Received: 20 April 2021 | Accepted: 22 September 2021

DOI: 10.1111/ene.15127

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Characterization and quantification of alcohol-related polyneuropathy by magnetic resonance neurography

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Funding information
The study was supported in part by the Medical Faculty of the University of Heidelberg (Olympia Morata stipend grant to J.K.) and the German Research Foundation (SFB 1118 to S.H., SFB 1158 to J.M.E.J. and M.B.)

Abstract

Background: We characterized and quantified peripheral nerve damage in alcohol-dependent patients (ADP) by magnetic resonance neurography (MRN) in correlation with clinical and electrophysiologic findings.

Methods: Thirty-one adult patients with a history of excessive alcohol consumption and age-/sex-matched healthy controls were prospectively examined. After detailed neurologic and electrophysiologic testing, the patient group was subdivided into ADP with alcohol-related polyneuropathy (ALN) and without ALN (Non-ALN). 3T MRN with anatomical coverage from the proximal thigh down to the tibiotalar joint was performed using dual-echo 2-dimensional relaxometry sequences with spectral fat saturation. Detailed quantification of nerve injury by morphometric (cross-sectional area [CSA]) and microstructural MRN markers (proton spin density [ρ], apparent T2-relaxation-time [$T2_{app}$]) was conducted in all study participants.

Results: MRN detected nerve damage in ADP with and without ALN. A proximal-to-distal gradient was identified for nerve T2-weighted (T2w)-signal and $T2_{app}$ in ADP, indicating a proximal predominance of nerve lesions. While all MRN markers differentiated significantly between ADP and controls, microstructural markers were able to additionally differentiate between subgroups: tibial nerve ρ at thigh level was increased in ALN ($p < 0.0001$) and in Non-ALN ($p = 0.0052$) versus controls, and $T2_{app}$ was higher in ALN versus controls ($p < 0.0001$) and also in ALN versus Non-ALN ($p = 0.0214$). T2w-signal and CSA were only higher in ALN versus controls.

Conclusions: MRN detects and quantifies peripheral nerve damage in ADP in vivo even in the absence of clinically overt ALN. Microstructural markers ($T2_{app}$, ρ) are most suitable for differentiating between ADP with and without manifest ALN, and may help to elucidate the underlying pathomechanism in ALN.

KEYWORDS
alcoholic neuropathy, electrophysiology, magnetic resonance neurography, polyneuropathy, quantitative imaging markers

INTRODUCTION

Alcohol-related polyneuropathy (ALN) is the second most common polyneuropathy (PNP) in the United States and is present in 25%–66% of individuals with alcohol dependence (alcohol-dependent patients [ADP]) [1]. It is characterized by slowly progressive, sensory-dominant symptoms and often incapacitating pain, while motor weakness and autonomic dysfunction occur at later stages [2,3]. Typically, electrophysiologic and histopathologic findings indicate an axonal neuropathy with predominant small-fiber loss, explaining the painfulness of the disease [4]. The exact pathophysiology of ALN is still unclear, but a multifactorial genesis including malnutrition, thiamine deficiency, and direct neurotoxic effects of ethanol and its metabolites is discussed [1].

The diagnostic gold standard in the assessment of PNPs is based on neurologic examinations and nerve conduction studies (NCS); however, well-known limitations make detecting early nerve lesions and identifying spatial nerve lesion patterns difficult [5,6]. Nerve biopsies are limited to functionally less relevant distal nerves and may not be indicated in patients with a typical clinical history. To date, comprehensive data on the exact extent and distribution of peripheral nerve lesions in ALN are not available, making the understanding of the pathomechanism challenging.

High-resolution magnetic resonance neurography (MRN) overcomes the typical limitations of conventional diagnostics by directly visualizing peripheral nerve lesions in vivo [5,7–12]. In this study, we aimed to characterize, localize, and quantify peripheral nerve lesions in ADP with and without ALN by MRN in correlation with clinical scores and electrophysiologic results, and in comparison with healthy controls.

METHODS

Study design, neurologic, electrophysiologic, and laboratory assessments

This prospective case-control study was approved by an institutional ethics board (University of Heidelberg; S-037/2018), and written informed consent was obtained from all participants according to the Declaration of Helsinki.

Thirty-one consecutive adult ADP who met the diagnostic criteria for alcohol dependence according to the Diagnostic Statistical Manual of Mental Disorders (DSM-IV; 21 males, 10 females, mean age 51.1 ± 2.1 years, range 27–74 years) were enrolled from May 2018 to January 2020 at the Department of Addictive Behavior and Addiction Medicine of the Central Institute of Mental Health Mannheim. Exclusion criteria were age <18 years, pregnancy, additional illegal drug consumption as excluded by urine drug screening and patient information, prior treatment with neurotoxic agents, concomitant causes of PNP such as diabetes mellitus, severe hypothyroidism, vitamin B12 deficiency, malignant or infectious diseases, and contraindications for magnetic resonance imaging (MRI). Twenty age- and sex-matched healthy volunteers (14 males, 6 females, 48.2 ± 2.6 years, range 30–67 years) were recruited upon public announcement by the Department of Neuroradiology of the Heidelberg University Hospital.

A detailed medical history was taken in all patients including specifications on the total duration of alcohol consumption, day of last consumption, quantity of alcohol consumption in grams per day, and tobacco use in pack years (J.M.B.; Table 1). Neurologic examinations included assessments for the Total Neuropathy Score (TNS), the Neuropathy Disability Score (NDS), the Neurological Severity Score (NSS), and the Neuropathy Impairment Score of the Lower Limbs (NIS-LL; A.B.). Motor NCS assessed distal motor latencies (DML), compound muscle action potentials (CMAP), nerve conduction velocities (NCV), and F waves of the left and right tibial and peroneal nerve. Sensory nerve action potentials (SNAPs) and NCVs were measured for the left and right sural nerve (G.S., M.W.; Table 1). Autonomic dysfunction was assessed by testing the palmar and plantar sympathetic skin response (SSR; A.B.) [13].

Blood samples were collected from all patients and levels of cholesterol, vitamins B1, B6, B12, folic acid, and glycated hemoglobin (HbA1c) were measured to exclude nutritional or metabolic causes for the development of a PNP.

MRN protocol

All participants underwent high-resolution MRN in a 3.0 Tesla MR-scanner (Magnetom PRISMA, Siemens-Healthineers) by using a 15-channel transmit-receive extremity coil (INVIVO) and the following sequence for T2-relaxometry:

Axial dual-echo turbo spin echo two-dimensional sequence with spectral fat saturation with four continuous slabs at the left leg: slab 1: proximal to mid-thigh; slab 2: mid to distal thigh with alignment of the distal edge of this imaging slab on the tibiofemoral joint space; slab 3: lower leg with alignment of the proximal edge with the tibiofemoral joint space; and slab 4: ankle with alignment of the distal edge on the tibiotalar joint space. One additional slab was acquired at the right leg with coverage from mid to distal thigh (same position as slab 2). Sequence parameters were: repetition time 5860 ms, lower echo time (TE_1) 14 ms, higher TE (TE_2) 86 ms, field-of-view 170×170 mm^2, matrix-size 512×512, slice thickness 3.5 mm, inter-slice gap 0.35 mm, voxel-size $0.3 \times 0.3 \times 3.5$ mm^3, flip angle 180°, 35 slices, acquisition time per slab 8:25 min.

The net acquisition time including survey scans was 44:39 min, with a total examination time of approximately 60 min per participant due to coil repositioning.

Image post-processing and analyses

MRN images were analyzed with FMRIB Software Library (FSL) software [14]. Tibial and peroneal fascicles of the left sciatic nerve and their distal continuation as either tibial (TN) or peroneal nerve (PN)

TABLE 1 Demographic, clinical, and electrophysiologic data

Parameter	ADP	ALN	Non-ALN	*P* value ALN vs. Non-ALN
Age (years)	51.1 ± 2.1	50.8 ± 2.1	52.2 ± 6.8	0.67 (ns)
Sex (M/F)	21/10	16/9	5/1	NA
Body weight (kg)	84.8 ± 2.9	83.4 ± 3.3	90.7 ± 5.6	0.30 (ns)
Height (cm)	174.0 ± 1.4	174.4 ± 1.7	172.5 ± 1.9	0.45 (ns)
Body mass index (kg/m²)	27.9 ± 0.9	27.4 ± 1.0	30.3 ± 1.4	0.11 (ns)
Duration of heavy drinking (years)	20.2 ± 2.4	20.3 ± 2.7	19.5 ± 5.6	0.65 (ns)
Last consumption before examination (months, 0 for persistent consumption)	1.5 ± 0.7	1.8 ± 0.9	0.5 ± 0.3	0.64 (ns)
Amount of alcohol (g/day)	180.6 ± 22.5	173.3 ± 24.5	208.3 ± 58.7	0.55 (ns)
Pack years (0 for non-smoking)	13.2 ± 2.9	16.7 ± 3.3	0.0 ± 0.0	0.0077*
Thiamine (reference value 28–85 μg/L)	81.63 ± 3.6	80.46 ± 4.0	86.33 ± 8.3	0.85 (ns)
Vitamin B12 (reference value >150 pmol/L)	364.3 ± 24.0	381.8 ± 21.3	291.5 ± 86.0	0.10 (ns)
HbA1c (reference value <6.5%)	5.4 ± 0.1	5.3 ± 0.1	5.5 ± 0.2	0.52 (ns)
TNS (range 0–40)	9.0 ± 1.3	10.4 ± 1.4	0.5 ± 0.5	0.0003***
NDS (range 0–8)	3.4 ± 0.5	3.8 ± 0.5	0.8 ± 0.8	0.0093*
NSS (range 0–10)	2.2 ± 0.5	2.6 ± 0.5	0.0 ± 0.0	0.0430*
NIS-LL (range 0–88)	8.7 ± 1.8	10.0 ± 2.0	0.4 ± 0.4	<0.0001***
SSR (positive)	3	3	0	NA
SNAP (μV)				
LSN	10.2 ± 1.2	10.1 ± 1.4	10.4 ± 1.5	0.69 (ns)
RSN	11.5 ± 1.3	11.2 ± 1.4	13.5 ± 2.9	0.35 (ns)
CMAP (mV)				
LTN	15.5 ± 1.4	15.9 ± 1.6	13.3 ± 1.9	0.48 (ns)
RTN	15.2 ± 1.3	15.2 ± 1.5	15.3 ± 3.6	0.92 (ns)
LPN	7.0 ± 0.7	6.5 ± 0.7	9.8 ± 1.1	0.08 (ns)
RPN	6.0 ± 0.6	5.5 ± 0.7	9.1 ± 1.0	0.0432*
DML (ms)				
LTN	3.7 ± 0.1	3.6 ± 0.1	3.7 ± 0.2	0.68 (ns)
RTN	3.4 ± 0.2	3.4 ± 0.2	3.4 ± 0.1	0.58 (ns)
LPN	4.0 ± 0.1	4.1 ± 0.1	3.6 ± 0.2	0.07 (ns)
RPN	3.8 ± 0.2	3.8 ± 0.2	3.5 ± 0.2	0.08 (ns)
F-wave (ms)				
LTN	50.2 ± 1.0	50.6 ± 1.1	48.5 ± 2.2	0.26 (ns)
RTN	49.5 ± 1.0	50.3 ± 1.1	45.1 ± 1.3	0.0489*
LPN	48.3 ± 1.0	49.1 ± 1.0	43.9 ± 1.3	0.0329*
RPN	47.9 ± 1.1	48.8 ± 1.1	43.2 ± 1.9	0.0390*
NCV (m/s)				
LTN	47.9 ± 0.9	47.4 ± 1.1	50.4 ± 1.4	0.36 (ns)
RTN	49.1 ± 0.7	48.6 ± 0.7	52.4 ± 1.8	0.11 (ns)
LPN	46.3 ± 0.8	45.3 ± 0.9	51.2 ± 1.0	0.0011*
RPN	46.6 ± 0.8	45.7 ± 0.8	52.3 ± 0.9	0.0029*
LSN	48.9 ± 1.1	49.3 ± 1.2	47.1 ± 2.6	0.42 (ns)
RSN	50.1 ± 1.0	50.0 ± 1.1	50.9 ± 2.9	0.41 (ns)

Abbreviations: ADP, alcohol-dependent patients; ALN, alcohol-related polyneuropathy; CMAP, compound muscle action potential; DML, distal motor latency; HbA1c, glycated hemoglobin; LPN, left peroneal nerve; LSN, left sural nerve; LTN, left tibial nerve; NA, not applicable; NCV, nerve conduction velocity; NDS, Neuropathy Disability Score; NIS-LL, Neuropathy Impairment Score of the Lower Limbs; Non-ALN, no signs of alcohol-related polyneuropathy; NSS, Neurological Severity Score; RPN, right peroneal nerve; RSN, right sural nerve; RTN, right tibial nerve; SNAP, sensory nerve action potential; SSR, sympathetic skin response; TNS, Total Neuropathy Score.

Significance: ns, not significant; *significant; ***highly significant.

with coverage from the proximal thigh down to the distal ankle were manually segmented on 140 axial slices per leg by one neuroradiologist (C.R.) blinded to the clinical data. Slice numbering for the TN was from 0 (most proximal slice at the proximal thigh) to 139 (most distal slice at the ankle), while the PN was evaluated from slice positions 0 to 69 (knee level). To exclude side differences, the TN and PN were additionally segmented on 35 axial slices from mid- to distal thigh level on the right side. This region was chosen as previous studies in different neuropathies identified nerve lesions predominantly at thigh level [11,15].

Signal quantification

Signal quantification was performed by calculating the apparent T2 relaxation time ($T2_{app}$) and proton spin density (ρ) according to the following two formulas by using data from the relaxometry sequence with TE_1 set at 14 ms and TE_2 set at 86 ms [16,17]:

$$T2_{app} = \frac{TE_2 - TE_1}{\ln\left(\frac{SI(TE_1)}{SI(TE_2)}\right)}$$

$$\rho = \frac{SI(TE_1)}{\exp\left(\frac{TE_1}{T2_{app}}\right)}.$$

Mean values of nerve ρ and $T2_{app}$ were calculated per slice position for each participant. Subsequently, we compared averaged mean TN ρ and $T2_{app}$ values of the thigh (imaging slabs 1 and 2, slice positions 0–69) to respective mean values of the lower leg (imaging slabs 3 and 4; slice positions 70–139) to test for potential location-dependent differences along the proximal-to-distal course of the TN. The PN was evaluated from the proximal thigh to the knee (imaging slabs 1 and 2). In the same way, mean values for nerve T2w-signal, the single most established yet not directly quantifiable MRN marker, were additionally calculated.

Morphometric quantification

Signal-independent, morphometric quantification of nerve caliber was performed by measuring the cross-sectional area (CSA) of the TN on each axial slice. The CSA of the PN was analyzed at the thigh only.

Statistical analyses

Statistical data analyses were performed with GraphPad Prism 8.4.2 (J.K., J.M.H.). Differences between ADP and controls, left and right distal thigh, as well as thigh and lower leg were evaluated with the Mann–Whitney test. Further subgroup analyses between ADP with ALN, ADP without ALN, and healthy controls were performed by using a one-way ANOVA for a priori assumptions. Subsequent post hoc analyses were corrected for multiple comparisons using the Tukey–Kramer test which allows for the possibility of unequal sample sizes. Pearson's correlation coefficients were calculated for correlation analyses. Statistical tests were two-tailed and an alpha level of significance was defined at $p < 0.05$. All results are documented as mean values ±SEM.

RESULTS

Clinical and electrophysiologic data

According to neurologic and electrophysiologic examination results, 25 of the 31 ADP were diagnosed with ALN, while 6 participants had no signs of a PNP (Non-ALN). Ten ADP with ALN had normal electrophysiologic results, but were classified as having PNP based on clinical findings. Detailed demographic, clinical, and electrophysiologic data are shown in Table 1. HbA1c, thiamine, and vitamin B12 levels were in physiologic ranges in all ADP (Table 1).

MRN data

Signal quantification: proton spin density (ρ)

The ρ of the TN and PN at thigh level was markedly increased in ADP versus controls (Table 2, Figure 1a). At lower leg level, TN ρ was higher in ADP versus controls (Table 2, Figure 1b). ANOVA revealed marked differences in ρ between ALN, Non-ALN, and controls at thigh (TN: $F = 20.70$; PN: $F = 17.82$; $p < 0.0001$, respectively) and lower leg level (TN: $F = 7.566$, $p = 0.0010$). In detail, ρ at thigh level was higher in ALN versus controls (TN and PN: $p < 0.0001$) and higher in Non-ALN versus controls (TN: $p = 0.0052$; PN: $p = 0.0190$), while we observed no differences between ALN and Non-ALN (Table 2, Figure 1c). At lower leg level, ρ of the TN differentiated well between ALN and controls ($p = 0.0008$), but not between Non-ALN and controls ($p = 0.12$) or between ALN and Non-ALN (Table 2, Figure 1d). A proximal-to-distal gradient or side differences in TN or PN ρ at mid- to distal thigh level were not identified in ADP or controls ($p > 0.05$).

Signal quantification: apparent T_2-relaxation time ($T2_{app}$)

The $T2_{app}$ of the TN and the PN was higher in ADP versus controls at the thigh (Figure 1e), but not at the lower leg (Table 2, Figure 1f). ANOVA revealed marked differences between the three subgroups at the thigh (TN: $F = 11.02$; PN: $F = 14.53$; $p < 0.0001$ for both nerves, respectively; Figure 1g), but not at the lower leg (TN: $F = 2.110$, $p = 0.13$; Figure 1h). Further post hoc comparisons showed that $T2_{app}$ at thigh level was higher in ALN versus controls (TN and

TABLE 2 Summary of magnetic resonance neurography results in alcohol-dependent patients, alcohol-related polyneuropathy, and no signs of alcohol-related polyneuropathy patients

Parameter	Controls	ADP	*P* value Controls vs. ADP	Non-ALN	ALN	*P* value ALN vs. Non-ALN
T2w-signal (ms)						
TN thigh	121.2 ± 3.9	136.5 ± 2.7	$p = 0.0004^{***}$	128.3 ± 4.9	138.1 ± 3.1	$p = 0.40$ (ns)
TN LL	110.2 ± 2.9	121.2 ± 3.0	$p = 0.0125^{*}$	115.9 ± 3.1	122.7 ± 3.7	$p = 0.58$ (ns)
PN thigh	122.1 ± 3.5	137.1 ± 2.4	$p = 0.0015^{*}$	129.5 ± 8.5	138.6 ± 2.8	$p = 0.41$ (ns)
ρ (a.u.)						
TN thigh	407.6 ± 6.3	474.4 ± 7.1	$p < 0.0001^{***}$	464.5 ± 10.6	476.4 ± 8.2	$p = 0.77$ (ns)
TN LL	408.0 ± 8.4	461.0 ± 10.0	$p = 0.0002^{***}$	452.0 ± 18.4	463.5 ± 11.8	$p = 0.86$ (ns)
PN thigh	410.0 ± 8.2	482.3 ± 9.1	$p < 0.0001^{***}$	470.8 ± 28.8	490.9 ± 9.2	$p = 0.62$ (ns)
$T2_{app}$ (ms)						
TN thigh	69.6 ± 0.8	76.3 ± 1.3	$p = 0.0046^{*}$	69.8 ± 2.3	77.6 ± 1.4	$p = 0.0214^{*}$
TN LL	67.6 ± 1.2	69.6 ± 1.1	$p = 0.18$ (ns)	66.3 ± 2.9	70.5 ± 1.1	$p = 0.23$ (ns)
PN thigh	66.7 ± 0.8	74.1 ± 1.3	$p = 0.0003^{***}$	66.9 ± 1.9	75.6 ± 1.4	$p = 0.0064^{*}$
CSA (mm^3)						
TN thigh	59.6 ± 1.2	67.3 ± 1.4	$p = 0.0004^{***}$	65.9 ± 3.0	67.6 ± 1.6	$p = 0.87$ (ns)
TN LL	34.0 ± 1.5	35.6 ± 1.0	$p = 0.25$ (ns)	33.2 ± 2.0	36.2 ± 1.1	$p = 0.50$ (ns)
PN thigh	27.5 ± 1.0	33.0 ± 0.9	$p = 0.0003^{***}$	31.6 ± 1.2	33.2 ± 1.1	$p = 0.74$ (ns)

Abbreviations: ADP, alcohol-dependent patients; ALN, alcohol-related polyneuropathy; a.u., arbitrary unit; CSA, cross-sectional area; LL, lower leg; Non-ALN, no signs of alcohol-related polyneuropathy; PN, peroneal nerve; $T2_{app}$, apparent T2-relaxation time; T2w, T2-weighted; TN, tibial nerve; ρ, proton spin density.

Significance: ns, not significant, *significant, ***highly significant.

PN: $p < 0.0001$), and higher in ALN versus Non-ALN (Table 2), but no differences existed between Non-ALN and controls (TN and PN: $p = 0.99$, respectively). In ADP, $T2_{app}$ of the TN showed a decrease from proximal (thigh) to distal (lower leg; $p = 0.0025$), while no such gradient existed in controls ($p = 0.08$). Side differences in $T2_{app}$ did not exist in ADP or controls ($p > 0.05$).

Semi-quantitative MRN marker: T2w-signal

Nerve T2w-signal separated well between ADP and controls at thigh and lower leg level (Table 2, Figure 2a,b, Figure 3). One-way ANOVA revealed distinct differences between subgroups at proximal and distal locations (thigh, TN: F = 6.329, $p = 0.0028$; PN: F = 6.667, $p = 0.0021$; lower leg, TN: F = 3.880, $p = 0.0247$). At thigh level, post hoc comparisons revealed a higher T2w-signal in ALN versus controls (TN: $p = 0.0019$; PN: $p = 0.0014$). Differences between Non-ALN and controls (TN: $p = 0.63$; PN: $p = 0.58$), as well as between ALN and Non-ALN were not observed (Table 2, Figure 2c, Figure 3). At lower leg level, TN T2w-signal was higher in ALN versus controls ($p = 0.0183$), but differences were absent between Non-ALN and controls ($p = 0.68$), as well as between ALN and Non-ALN (Table 2, Figure 2d). A proximal-to-distal decrease in TN T2w-signal was observed in ADP ($p < 0.0001$) but not in controls ($p = 0.11$). Side differences were not detected ($p > 0.05$). Nerve lesion distribution in ADP was heterogenous and diffuse, with pathologically T2w-hyperintense nerve fascicles being located next to normointense-appearing nerve fascicles on nerve cross-sections (Figure 3).

Morphologic quantification: cross-sectional area (CSA)

The CSA of the TN and PN at thigh level was markedly higher in ADP than in controls (Figure 4a), while differences between the two groups were not observed at the lower leg (Table 2, Figure 4b). Further subgroup analyses revealed marked CSA differences at thigh level (TN: F = 6.852, $p = 0.0018$; PN: F = 7.915, $p = 0.0007$; Figure 4c), but not at the lower leg (TN: F = 1.068, $p = 0.35$; Figure 4d). Further post hoc comparisons identified an increased CSA at the thigh in ALN compared to controls (TN: $p = 0.0012$; PN: $p = 0.0005$), while no differences existed between Non-ALN and controls (TN: $p = 0.19$; PN: $p = 0.20$), as well as between ALN and Non-ALN (Table 2). Side differences were not observed for ADP or controls ($p > 0.05$).

Correlation analyses

We found no correlation between age, sex, body weight, body height, or body mass index (BMI) of ADP with any of the evaluated MRN makers. The duration of heavy drinking, total lifetime alcohol amount, and time since last alcohol consumption had no measurable

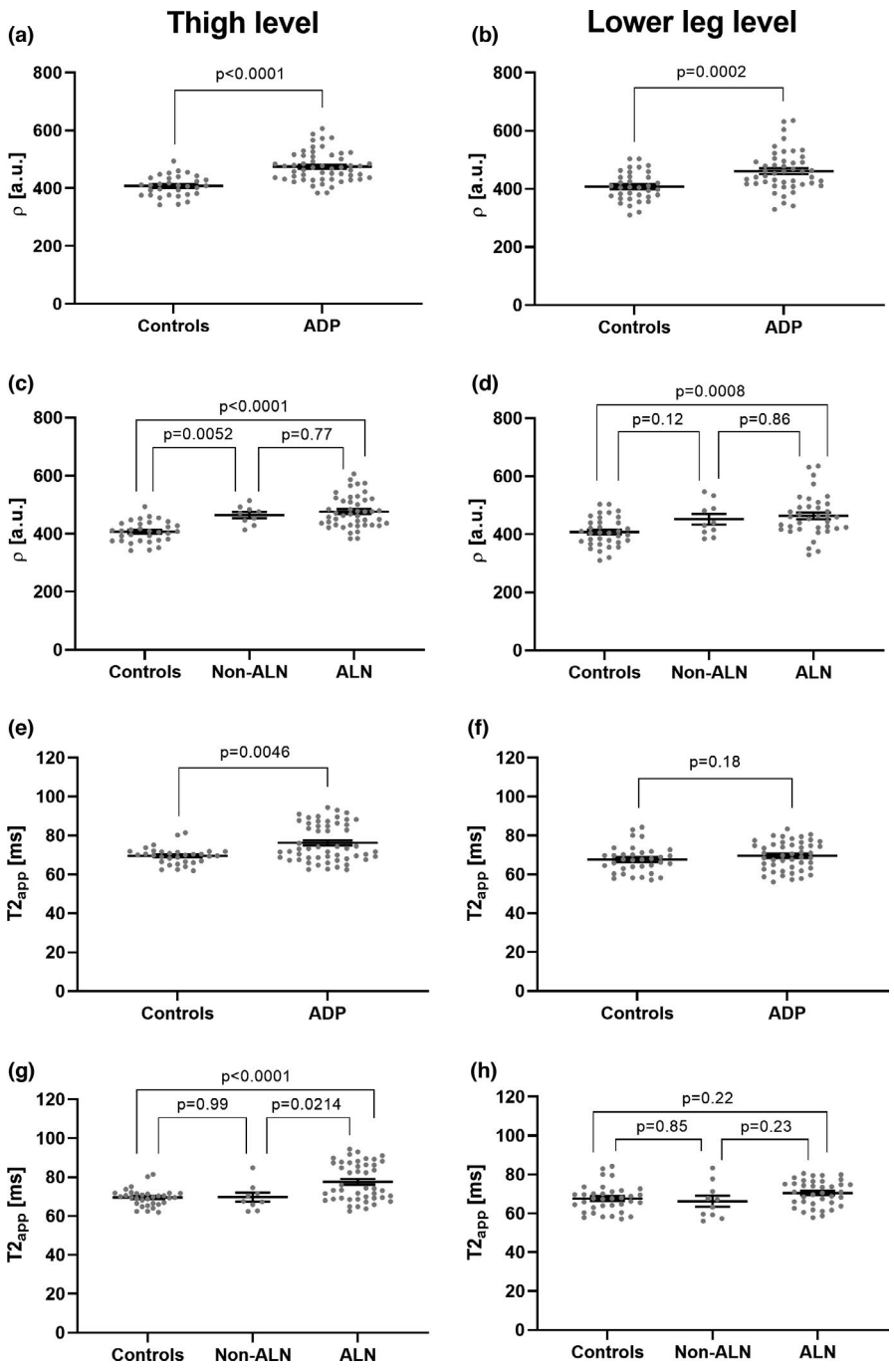

FIGURE 1 Signal quantification. Mean values of tibial nerve proton spin density (ρ) and apparent T2-relaxation-time ($T2_{app}$) were plotted at thigh (ρ: a, c; $T2_{app}$: e, g) and lower leg level (ρ: b, d; $T2_{app}$: f, h) for controls and alcohol-dependent patients (ADP) (ρ: a, b; $T2_{app}$: e, f) as well as for controls, patients without alcohol-related polyneuropathy (Non-ALN) and alcohol-related polyneuropathy (ALN) patients (ρ: c, d; $T2_{app}$: g, h). ρ was clearly higher in ADP than in controls and also higher in ALN versus controls in both proximal and distal locations. In addition, ρ differentiated well between Non-ALN and controls when measured in the tibial nerve at the thigh. In contrast, differences in tibial nerve $T2_{app}$ between ADP and controls, and between ALN and controls, were only found at the thigh. Here, $T2_{app}$ was also higher in ALN than in Non-ALN patients. Error bars represent SEM. Significant differences are indicated by *p* values

influence on MRN parameters. A positive correlation was found between nicotine consumption and proximal TN $T2_{app}$ ($r = 0.3452$; $p = 0.0106$), while no correlation existed with HbA1c, thiamine, and vitamin B12 levels. Besides positive correlations between the NSS and lower leg TN T2w-signal ($r = 0.3555$; $p = 0.0174$), ρ ($r = 0.3277$; $p = 0.0299$), and CSA ($r = 0.5084$; $p = 0.0004$), we identified no consistent correlations with other neuropathy symptom scores. Left TN F-waves correlated with TN ρ at the thigh ($r = 0.3223$; $p = 0.0351$) and lower leg ($r = 0.3752$; $p = 0.0264$), as well as with TN T2w-signal at the lower leg ($r = 0.4345$; $p = 0.0102$), while F-waves of the right TN correlated with TN ρ ($r = 0.3736$; $p = 0.0227$) and T2w-signal ($r = 0.4379$; $p = 0.0077$) at the lower leg. Negative correlations were found between the NCV of the right ($r = -0.1256$; $p = 0.0339$) and left TN ($r = -0.3266$; $p = 0.0485$) with the lower leg TN $T2_{app}$, and between CMAPs of the left TN and the TN CSA at the lower leg ($r = -0.3838$; $p = 0.0229$).

DISCUSSION

ALN accounts for the second most common PNP, and it is likely that the PNS of ADP is affected long before the first PNP symptoms occur [1]. While different pathophysiologic pathways are under debate, the exact pathomechanism of peripheral nerve

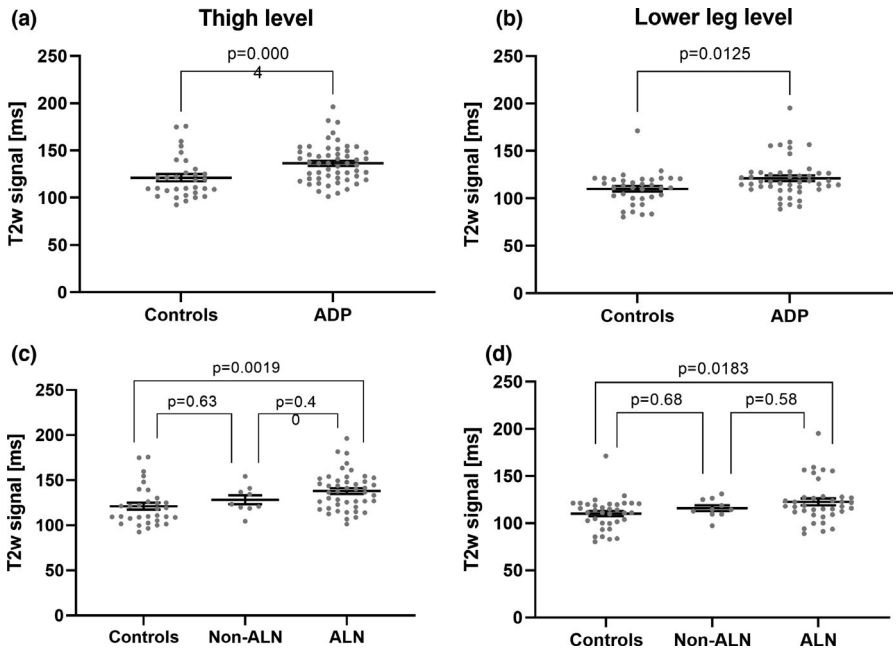

FIGURE 2 T2-weighted (T2w)-signal. Mean values of T2w-signal of the left tibial nerve at thigh (a, c) and lower leg level (b, d) are plotted for controls and alcohol-dependent patients (ADP) (a, b) as well as for the subgroups consisting of controls, patients without alcohol-related polyneuropathy (Non-ALN) and alcohol-related polyneuropathy (ALN) patients (c, d). Tibial nerve T2w-signal was clearly increased in ADP compared to controls in both anatomical regions. When evaluating the different subgroups, T2w-signal differentiated well between ALN and controls, but not between Non-ALN and controls or between Non-ALN and ALN patients. Error bars represent SEM. Significant differences are indicated by *p* values

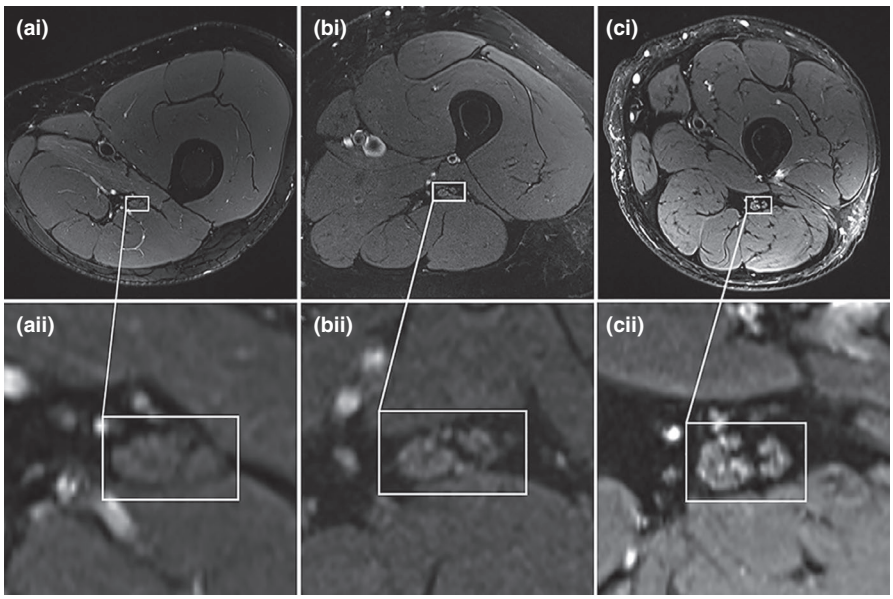

FIGURE 3 Magnetic resonance neurography (MRN) source images. Representative MRN images (axial dual-echo turbo spin echo relaxometry sequences with spectral fat saturation) at left mid-thigh level are shown at equal slice positions in a healthy control (a(i), a(ii)), an alcohol-dependent patient (ADP) without alcohol related polyneuropathy (Non-ALN); b(i), b(ii)) and an ADP with alcohol-related polyneuropathy (ALN) (c(i), c(ii)). The first row presents complete cross-sectional images of the respective thigh, while the details in the second row show the tibial and peroneal fascicles within the sciatic nerve as indicated by the white boxes. While only very few T2-weighted (T2w) hyperintense fascicles are visible in the Non-ALN patient (b(ii)), a clearly increased T2w-signal in multiple sciatic nerve fascicles can be observed in a representative ALN patient (c(ii)). a(i) shows a healthy control with a regular T2w-signal of the sciatic nerve that is similar to the signal of the surrounding muscles

injury in ADP is still unknown [1]. Reliable biomarkers for early diagnosis as well as ALN monitoring are not yet available, and comprehensive histopathologic data of peripheral nerve lesions in ADP do not exist. However, a better understanding of the pathomechanism together with an earlier diagnosis of ALN would be highly relevant and contribute to an improved management of these patients.

Here we report that high-resolution MRN characterizes and quantifies lower extremity peripheral nerve lesions in ADP with and without ALN. Our results show that all MRN markers differentiate well between ADP and controls. However, only the quantitative microstructural markers ρ and $T2_{app}$ were able to differentiate between subgroups. In detail, while both ρ and $T2_{app}$ were markedly increased in ALN compared to controls, only ρ was higher in Non-ALN

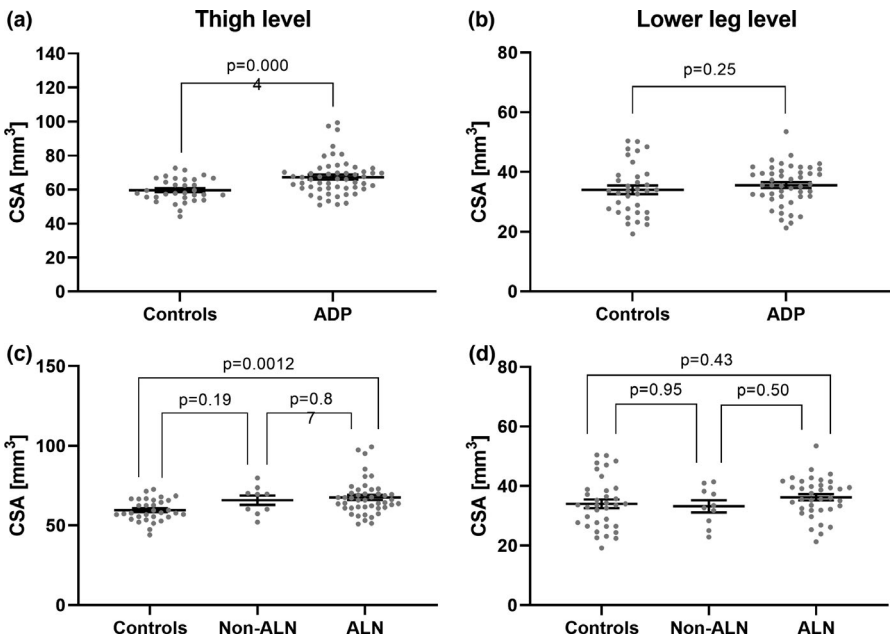

FIGURE 4 Morphometric quantification. Mean values of tibial nerve cross-sectional areas (CSA) at thigh (a, c) and lower leg level (b, d) are plotted for controls and alcohol-dependent patients (ADP) (a, b) as well as for controls, patients without alcohol-related polyneuropathy (Non-ALN), and alcohol-related polyneuropathy (ALN) patients (c, d). At thigh level, tibial nerve CSA was markedly higher in ADP versus controls, and also in ALN versus controls, while no such differences existed at the lower leg or between other subgroups. Error bars represent SEM. Significant differences are indicated by *p* values

versus controls (Figure 1c), and only $T2_{app}$ was higher in ALN versus Non-ALN (Figure 1g). T2w-signal and CSA were also increased in ADP versus controls, but did not distinguish between subgroups (Figures 3 and 4).

From central nervous system (CNS) studies, ρ and $T2_{app}$ are known as distinct microstructural markers of nerve tissue integrity [16–18]. After successful implementation in the PNS in patients with hereditary transthyretin (ATTRv) amyloidosis [11], we validated them in other diffuse neuropathies such as diabetic PNP or light-chain amyloidosis, where they reliably correlated with disease severity [15,19]. The exact mechanism leading to an alteration of ρ and $T2_{app}$ is still unknown, but most CNS studies concluded that changes in ρ and $T2_{app}$ are induced by changes in the density and macromolecular composition of nerve tissue [16–18]. In PNPs, such a variation in macromolecules with a subsequent increase of ρ might be caused, for example, by an accumulation of proteins in hereditary or systemic amyloidosis [11,19] or by an accumulation of glycosylated end-products in diabetes [9,15].

The observed alteration of microstructural MRN markers in ALN has similarly been described in PNPs of other origin. In detail, ρ seems to be most sensitive for an early nerve lesion detection: It was previously found to identify asymptomatic carriers of the variant *transthyretin*-gene in ATTRv amyloidosis [11,12] and is now the only parameter that can distinguish between clinically and electrophysiologically completely asymptomatic Non-ALN patients and healthy controls. A likely explanation for the increased ρ in Non-ALN patients is that nerve lesions, altered in their macromolecular composition, accumulate over time, but remain clinically unapparent until a certain threshold is exceeded. Further evidence that ρ is the most sensitive marker comes from the observed positive correlation between TN ρ and F-waves, as F-waves often show abnormalities long before NCVs are reduced. $T2_{app}$, on the other hand, was only increased in symptomatic ALN, and inversely correlated with NCVs as indicators of more advanced disease stages. This is in line with previous studies where an additional increase of $T2_{app}$ was only identified in manifest PNP, potentially caused by the occurrence of an endoneural edema at more advanced PNP stages [11,12,19].

In other non-PNP diseases with PNS involvement, the direction of change in quantitative MRN markers (i.e., an increase or decrease in ρ and/or $T2_{app}$) was also specific and seemingly reflected the underlying pathomorphology. A study conducted by our group in multiple sclerosis (MS), found an increased ρ (similar to the results found in PNPs) and a decreased $T2_{app}$ (opposing to the results in PNPs) in lower extremity nerves, excluding an endoneural edema as the predominant pathomechanism of PNS lesions [20]. Instead, an inflammatory process leading to an impaired blood–nerve barrier with subsequent leakage of plasma proteins was favored as a potential explanation. Additionally, as a post-mortem study found an increased ρ in demyelinated areas in the CNS of MS patients [21], we hypothesized a potential peripheral co-demyelination to be the origin of the observed increase in sciatic nerve ρ [20]. Another study conducted in 5q-linked spinal muscular atrophy (SMA), a motor neuron disease of degenerative etiology, revealed a decreased ρ (opposing to the results in PNPs), and an increased $T2_{app}$ (similar to the results in PNPs) in the PNS of these patients [10]. Again, the observed specific alteration of microstructural markers can be well explained with the decay of lower motor neurons and axonal loss in SMA [10]. However, etiology-specific alterations of microstructural markers in different PNP have not yet been reported. Here, ongoing studies evaluating diffusion tensor or magnetization transfer contrast imaging might increase the diagnostic accuracy in the future.

In ALN, the pathomechanism is still not sufficiently understood. Histopathologic and electronmicroscopy studies point towards direct axonal damage by ethanol and its metabolites followed by secondary demyelination of sensory and motor nerve fibers [22]. Acetaldehyde, an important metabolite in the degradation of ethanol, binds

irreversibly to proteins, creating cytotoxic proteins that adversely affect the function of nerve cells [1]. A subsequent deceleration of the axoplasmic flow in combination with the degradation of axonal enzymes and proteins is hypothesized to be the origin of the secondary demyelination [22]. This alcohol-induced accumulation of altered proteins, together with demyelinating processes at later stages, might explain the observed increase in nerve ρ in the present study.

Additional nutritional aspects are discussed in the literature, but the results are inconclusive. While thiamine deficiency has known neurotoxic effects [23], axonal degeneration and PNP occurred in a rat model of alcoholism despite an adequate nutrition status [24]. In our study, malnutrition was also a negligible factor as all ADP had a normal BMI, and serum levels of glucose, HbA1C, and important B vitamins were in the physiologic ranges. We cannot exclude an existing thiamine deficiency during the patients' time of chronic alcohol intake as all ADP were treated with vitamin B1 supplements for approximately 1 week starting from the day of their admission, and therewith prior to the conduction of MRN and electrophysiologic examinations. However, a multifactorial genesis of ALN including nutritional and genetic factors is discussed in the literature, potentially explaining that the amount of alcohol did not correlate with clinical or electrophysiologic findings [25,26].

One of the problems in diagnosing and treating ALN is the lack of validated clinical symptom scores that represent the severity and functional impairment in ALN. While the NIS-LL is validated for amyloidotic and diabetic PNP, the NDS and NSS for diabetic PNP, and the TNS for neurotoxic PNP under chemotherapy, it is unclear which score is best suitable for ALN. The positive correlation between MRN markers (ρ, T2w-signal, CSA) with the NSS, and the missing correlation with any of the other symptom scores, might point towards a greater importance of using the NSS in ALN.

Previous MRN studies gathered information on the proximal-to-distal distribution of nerve lesions only from evaluations of the semi-quantitative T2w-signal [5,11,15,19,20]. In the present study, we performed an additional signal quantification from proximal thigh to distal ankle, showing a clear proximal-to-distal gradient in ADP for nerve T2w-signal and, more importantly, for $T2_{app}$. Such a gradient was not found in controls, pointing towards a proximal predominance of nerve lesions in ALN, a phenomenon that we previously identified in other PNPs [11,15,19]. However, group differences in T2w-signal and ρ were also observed at the lower leg, indicating the involvement of the whole lower extremity nerves in ALN.

The cross-sectional study design limits any interpretation regarding the temporal development of ALN so that it remains unclear when first PNS lesions occur in ADP. This would be particularly interesting as some ADP present with polyneuropathic symptoms soon after starting their chronic alcohol abuse, while others remain asymptomatic despite a long history of heavy alcohol consumption, similar to a phenomenon described for alcohol-induced brain atrophy [27,28]. Therefore, longitudinal studies in long-term ADP who are still active drinkers, and in ADP who have just started their chronic alcohol abuse, would be desirable. In addition, the majority of our patients were alcohol-dependent since their 30s, so that MRN findings could be potentially different if patients became addicted to alcohol earlier in their lives. Another limitation is the small sample size in our Non-ALN group, potentially explaining why (i) differences between ALN and Non-ALN were only observable for $T2_{app}$ and (ii) results from NCS failed to reach consistent statistical significance between ALN and Non-ALN.

Our study provides a comprehensive in vivo characterization of peripheral nerve damage in ADP by applying high-resolution MRN and by analyzing different signal-dependent (ρ, $T2_{app}$) and signal-independent (CSA) quantitative markers in relation to clinical and electrophysiologic findings. While the most established MRN markers, T2w-signal and CSA, can differentiate between ADP and healthy controls, the microstructural markers ρ and $T2_{app}$ are better suited to differentiate between ALN, Non-ALN, and controls. Furthermore, these microstructural markers might contribute to a better understanding of the underlying pathomechanism in ALN as they seemingly reflect the altered protein composition combined with axonal damage and demyelination in ALN.

ACKNOWLEDGEMENT

Open access funding enabled and organized by Projekt DEAL. WOA Institution: UNIVERSITATSKLINIKUM HEIDELBERG Blended DEAL: Projekt DEAL.

CONFLICT OF INTEREST

C.R. reports no disclosures relevant to this work. J.M.B. reports no disclosures relevant to this work. M.W. reports no disclosures relevant to this work. A.B. reports no disclosures relevant to this work. G.S. reports no disclosures relevant to this work. J.M.H. reports no disclosures relevant to this work. A.P. reports no disclosures relevant to this work. K.K.-J. reports no disclosures relevant to this work. J.M.E.J. reports grants from the German Research Foundation (SFB1158) and the International Foundation for Research in Paraplegia (IRP). S.H. received a research grant from the German Research Foundation (SFB 1118). F.K. reports no disclosures relevant to this work. M.B. reports personal fees from Boehringer Ingelheim; grants and personal fees from Novartis and Guerbet; grants from Siemens, the Hopp Foundation, the German Research Foundation (SFB 1158), the European Union, and Stryker; and personal fees from Merck, Bayer, Teva, BBraun, Vascular Dynamics, Grifols, and Neuroscios. J.K. received a research grant, personal fees, lecture honoraria, and financial support for conference attendance from Alnylam Pharmaceuticals, the Olympia Morata stipend grant from the Medical Faculty of the University of Heidelberg, lecture honoraria and financial support for conference attendance from Pfizer, and advises for Akcea Therapeutics.

AUTHOR CONTRIBUTIONS

Christian Rother: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Visualization (supporting); Writing-original draft (equal). **Jan Malte Bumb:** Data curation (supporting); Investigation (supporting); Writing-review & editing (equal). **Markus Weiler:** Data curation (equal);

Investigation (equal); Methodology (equal); Validation (equal); Writing-review & editing (equal). **Anna Brault:** Data curation (supporting); Investigation (supporting); Writing-review & editing (equal). **Georges Sam:** Data curation (equal); Investigation (supporting); Writing-review & editing (equal). **John M. Hayes:** Data curation (supporting); Formal analysis (supporting); Methodology (supporting); Visualization (equal); Writing-review & editing (equal). **Adriana Pietsch:** Data curation (equal); Investigation (supporting); Methodology (supporting); Writing-review & editing (equal). **Kianush Karimian-Jazi:** Methodology (supporting); Visualization (supporting); Writing-review & editing (equal). **Johann M. E. Jende:** Data curation (supporting); Writing-review & editing (equal). **Sabine Heiland:** Data curation (supporting); Formal analysis (supporting); Funding acquisition (equal); Investigation (equal); Methodology (equal); Writing-review & editing (equal). **Falk Kiefer:** Data curation (supporting); Investigation (supporting); Validation (equal); Writing-review & editing (equal). **Martin Bendszus:** Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal); Validation (equal); Writing-review & editing (equal). **Jennifer Kollmer:** Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (equal); Investigation (lead); Methodology (lead); Project administration (lead); Resources (equal); Software (equal); Supervision (lead); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

All data used to conduct this study are documented in the Methods section. Additional anonymized datasets will be shared at the request of any qualified investigator.

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How to cite this article: Rother C, Bumb JM, Weiler M, et al. Characterization and quantification of alcohol-related polyneuropathy by magnetic resonance neurography. *Eur J Neurol*. 2022;29:573–582. https://doi.org/10.1111/ene.15127