain-derived neurotrophic factor (BDNF) and the induction of cell death.[64] Moreover, pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-1β directly contribute to excitotoxicity in the gray and white matter by hampering glutamate reuptake through astrocytes and oligodendrocytes, which might be of particular importance in the context of MS.[61,62,65]

Summary

In their anhedonic presentation, fatigue, depression, and pain in MS resemble the clinical picture of sickness behavior that has been directly linked to pro-inflammatory cytokines. These symptoms might directly result from cytokine-induced disruption of monoaminergic neurotransmission and, ultimately, degeneration of mesocorticolimbic pathways that are

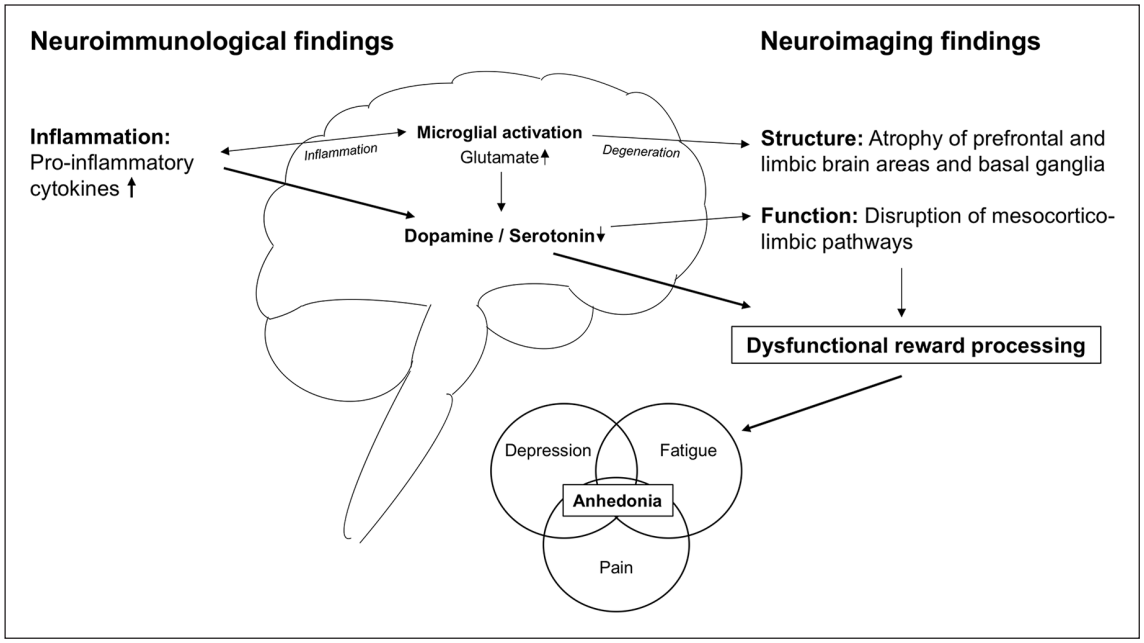

Figure 1. A translational framework for neuroinflammation-induced dysfunction of reward processing.
Pro-inflammatory cytokines affect the function and structure of mesocorticolimbic pathways and brain areas. Functionally, monoamine depletion causes disruption of neurotransmission. Structurally, excess glutamate levels fostered by microglial activation lead to degeneration and atrophy. The resulting dysfunction of reward processing manifests in anhedonia that is a prominent feature of fatigue, depressive symptoms, and pain in MS patients.

important for valence and reward processing. Microglial activation and excitotoxicity might play a prominent role in these processes.

A framework of how neuroinflammation translates into dysfunctional reward processing and anhedonic symptoms in MS

The evidence outlined above suggests that dysfunctional reward processing might represent a common pathophysiological feature underlying fatigue, depression, and pain in MS. Figure 1 summarizes this evidence and proposes a framework of how neuroinflammation might translate into anhedonic symptoms.

In this framework, neuroinflammation causes cytokine-induced disruption of monoaminergic neurotransmission. This disruption leads to altered mesocorticolimbic function and connectivity, which culminates in dysfunctional reward processing. In addition, sustained neuroinflammation, sub-served by microglial activation as well as demyelinating lesions, might foster neurodegeneration of brain structures involved in valence and reward processing in more advanced disease stages. The resulting inability to assign hedonic valence and, thus, to anticipate, seek, and perceive reward might underlie the common leitmotif of anhedonia observed in MS patients suffering from fatigue, depression, and pain.

Therapeutic implications

The framework has potential implications for the pharmacologic and non-pharmacologic treatment of anhedonic symptoms in MS.

Pharmacologically, drugs enhancing monoamine neurotransmission such as selective serotonin and noradrenaline reuptake inhibitors (SSRIs and SSNRIs) and psychostimulants with dopaminergic effects are already used as treatment for fatigue and depression also in MS.[1,4] Along the same line, drugs strengthening dopamine synthesis through supplementation of BH4, such as L-Methylfolate as well as L-DOPA, might be considered as potential treatments.[11,21] Furthermore, IDO inhibitors like 1-methyltryptophan (1-MT), with beneficial effects on excess glutamatergic neurotransmission, might represent a treatment approach for anhedonic symptoms in MS and beyond.[11,21]

As the framework considers disrupted monoaminergic neurotransmission to be a downstream effect of neuroinflammation, targeting neuroinflammation for

the treatment of anhedonic symptoms is obvious.[11,21] Anti-inflammatory therapy has already been discussed for the treatment of fatigue, depression, and chronic pain in neuropsychiatric disorders independently of MS.[11,19,21,22] In particular, Minocycline—which stabilizes glia function and might positively influence MS progression[66]—has been considered as a promising drug for the treatment of anhedonic symptoms.[11,21,22] Moreover, antibodies targeting TNF-α and the IL-6 receptor (IL-6R) have shown beneficial effects on anhedonic symptoms in other immune-mediated diseases such as rheumatoid arthritis,[67] ankylosing spondylitis, Crohn's disease, and psoriasis.[11] However, there have been reports that these antibodies induce relapses in MS patients.[41] Furthermore, the framework might increase awareness of the potential effects of disease-modifying treatments (DMTs) on anhedonic symptoms in MS. For instance, flu-like symptoms resembling sickness behavior occur during treatment with interferons.[68] Correspondingly, awareness of such potential effects does influence the choice of the individual DMT. Moreover, positive as well as negative effects on anhedonic symptoms might be considered as a secondary endpoint for future clinical trials on DMTs.

Non-pharmacologically, the framework advocates the use of behavioral and biopsychosocial interventions, such as cognitive-behavioral therapy, to counteract the detrimental affective and motivational effects of anhedonia.[69] Such behavioral approaches might not only alleviate anhedonic symptoms but also, in turn, positively influence levels of inflammatory markers in neuropsychiatric disorders associated with anhedonia.[21] Moreover, non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) hold considerable potential to alleviate this symptom cluster[7,70] and might have beneficial effects on cortico-subcortical network functioning including inflammation-induced synaptopathy.[71]

Limitations

The proposed framework is far from being fully elaborated. First, although fatigue, depression, and pain share a largely overlapping anhedonic clinical presentation, the framework does not take the differences between these symptoms into account. It rather interprets the mechanisms leading to anhedonia as a semi-specific element of fatigue, depression, and pain. Disentangling shared mechanisms and manifestations of anhedonia from those specific for fatigue, depressive symptoms, and pain will be crucial for a better understanding of all three symptoms. However, alleviation of their common clinical core feature anhedonia might yield beneficial effects on all three symptoms. Moreover, such positive effects might involve additional clinically relevant and closely related symptoms such as sleep disturbances and anxiety.[7] Second, the framework focusses on monoaminergic neurotransmission, only briefly touches on the role of microglia, glutamatergic function, and neurotrophic factors but does not cover other highly important interrelated mechanisms, for example, the hypothalamic-pituitary-adrenal (HPA)-axis, GABA ergic as well as opioidergic neurotransmission and the role of other immune cell populations.[11,20,22] Moreover, the role of demyelinating lesions in causing anhedonic symptoms by directly affecting meso-corticolimbic structures is not being discussed in detail. In addition, the framework focusses on neurobiological mechanisms and does therefore not include important cognitive-behavioral and other psychosocial factors that are well-known to influence anhedonic symptoms in MS patients.[69] Third, the proposed framework does not claim specificity for MS but rather aims to transfer and link findings on neuroimmune interactions important for anhedonic symptoms from various contexts.[11,18,19,21] However, since neuroinflammation is the hallmark of MS pathology, it appears logical to apply these findings to explain why anhedonic symptoms occur with such high frequency already in early MS.

Outlook

Considering the relationships between anhedonic MS symptoms, the function of valence and reward systems in the brain, and neuroinflammation, further research on neuro-immune interactions promises to advance the understanding and therapy of these burdensome conditions. For instance, assessing the relationship between peripheral and central inflammatory biomarkers, such as cytokine levels in the serum and CSF, the structure and function of meso-corticolimbic pathways and anhedonic symptoms in a large cohort of MS patients and in a longitudinal fashion would represent a logical next step. In addition, the influence of the HPA-axis and different immune cell populations on neurotransmitter systems implicated in valence and reward processing might be further evaluated in MS patients. Moreover, NMDA receptor antagonists such as ketamine have been shown to be effective in treating depression by rapidly reversing reward deficiency via normalizing monoamine neurotransmission.[72] Thus, glutamatergic function, which also shows responses to non-invasive brain stimulation techniques, might represent another promising mechanism for future research on the symptom cluster of fatigue, depression, and pain in

MS.[21,71,72] Eventually, interventional studies are needed to probe the effectiveness of the different pharmacological and non-pharmacological therapeutic approaches in MS patients. These steps might help to better understand and treat anhedonic symptoms in MS and beyond.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: H.H., T.F.M.A., T.K., M.M., P.H., and M.P. declare that there is no conflict of interest. During the last 2 years, B.H. has served on scientific advisory boards for Novartis; he has served as DMSC member for AllergyCare, Polpharma, and TG therapeutics; he or his institution have received speaker honoraria from Desitin; his institution received research grants from Regeneron for MS research. He holds part of two patents; one for the detection of antibodies against KIR4.1 in a subpopulation of patients with MS and one for genetic determinants of neutralizing antibodies to interferon. All conflicts are not relevant to the topic of the study.

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