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Original article

Ventral posterior nucleus volume is associated with neuropathic pain intensity in neuromyelitis optica spectrum disorders

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ABSTRACT

Background: Neuropathic pain (NP) is frequent in neuromyelitis optica spectrum disorders (NMOSD). The ventral posterior nucleus (VPN) of the thalamus receives sensory afferences from the spinothalamic tracts and is associated with central pain in other conditions.
Objective: To investigate associations between NP and VPN volume in aquaporin-4-IgG- positive (AQP4-IgG+) NMOSD.
Methods: This cross-sectional study included 32 AQP4-IgG+ NMOSD patients and 37 healthy controls. NP intensity was determined by the PainDetect Questionnaire. Spinal cord lesion number and location as well as VPN volume were assessed by MRI, the latter using a multi-atlas-based automated segmentation.
Results: Twenty-five patients (78%) suffered from NP and seven had no pain. Mean VPN volume did not differ between patients with and without NP ($p = 0.533$) or between patients and controls. However, mean VPN volume correlated with average (rho = -0.486, $p = 0.019$) and worst pain intensity (rho = -0.593, $p = 0.003$). Of note, no other thalamic nuclei volumes correlated with measures of pain intensity. Compared to pain-free patients, patients with NP had more lesions involving the thoracic spinal cord ($p = 0.007$). The relationships between VPN and pain intensity measures remained after adjustment for age, myelitis count, and spinal cord lesion location.
Conclusion: Our data support a model where thoracic spinal cord lesions are associated with the development of NP in AQP4-IgG+ NMOSD and the VPN plays a role in the modulation of NP intensity. VPN volume as assessed in our study may be a clinically meaningful imaging marker of pain severity in AQP4-IgG+ NMOSD.

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1. Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are chronic relapsing inflammatory disorders of the CNS, defined by pathogenic immunoglobulin G (IgG) antibodies against astrocytic aquaporin-4 (AQP4) in most cases. (Borisow et al., 2018) Patients typically present with optic neuritis and/or longitudinally extensive transverse myelitis. (Wingerchuk et al., 2015) It has been shown, that 89% of AQP4-IgG-positive patients had a history of myelitis within a disease duration of five years. (Jarius et al., 2012)

Over 80% of patients with NMOSD suffer from chronic pain, (Asseyer et al., 2018, Kanamori et al., 2011, Qian et al., 2012, Asseyer et al., 2020) most frequently from neuropathic pain (NP) following myelitis. (Asseyer et al., 2018, Asseyer et al., 2020) Pain in NMOSD is typically severe and has a negative impact on the patients' quality of life. (Asseyer et al., 2018, Kanamori et al., 2011, Qian et al., 2012, Chavarro et al., 2016, Beekman et al., 2019)

Spinal dorsal horn and/or ascending spinothalamic tract (STT) affection play crucial roles in NP development. (Pellkofer et al., 2013) Disinhibition of pain pathways within the dorsal columns and the disruption of decussating fibers of the STT in multiple sclerosis (MS), (Osterberg and Boivie, 2010) as well as grey matter damage after spinal cord injury (SCI) (Finnerup et al., 2003) may all induce NP. As the typically extensive spinal cord lesions in NMOSD can affect both the spinal dorsal horns and the ascending STT, (Hayashida et al., 2017, Elsone et al., 2012) an association between such lesions and the development of NP is conceivable.

Currently, one MRI-based study has examined the relation between myelitis-associated lesion location and chronic NP in AQP4-IgG-positive NMOSD. (Tackley et al., 2017) Besides, a negative correlation between pain intensity and thalamic volume has been shown recently in female AQP4-IgG-positive NMOSD patients. (Wang et al., 2020) Of note, the posterior thalamus plays a pivotal role in central pain pathways (Krause et al., 2012; Nagasaka et al., 2017; Sprenger et al., 2012) and the STT projects to the thalamic ventral posterior nucleus (VPN). (Sánchez and Linera, 2004) However, the involvement of strategic brain areas like thalamic subnuclei for processing of NP in NMOSD has not yet been studied. Thus, there is need for comprehensive imaging studies investigating the role of different lesion characteristics and imaging markers in the development and severity of NP in AQP4-IgG-positive NMOSD. We hypothesized VPN volume changes to be involved in central pain modulation and perception in NMOSD.

Our primary aim was to investigate VPN volume changes in patients with NP compared to pain-free patients and the association between VPN volume and pain intensity in AQP4-IgG-positive NMOSD. We also evaluated whether the associations of NP with VPN volume would be independent of damage in other strategic areas for NP (spinal cord, brainstem, and thalamus).

2. Methods

2.1. Ethics, study protocol, and participants

Patients' data were derived from the baseline visit of an ongoing prospective observational cohort study that is following patients with NMOSD and related disorders, including NMO according to Wingerchuk 2006, AQP4-IgG-positive NMOSD and AQP4-IgG-negative NMOSD according to Wingerchuk 2015, MOG-IgG associated disease (Narayan et al., 2018), longitudinal extensive transverse myelitis (LETM), and chronic relapsing inflammatory optic neuropathy (CRION)/ recurrent optic neuritis, at the NeuroCure Clinical Research Center at Charité – Universitätsmedizin Berlin. All study participants receive the same study protocol, irrespective of the underlying diagnosis. The study was approved by the local ethics committee (EA1/041/14) and conducted according to the Declaration of Helsinki in its currently applicable version. Study participation is voluntary and all participants provided written informed consent prior to inclusion.

We screened 76 patients of our database for a diagnosis of AQP4-IgG-positive NMOSD according to the 2015 international consensus diagnostic criteria. (Wingerchuk et al., 2015) AQP4-IgG-seropositivity was determined by a cell-based assay (Euroimmun, Lübeck, Germany). Thirty-five patients were excluded, because of i) seronegative AQP4-IgG-status (n = 25), ii) incomplete clinical data and/or unknown AQP4-IgG-status (n = 10). Forty-one patients met the criteria for AQP4-IgG-positive NMOSD. Out of them, nine patients were excluded due to i) only non-neuropathic pain conditions (headache (n = 1), arthralgia (n = 2), osteoporosis-associated pain (n = 1), and pain of unknown origin (n = 1), ii) no MRI data (n = 3) or iii) an attack within three months prior to baseline (n = 1) (for details see Fig. 1).

The remaining 32 AQP4-IgG-positive NMOSD patients were included in the analysis.

Moreover, data from 37 healthy controls (HC) were included from the institute's research database (EA1/163/12), to be as well matched as possible to the patients regarding age and sex. Inclusion criteria for HC were: i) age ≥ 18 years and ii) no history of neurological or ophthalmological diseases. All participants were Caucasian, except two

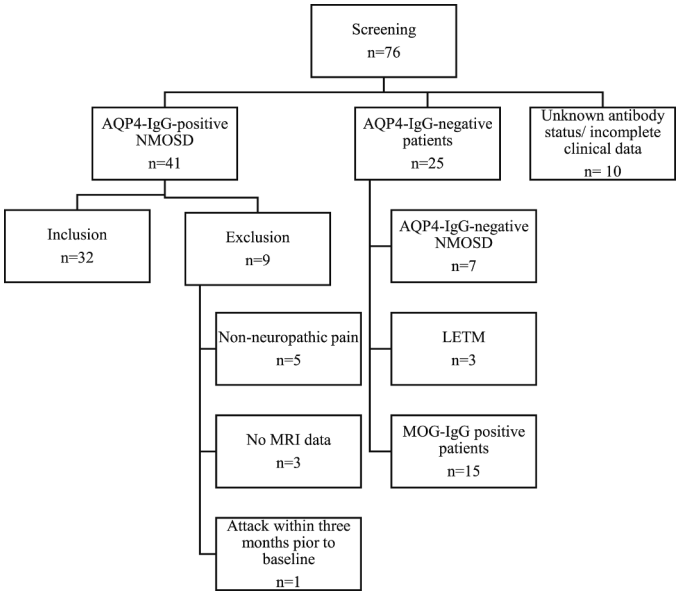

Fig. 1. The algorithm explains the screening process, leading to inclusion of 32 AQP4-IgG-positive NMOSD patients. Note that from 25 patients excluded due to negative AQP4-IgG-antibodies, only seven fulfilled the diagnostic criteria according to Wingerchuk 2015 for NMOSD (three patients had LETM, but did not fulfill the criteria for NMOSD according to Wingerchuk 2015 and 15 patients were positive for MOG antibodies). No definite diagnosis was available for the remaining 10 patients with unknown antibody status/ incomplete clinical data. Abbreviations: AQP4-IgG: Aquaporin 4 immunoglobulin G, LETM: longitudinal extensive transverse myelitis, MOG-IgG: myelin oligodendrocyte glycoprotein immunoglobulin G, MRI: magnet resonance imaging, NMOSD: neuromyelitis optica spectrum disorders.

Table 1
Demographic and clinical characteristics of patients and healthy controls included in this study.

Demographics and clinical characteristics	AQP4-IgG + NMOSD Patients (n = 32)	Healthy Controls (n = 37)	NMOSD vs. HC
Sex, female/male (female %)	31/1 (96.9%)	32/5 (86.5%)	OR = 4.75 (95% CI 0.491-236.0) $p = 0.206$
Age, years: mean ± SD	51.1 ± 14.4	47.8 ± 12.5	t = -0.997 $p = 0.323$
Handedness: right/left	29/3	33/2	OR = 0.59 (95% CI 0.046-5.533) $p = 0.664$
Disease duration, years: median (min-max)	6.33 (0.48-32.25)	-	-
Total number of previous attacks: median (min-max)	3 (1-22)	-	-
Patients with ON: n (%)	18 (56.3%)	-	-
Patients with myelitis: n (%)	32 (100%)	-	-
Patients with brainstem attacks: n (%)	5 (15.6%)	-	-
Number of myelitis episodes per patient: median (min-max)	1.5 (1-15)	-	-
EDSS: median (min-max)	4 (1-7)	-	-
Sensory Functional System Score: median (min-max)	2 (0-4)	-	-
Patients on immunosuppressive treatment: n (%)	29 (90.6%)	-	-

Legend: Abbreviations: AQP4-IgG: Aquaporin 4 immunoglobulin G, EDSS = expanded disability status scale; min-max = minimum-maximum; n = number; NMOSD = neuromyelitis optica spectrum disorders, ON = optic neuritis; SD = standard deviation; vs. = versus

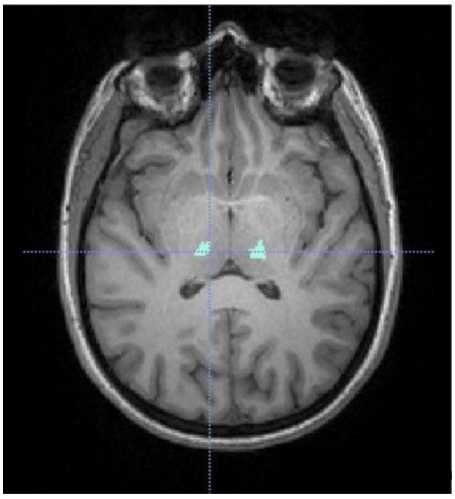

Fig. 2. Example of VPN segmentation in a healthy control
Axial T1-weighted MPRAGE image showing an example of VPN segmentation (turquoise) using the MAGeT brain algorithm in a healthy control. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

NMOSD patients, one of whom was Asian and the other was of African descent. Table 1 provides study participants' characteristics.

2.2. Clinical data and assessment

Clinical data collection included the Expanded Disability Status Scale (EDSS). Neuropathic pain was defined as pain arising as a consequence of a NMOSD lesion, confirmed by MRI, affecting the somatosensory system. The diagnosis was made taking into account anamnesis, neurological examination, and imaging results. (Treede et al., 2008) The PainDetect Questionnaire (PDQ) was administered to support the discrimination of neuropathic and nociceptive pain, to record pain localization, and to ask about current, average, and worst pain intensity within the last four weeks. Pain intensity is based on a numeric rating scale from 0 (no pain) to 10 (worst pain imaginable). (Freynhagen et al., 2006)

We administered the Beck Depression Inventory (BDI-II), scored from 0 (best) to 63 (worst) (0–9: non depressive affect; 10–19: minimal mood disturbance; 20–29: moderate depression; 30 and above: severe depression) (Beck et al., 1996) to detect a possible interference of depressive symptoms and pain.

The number of previous myelitis attacks (based on history and medical records) was assessed as measure of spinal cord affection.

2.3. MRI acquisition

MRI of the brain (patients: n = 32, HC: n = 37) and the spinal cord (patients: n = 31, HC: n = 37) was performed with a 3T MAGNETOM Tim Trio scanner (Siemens, Erlangen, Germany). The MRI protocol for this study included a 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) images (repetition time (TR) = 1900 ms, echo time (TE) = 3.03 ms, resolution = 1 × 1 × 1 mm), a 3D T2-weighted fluid attenuated inversion recovery (FLAIR) sequence (TR = 6000 ms, TE = 388 ms, isotropic resolution 1 × 1 × 1 mm), and spinal 2D-sagittal T2-weighted sequence (slice thickness = 2 mm, TR = 3500 ms, TE = 101 ms, in-plane resolution = 0.91 mm × 0.91 mm). MRI and clinical examination were done on the same day, except for two participants where data collection was done on two consecutive days.

2.3.1. VPN volume

VPN volume as well as the volumes of the other thalamic nuclei (anterior nuclei, central nuclei, lateral dorsal nucleus, lateral posterior nucleus, medial dorsal nucleus, ventral anterior nucleus, ventral lateral nucleus, and pulvinar) were measured for all participants using the Multiple Automatically Generated Templates (MAGeT) brain algorithm (Chakravarty et al., 2006, Chakravarty et al., 2013) on MPRAGE scans (Fig. 2). MAGeT uses an atlas derived from manually segmented serial histological data, including delineation of the thalamic nuclei. It first customizes the atlas to a subset of participants, representative of the study population, using nonlinear registration. This newly segmented subset is then used as a template library for the remaining participants. Thereby, a correction for the neuroanatomical variability of the study population is provided. (Chakravarty et al., 2013) The segmentation results of all thalamic nuclei were visually inspected by one experienced rater (L.G.). All volumes were normalized using the SIENAX V-scaling factor for head-size. (Smith et al., 2002)

2.3.2. Lesions in spinal cord, brainstem, and thalamus

Two experienced neurology residents (J.K., S.A.) supervised by a board-certified radiologist (M.Sch.) reviewed all patients' MRIs for the detection of lesions in strategic locations for NP: spinal cord, brainstem, and thalamus. Thalamic and brainstem lesions were assessed from 3D T2-weighted fluid-attenuated inversion recovery (FLAIR) images and counts were recorded. Spinal cord lesions were identified in T2-weighted spinal cord images where lesion number, length (as number of

Table 2
Comparison between patients with NP and pain-free patients regarding demographic and clinical characteristics.

Demographic and clinical characteristics	NP (n = 25)	No Pain (n = 7)	NP vs. no pain
Age, years: mean ± SD	53.3 ± 13.1	43.1 ± 17.3	t = -1.450 $p = 0.184$
Sex, female/male: (female%)	24/1 (95.8%)	7/0 (100%)	OR: 4.75 (95% CI 0.491-236.1) $p = 0.206$
Disease duration, years: median (min-max)	6.8 (0.99-32.25)	4.4 (0.48-14.70)	$p = 0.112$
EDSS: median (min-max)	4.0 (1-7)	2.0 (1-4)	$p = 0.021$
Sensory functional system score: median (min-max)	3.0 (0-4)	0.0 (0-2)	$p = 0.004$
BDI-II:	(n = 24)	(n = 7)	
No depression (0-9), n (%)	18 (75%)	5 (71.4%)	OR = 1.19 (95% CI 0.091-10.112) $p > 0.999$
Mild depression (10-19)	5 (20.8%)	1 (14.3%)	OR = 1.56 (CI 0.130-86.920) $p > 0.999$
Moderate depression (20-29)	1 (4.2%)	1 (14.3%)	OR = 0.276 (CI 0.003-23.864 $p = 0.407$
Severe depression (≥ 30)	0	0	
Total number of prior attacks: median (min-max)	4 (1-22)	3 (1-5)	$p = 0.332$
Number of prior myelitis episodes: median (min-max)	2 (1-15)	1 (1-3)	$p = 0.178$
Patients with history of myelitis: n (%)	25 (100%)	7 (100%)	
Time since last myelitis episode, years: median (min-max)	4.2 (0.5-14.1)	4.4 (0.5-14.5)	$p = 0.901$
Patients with history of brainstem attacks: n (%)	4 (16%)	1 (14.3%)	OR = 1.14 (95% CI 0.087-65.520) $p > 0.999$

Legend: Of note, all patients with and without neuropathic pain had a history of myelitis. However, we excluded two patients with non-neuropathic pain conditions who did not have a history of myelitis, which leads to a percentage of 95% of history of myelitis among all our AQP4-IgG-positive patients (data not shown). Note that these group comparisons were performed using t-test for age, Fisher's exact test for sex, BDI-II score categories, history of myelitis, and history of brainstem attacks and Wilcoxon test for disease duration, time since last myelitis, number of prior attacks and prior myelitis episodes, EDSS, and sensory functional system score (not normally distributed variables). Abbreviations: BDI = Beck's depression inventory; EDSS = expanded disability status scale; min-max = minimum-maximum; n = number; NP = neuropathic pain, ON = optic neuritis, OR = odds ratio, SD = standard deviation; vs. = versus.

involved segments) and location were recorded. The location of chronic spinal cord lesions was classified as isolated cervical, isolated thoracic or cervicothoracic (lesions in both cervical and thoracic spinal cord). In addition, the estimated lesion midpoint was recorded, as previously described (Tackley et al., 2017) (e.g. a lesion from C3 to C7 gives a C5 midpoint; two lesions in the same patient: one C5–6 and one T1–2 give a C7 midpoint).

2.3.3. Spinal cord atrophy

The mean upper cervical cord area (MUCCA) was used as a measure to assess atrophy of the spinal cord in patients with NMOSD. (Chien et al., 2018) MUCCA was used as a sensitive measure to assess spinal cord atrophy in patients with NMOSD. MUCCA was measured from MPRAGE-scans using an active surface model by averaging the cross-sectional areas from five consecutive slices at the C2/C3 intervertebral space level, as described previously. (Chien et al., 2018)

Of note, all clinical and MRI data were assessed at the same time point, outside of any attack.

2.4. Statistical analysis

Statistical analysis was performed using R with the packages pastecs, lmer, lme4, MuMIn, and ggplot2. (R Core Team, 2013)

To investigate demographic and clinical group differences between patients with and without NP, we used Fisher's exact test for sex, attack history, and BDI-II categories, two-sample t-test for age (normally distributed), and Wilcoxon rank-sum test for disease duration, time since last myelitis, EDSS, and sensory functional system score.

First, we investigated comparisons regarding VPN volume (sum of both hemispheres) using linear regression analysis with group (patients with vs. without NP and patients vs. HC), age, and sex as independent variables. To test for correlations between VPN volume and measures of pain intensity we performed Spearman-correlation analyses.

Second, lesion location as a relevant and previously suggested pain cause was compared between groups using Fisher's exact test for categorical variables (presence of spinal cord, brainstem and thalamic lesions, lesions at different spinal cord levels and number of involved segments), and non-parametric Wilcoxon rank-sum test for ordinal or non-normally distributed variables (number of spinal cord lesions, estimated lesion midpoint, and number of brainstem lesions).

Third, a linear regression analysis including age, number of previous myelitis episodes (0-1 versus ≥ 2) and spinal cord lesion location on MRI (any thoracic versus no thoracic involvement) was performed to evaluate whether the associations of VPN volume with measures of pain intensity were independent of age and spinal cord affection (no adjustment was made for sex, since only one male had NP).

Spinal cord damage was evaluated using the number of previous myelitis attacks, which is a good representative measure in our cohort, rather than the number of chronic spinal cord lesions. Since the myelitis episodes often occurred several years before the baseline visit, a higher apparent number of chronic MRI lesions would be a likely consequence of partial recovery after LETM. Furthermore, MUCCA was used to compare spinal cord atrophy between groups with linear regression analysis, corrected for age and sex.

Finally, in a control analysis, we checked for correlations between measures of pain intensity and the volumes of the other thalamic nuclei (anterior, central, lateral dorsal, lateral posterior, medial dorsal, ventral anterior, ventral lateral nucleus and the pulvinar).

For all models, statistical significance was achieved at $p < 0.05$. This study was exploratory, without an a priori sample size calculation.

3. Results

3.1. Frequency and characteristics of neuropathic pain

A total of 25 (78.1%) out of 32 AQP4-IgG-positive NMOSD patients suffered from NP, seven patients were free of pain. Patients with NP and pain-free patients did not differ regarding age, sex, disease duration, number of previous myelitis episodes, and BDI-II score (Table 2).

Patients with NP had a higher EDSS ($p = 0.021$) and sensory functional system score ($p = 0.004$) than patients without pain. Moreover, both scores correlated with measures of pain intensity (EDSS with present pain intensity: rho = 0.397, $p = 0.016$; average pain intensity: rho = 0.389, $p = 0.021$,worst pain intensity: rho = 0.423, $p = 0.013$;

Table 3
Neuropathic pain characteristics and medication.

Neuropathic pain patients	NP (n = 25)
Pain intensity	
Present pain intensity: median (min-max)	4/10 (0-10)
Average pain intensity: median (min-max)	4/10 (0-10)
Worst pain intensity: median (min-max)	6/10 (3-10)
Pain course	
Persistent pain: n (%)	10 (40%)
Intermittent pain: n (%)	11 (44%)
N.A.: n (%)	4 (16%)
Pain localization	
Legs: n (%)	9 (36%)
Trunk/ torso: n (%)	8 (32%)
Feet: n (%)	6 (24%)
Buttock/ hip: n (%)	3 (12%)
Head/ neck: n (%)	2 (8%)
Arms: n (%)	2 (8%)
Hands: n (%)	2 (8%)
Pain medication	25 (40%)
Anticonvulsants: n	8
Antidepressants: n	2
Nonsteroidal anti-inflammatory drugs: n	1
Muscle relaxants: n	1

Legend: Information on pain characteristics derive from PainDetect Questionnaire. Note that average and worst pain intensity refer to the last four weeks. Abbreviations: n = number; N.A. = not available.

sensory functional system score with average pain intensity: rho = 0.439, $p = 0.008$; and worst pain intensity: rho = 0.466, $p = 0.005$). Overall, there were no correlations between the other demographic and clinical characteristics (age, disease duration, number of myelitis) and measures of pain intensity (data not shown). Table 3 provides information about pain characteristics and medication. No patient under pain medication was permanently free of pain.

3.2. Neuropathic pain and VPN volume

VPN volume did not differ between patients with NP (667.5 ± 68.8mm^3) and patients without pain (699.0 ± 62.5 mm^3, B = -32.16, SE = 50.98, $p = 0.533$). In fact, mean VPN volume was also not different between NMOSD patients (674.4 ± 68.3 mm^3) and HC (679.7 ± 68.3; B = -12.3, SE = 29.2, $p = 0.674$). The entire thalamic volume did not differ between NMOSD patients (7360.1 ± 66.1 mm^3) and HC (7473.1 ± 64.6 mm^3, B = -60.5, SE = 137.9, $p = 0.662$), either.

In patients with NP mean VPN volume inversely correlated with average pain intensity (rho = -0.486, $p = 0.019$) and worst pain intensity (rho = -0.593, $p = 0.003$) (Fig. 3 B and C). The correlation with present pain intensity did not reach statistical significance (rho = -0.374, $p = 0.072$) (Fig. 3 A). In a linear regression analysis adjusting for age, number of myelitis attacks, and spinal cord lesion location (any thoracic versus no thoracic involvement), VPN volume remained inversely associated with average (B = -0.01, SE = 0.006, $p = 0.033$) and worst pain intensity (B = -0.01, SE = 0.005, $p = 0.015$), while the association with present pain intensity was still not significant (B = -0.01, SE = 0.007, $p = 0.301$).

In a control analysis, the other thalamic nuclei did not correlate with any measures of pain intensity (details are given as supplementary material).

3.3. Associations of neuropathic pain with MRI lesions (spinal cord, brainstem, thalamus)

Regarding the presence of thalamic and brainstem MRI lesions, there were no differences between patients with and without NP (Table 4). Although this was also true for the number of spinal cord lesions (no difference regarding total lesion number between the two groups, Table 4), we found an association between NP and lesion location in the spinal cord: The proportions of patients with combined cervical and thoracic lesions as well as with any thoracic involvement were higher in the NP group, while more pain-free patients had isolated cervical lesions (Table 4). We also observed that the estimated median lesion midpoint in patients with NP was more caudally located than in pain-free patients (Table 4).

MUCCA -as a measure of spinal cord atrophy- was smaller in all patients compared to HC (68.34 ± 7.03 vs. 74.8 ± 6.42 mm^2; B = -7.74, SE = 1.65, $p < 0.001$), but did not differ between patients with and without NP (Table 4).

We did not find any correlations between the MRI measures shown in Table 4 (presence of thalamic lesions, brainstem and myelitis number, spinal cord lesion location, MUCCA) and pain intensity (data not shown).

4. Discussion

Neuropathic pain is a frequent symptom in NMOSD. (Asseyer et al., 2018, Kanamori et al., 2011, Qian et al., 2012, Asseyer et al., 2020, Chavarro et al., 2016, Bradl et al., 2014) However, clinical data on its pathogenesis and anatomical correlates are very limited. Since the VPN is the thalamic nucleus that receives sensory afferences from the STT, (Sánchez and Linera, 2004, Nagalski et al., 2016) we hypothesized that it may be involved in the development and/or modulation of central pain in patients with NMOSD and myelitis.

Indeed, we found an inverse correlation of VPN volume with average and -even stronger- with worst pain intensity in AQP4-IgG-positive NMOSD patients. This would support the hypothesis that the VPN is involved in the processing of NP in NMOSD. There were no associations between the volume of the other thalamic nuclei and any measures of pain intensity, suggesting that our results were likely specific for the VPN. Interestingly, a recently published Chinese study showed a negative correlation between pain intensity and volume of the entire thalamus in female AQP4-IgG-positive NMOSD patients. (Wang et al., 2020) In this previous study the different thalamic nuclei were not assessed separately as in our study. Moreover, the controversial results between the Chinese and our study regarding entire thalamic volume might be associated with differences between European and Asian NMOSD populations. (Liu et al., 2015, Hyun et al., 2017, Finke et al., 2016, Pache et al., 2016)

The thalamus is relevant to nociceptive processing and sensitive to pain-related pathologies. Disabilities, including back pain, (Apkarian et al., 2004) limb amputation, (Draganski et al., 2006) and peripheral neuropathy (Jutzeler et al., 2016, Gustin et al., 2010) can lead to acute and chronic structural and functional plastic changes and/or atrophy within the thalamus. Moreover, changes in the thalamus and specifically the ventral posterior thalamus have been shown to have an association with NP due to spinal cord lesions. (Gustin et al., 2010, Ziegler et al., 2018) For example, nociceptive processing was observed to be modulated by activated microglia in the thalamus after SCI in rats. (Zhao et al., 2007) In humans, an association between decreased thalamic grey matter volume and pain was shown after SCI. (Jutzeler et al., 2016) Moreover, in SCI another study showed decreased mean diffusivity (MD) in the ventral posterior thalamic nuclei, which correlated inversely with pain intensity. (Gustin et al., 2010) The interpretation of this MD decrease could be a complex reorganization process including neuronal loss but also sprouting, (Gustin et al., 2010) which could also explain the lack of VPN atrophy seen in our study. The critical role of the VPN in NP was also suggested by previous studies in stroke. It was shown that thalamic ischemic lesions at the VPN-pulvinar border, or at the ventral posterolateral nucleus, are associated with the highest risk of developing central post-stroke pain. (Krause et al., 2012; Nagasaka et al., 2017; Sprenger et al., 2012)

Of note, the correlation of present pain intensity and VPN volume was not significant. Present pain intensity may be a less robust measure than average and worst pain intensity, e.g. as intermittent pain attacks

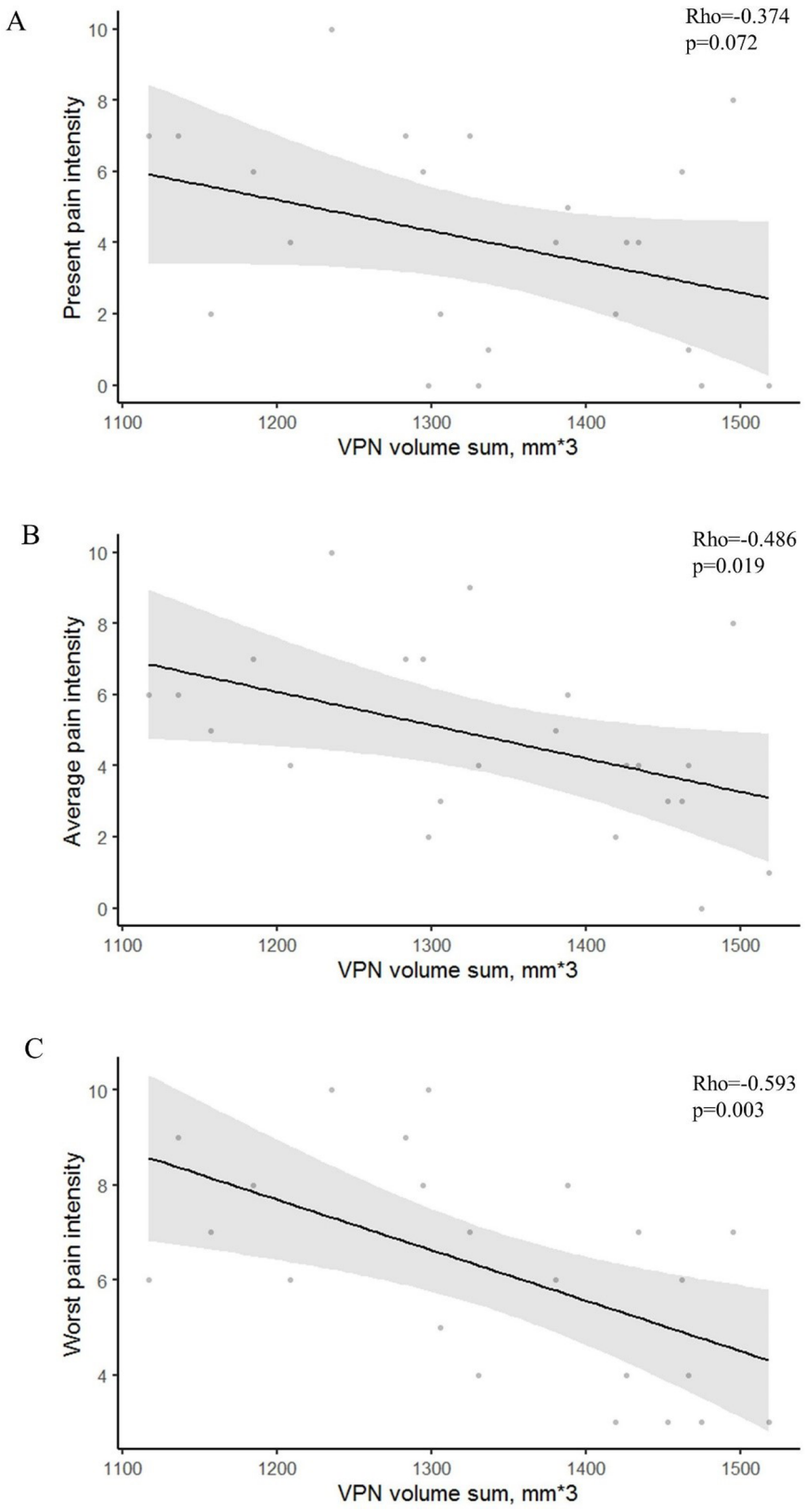

Fig. 3. Relationship between pain intensity and VPN volume in patients with NP
VPN volume sum refers to the VPN sum of both hemispheres since these correlations are performed per patient. A: Inverse correlation of present pain intensity and VPN volume sum ($p = 0.072$). B: Inverse correlation of the average pain intensity within the previous four weeks and VPN volume sum ($p = 0.019$). C: Inverse correlation of the worst pain intensity within the previous four weeks and VPN volume sum ($p = 0.003$).

Table 4
Comparison between patients with NP and pain-free patients regarding MRI characteristics.

MRI characteristics	NP (n = 25)	No Pain (n = 7)	NP vs. no pain
Patients with at least one brainstem lesion (MRI): n (%)	6 (24%)	1 (14.3%)	OR: 1.86 (95% CI 0.164-101.42) $p > 0.999$
Number of brainstem lesions: median (min-max)	0 (0-3)	0 (0-1)	$p = 0.549$
Patients with one thalamic lesion (MRI): n (%)	2/25	0/7	OR: Inf (95% CI 0.050-Inf) $p = 1.0$
Spinal cord affection (MRI)	n = 24	n = 7	NP vs. no pain
Total spinal cord lesion number: median (min-max)	1 (0-3)	1 (0-1)	$p = 0.080$
Number of involved segments: median (min-max)	5 (0-12)	3 (0-7)	$p = 0.199$
Lesion Location			
Patients with isolated cervical lesions: n (%)	3 (12.5%)	5 (71.4%)	OR:0.07 (95% CI 0.004-0.606) $p = 0.006$
Patients with isolated thoracic lesions: n (%)	5 (20.8%)	1 (14.3%)	OR:1.56 (95% CI 0.13-86.92) $p > 0.999$
Patients with combined cervical and thoracic lesions: n (%)	13 (54.2%)	0	OR:inf (95% CI 1.3-inf) $p = 0.025$
Patients with any cervical involvement: n (%)	16 (66.7%)	5 (71.4%)	OR:0.81 (95% CI 0.06-6.4) $p > 0.999$
Patients with any thoracic involvement: n (%)	18 (75%)	1 (14.3%)	OR:16.11 (95% CI 1.52-867.1) $p = 0.007$
Lesion midpoint: median (min-max)	Th1/2 (C3-Th5/6)	C4/5 (C3/4-Th5)	$p = 0.035$
MUCCA, mm^2: mean ± SD	66.95 ± 6.85	68.00 ± 7.11	B = -0.86, SE = 3.24 $p = 0.793$

Legend: Note that these group comparisons were performed Fisher's exact test for brainstem, thalamic, cervical, thoracic, and combined spinal cord lesions and Wilcoxon test for total spinal lesion number and number of involved segments. MUCCA was compared between groups using a linear regression analysis with correction for age and sex.
Abbreviations: min-max = minimum-maximum; n = number; NP = neuropathic pain, OR = odds ratio, SD = standard deviation; vs. = versus, MUCCA = mean upper cervical cord area.

may be absent while fulfilling the assessment.

Despite the associations with pain intensity, VPN volume was not reduced in patients with vs. without pain in our study. An intriguing hypothesis to explain this finding is that the VPN might be mainly involved in the physiological modulation of pain perception rather than in the development of pain itself. The latter may be rather associated with thoracic spinal cord lesions, based in our results, which on the other hand do not seem to affect pain intensity measures.

Potentially, the variability in size and anatomy of the VPN prior to myelitis may modify the risk of developing severe NP, with a larger VPN being protective against higher pain intensity. This would be in line with the normal VPN and entire thalamic volumes of our NMOSD patients compared to HC, which also confirms previous results. (Finke et al., 2016) A similar association between anatomical variability prior to disease and risk of developing specific symptoms was studied in MS, where measures of intracranial volume representing a neuronal compensatory capacity might be protective against cognitive dysfunction. (Sumowski et al., 2016)

The association between NP and spinal cord lesion location in our cohort confirms results from a previous independent study, (Tackley et al., 2017) which showed that persistent thoracic cord lesions in AQP4-IgG-positive patients were associated with higher pain severity, independently of number of myelitis attacks, lesion length, and lesion burden. Although there was no correlation between thoracic lesion location and pain intensity in our cohort, we found a more frequent thoracic involvement and further caudally located lesion midpoint in patients with NP versus pain-free patients. Some differences between our study and the other study have to be noted: (i) we assessed chronic spinal cord lesions (months to years after the myelitis episodes) compared to acute lesions associated with myelitis; (ii) we used a different pain measure and (iii) we had a smaller sample size. Despite these different methods, an association between affection of the thoracic spinal cord and NP in NMOSD is suggested by both studies. A possible explanation for this is the damage of the thoracically located autonomic nuclei of the spinal cord, which may dysregulate pain processing. (Tackley et al., 2017)

Of note, in our cohort patients with pain had more sensory deficits (higher sensory functional system score) than patients without pain, but both groups did not differ with respect to depression scores. This finding is in contrast with previous results in MS, where pain is associated with higher depression scores (O'Connor et al., 2008) and suggests that NP in AQP4-IgG-positive NMOSD is predominantly a physical issue, more than a psychological phenomenon. This can be also supported by the positive effect of tocilizumab on pain in AQP4-IgG-positive NMOSD (Araki et al., 2014) and should be taken into consideration when choosing an appropriate treatment.

The main limitation of our study is the relatively small sample size of our cohort, particularly of pain-free patients (n = 7), which might also be responsible for the lack of between-group differences in VPN volume and other measures. Due to the cross-sectional nature of our study, information about pain duration was not available and longer pain duration might be associated with more severe thalamic affection.

It has to be noted, that patients included in this study were chosen (as described in "Methods") from our research database, which however does not include all patients suffering from AQP4-IgG-positive NMOSD that are followed and treated in our center. Inclusion criteria to our database following patients with NMOSD and related disorders are age between 18 and 70 years, exclusion criteria comprise significant comorbidities (medically not controlled severe arterial hypertonia, severe diabetes mellitus, chronic infectious diseases, drug abuse, and severe psychiatric or psychological disorders), MRI contraindications, as well as medical or psychological constraints to give informed consent to study participation and to fulfill the study protocol. Study participation is voluntary and thus a potential selection bias of participating patients cannot be excluded. There is, however, no obvious reason to assume that patients willing to participate in a longitudinal observational study are significantly different in their disease characteristics than patients not willing to participate.

Still, to assess how representative the patients included in the current study are, we checked the frequency of myelitis and neuropathic pain and compared it to the scientific literature. Interestingly, all 32 AQP4-IgG-positive patients included in our analysis, both with and without neuropathic pain, had a history of myelitis at baseline. This is a high proportion of myelitis for AQP4-IgG-positive NMOSD. However,

first the disease duration at baseline visit was around 6 years. A frequency of 89% for myelitis after a median disease duration of 4.8 years in 92 AQP4-IgG-positive patients has been reported previously. (Borisow et al., 2018) Second, we excluded patients with non-neuropathic pain conditions. Two excluded AQP4-IgG-positive NMOSD patients with non-neuropathic pain conditions did not have a history of myelitis, which leads to a percentage of 95% of history of myelitis among all our AQP4-IgG-positive patients. Third, the study is conducted by the Neuroimmunology Group at Charité, which may indicate a bias towards patients with neurological symptoms (e.g. LETM) versus patients who are primarily seen only by ophthalmologists (e.g. isolated ON).

Furthermore, we could not assess the structure of other strategic brain/brainstem regions that might be involved in the generation of central pain (like insula, periaqueductal grey matter etc.). Finally, pain medication can influence the relation of measures of pain intensity and VPN volume. However, the proportion of patients on medication was small and none of the pain patients under medication was pain-free.

The main strength of our study is that we assessed both thalamic and spinal cord structural measures in a well characterized cohort of AQP4-IgG-positive NMOSD patients, and that we used a novel and highly reliable atlas-based automated segmentation approach for the VPN assessment. (Chakravarty et al., 2013, Papadopoulou et al., 2019)

5. Conclusion

In summary, our study suggests that the thalamic VPN influences the severity of neuropathic pain in patients with AQP4-IgG-positive NMOSD. Moreover, we confirm the high prevalence of neuropathic pain and its association with spinal cord lesions in NMOSD.

Author statement

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SA received conference registration fees from Celgene and speaking fees from Bayer and Roche, unrelated to this project.

JK received conference registration fees from Biogen and financial research support from Krankheitsbezogenes Kompetenznetzwerk Multiple Sklerose (KKNMS), unrelated to this project.

LG is currently an employee of F. Hoffmann-La Roche Ltd. (not during her work on this paper).

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SM received travel support from Biogen and Genzyme and is currently an employee of F. Hoffmann-La Roche Ltd. (not during his work on this paper).

JW is CEO of MIAC AG Basel, Switzerland. He served on scientific advisory boards of Actelion, Biogen, Sanofi-Aventis/Genzyme, Idorsia, Novartis, and Roche.

FP serves on the scientific advisory board for Novartis; received speaker honoraria and travel funding from Bayer, Novartis, Biogen Idec, Teva, Merck Serono, Alexion, Chugai, MedImmune, and Shire; is an academic editor for PLoS ONE; is an associate editor for Neurology® Neuroimmunology & Neuroinflammation; consulted for SanofiGenzyme, Biogen Idec, MedImmune, Shire, and Alexion; and received research support from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Alexion, Merck Serono, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis of the USA.

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AUB is cofounder and shareholder of medical technology companies Motognosis GmbH and Nocturne GmbH. He is named as inventor on several patent applications describing MS serum biomarkers, perceptive visual computing and retinal image analysis.

CC, DK, NS, MC, and MSch have nothing to disclose.

Declaration of Competing Interest

None.

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Supplementary materials

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