Quantitative sensory testing predicts histological small fiber neuropathy in postural tachycardia syndrome

Sophia C.I. Billig, Joana C. Schauer mann, Roman Rolke, MD, Istvan Katona, MD, Jörg B. Schulz, MD, and Andrea Maier, MD

Correspondence

Dr. Maier
amaier@ukaachen

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Abstract

Background

Retrospective investigation of the somatosensory profile and prediction of histologic small fiber neuropathy (SFN) in postural orthostatic tachycardia syndrome (POTS) was performed using quantitative sensory testing (QST) as a standardized noninvasive test.

Methods

In this investigation, full data sets from 30 patients (age: 34.03 ± 10.82 years, $n = 6$ males), including results of autonomic function testing, norepinephrine values, skin biopsy, and QST, were retrospectively analyzed. The QST data were compared with healthy controls (HCs) (age: 34.20 ± 10.5 years, $n = 6$ males, t test: 0.95).

Results

The evaluation of all QST parameters in POTS compared with HCs yielded differences in all thermal parameters (cold detection threshold: $p < 0.05$, warm detection threshold: $p < 0.001$, thermal sensory limen: $p < 0.001$, cold pain threshold: $p < 0.05$, and heat pain threshold: $p < 0.001$) and in paradoxical heat sensations ($p < 0.05$). Differences in nonpainful stimuli (mechanical detection threshold: $p < 0.05$ and vibration detection threshold: $p < 0.001$) were also detected. All patients who had clinical signs of SFN in combination with impairment of small fibers in QST also had SFN on skin biopsy.

Conclusion

These results suggest that a non-region-specific SFN in POTS compared with controls can be detected by noninvasive QST that predicts histologic small fiber pathology.

With an estimated prevalence of 0.2%,¹ postural orthostatic tachycardia syndrome (POTS) is one of the most common autonomic disorders; POTS particularly affects young women² and is associated with symptoms such as palpitations, dizziness³ or pre-/syncope⁴ with upright posture. Diagnostic criteria for different POTS subtypes are distinct; although heterogeneous pathophysiologic concepts have been discussed, universal criteria for its classification and their significance for diagnosis and therapy are still not established.^{5–8} POTS often coexists with other diseases, e.g., small fiber neuropathy (SFN).⁷ In previous reports, a reduced

Department of Neurology (SCIB, JCS, AM, JBS), Department of Neuropathology (IK), Department of Palliative Care (RR), RWTH Aachen University; Research Training Group 2416 MultiSenses-MultiScales (JBS), Aachen; and Forschungszentrum Jülich GmbH (JBS), JARA-Brain Institute Molecular Neuroscience and Neuroimaging, Jülich, Germany.

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intraepithelial nerve fiber density (rIENFD) was described in up to 45% of patients with POTS.^{4,7}

Whereas a skin biopsy is an invasive diagnostic test, quantitative sensory testing (QST) is a standardized noninvasive test⁹ designed to diagnose SFN.¹⁰ It can be performed easily and analyzed immediately, detecting small fiber dysfunction in neuropathies.^{5,7} Whether QST can differentiate patients with POTS from healthy controls (HCs) and predict an rIENFD or an SFN in POTS has yet to be investigated.

The absence of a distal to proximal gradient in sudomotor dysfunction might suggest an immune-mediated process in POTS.⁷ Thus, we wondered if there was a distinct somatosensory profile suggestive of possible pathomechanisms,

such as localized peripheral vs generalized nerve fiber damage, in POTS compared with HC.

Methods

Neurophysiologic and clinical parameters from 65 patients with POTS diagnosed and treated in the autonomic center in Aachen, Germany, between January 2013 and August 2017 were retrospectively analyzed.

Of these 65, 30 patients (age: 34.03 ± 10.82 years, $n = 6$ male) fulfilled the inclusion criteria (with full data sets). These included a diagnosis of idiopathic POTS based on the 2015 Heart Rhythm Society Expert Consensus Statement¹ with symptomatic increase in heart rate >30 beats per minute

Table 1 Demographic, laboratory, cardiovagal, and sympathoneural data of all patients with POTS with a full data set (POTS cohort, $n = 30/65$ screened) and comparison of patients with POTS with nIENFD vs rIENFD intraepithelial nerve fiber density

	POTS cohort $n = 30$	nIENFD $n = 13/30$ (43.33%)	rIENFD $n = 17/30$ (56.67%)
Demographics			
Age, y	34.03 ± 10.82	36.8 ± 12.94	31.8 ± 8.68
Sex	24 female (80.00%), 6 male (20.00%)	11 female (84.62%), 2 male (15.38%)	13 female (76.47%), 4 male (23.53%)
Laboratory			
IENFD, fiber/mm	6.06 ± 3.17	$9.03 \pm 2.07^{**}$	$3.78 \pm 1.53^{**}$
NE supine, pg/mL	276.77 ± 111.51	307 ± 104.90	253.65 ± 113.90
NE upright, pg/mL	651.86 ± 315.79	699.85 ± 162.61	615.16 ± 397.00
Sympathoneural			
Mean supine systolic BP, mm Hg	113.14 ± 30.82	112.14 ± 32.14	113.90 ± 30.74
Mean supine diastolic BP, mm Hg	65.95 ± 21.46	69.79 ± 11.41	71.31 ± 13
Mean HR supine, beats/min	71.94 ± 25.03	75.14 ± 11.27	69.49 ± 9.45
Max systolic BP change, mm Hg	-26.90 ± 20.10	-26.44 ± 11.81	-27.26 ± 25.04
Max diastolic BP change, mm Hg	-12.12 ± 12.30	-11.62 ± 5.70	-12.50 ± 15.75
Max HR raise, beats/min	46.27 ± 12.73	47.16 ± 15.50	45.60 ± 10.60
Max BP change mean systolic, mm Hg	1.22 ± 10.96	0.01 ± 12.15	2.14 ± 10.23
Max BP change mean diastolic, mm Hg	9.40 ± 5.62	8.45 ± 5.41	10.11 ± 5.83
Cardiovagal			
RSA difference RRmax/RRmin, ms	246.13 ± 158.08	180.46 ± 84.30	296.35 ± 183.79
HR variability supine, ms	7.85 ± 2.73	$6.77 \pm 1.41^*$	$8.67 \pm 3.22^*$
Valsalva quotient (RRmax/RRmin)	1.95 ± 0.39	1.98 ± 0.35	1.92 ± 0.42
Ewing 30:15 quotient	1.19 ± 0.16	1.21 ± 0.19	1.18 ± 0.13

Abbreviations: BP = blood pressure; HR = heart rate; nIENFD = normal intraepithelial nerve fiber density; NE = norepinephrine; rIENFD = reduced intraepithelial nerve fiber density; RR = Riva Rocci; RSA = respiratory sinus arrhythmia.

Data are presented as the mean $\pm$ SD.

* $p < 0.05$, ** $p < 0.001$.

within 10 minutes of an upright tilt or a heart rate >120 beats per minute in the absence of orthostatic hypotension accompanied by orthostatic symptoms for at least 6 months. In addition, sympathoneural and cardiovagal data from tilt testing, norepinephrine (NE) values supine and upright, and IENFD of skin biopsies were evaluated by an expert in this field; furthermore, QST was performed as recommended by the German Research Network on neuropathic pain, and the results of a comprehensive autonomic history as well as a physical examination focusing on possible SFN⁵ had to be available. Exclusion criteria were secondary POTS (e.g., induced by anemia, sensorimotor polyneuropathy detected by reduced vibration sensation/pallesthesia, and/or electrophysiologic studies), hyperthyroidism, and medications causing tachycardia.

Clinical tests in the autonomic center Aachen were always performed using standardized conditions as follows. Cardiovascular autonomic testing was performed in the morning on an empty stomach using standardized conditions¹¹: morning medications, caffeine intake, and smoking were not allowed 12 hours before the test. We continuously measured blood pressure and heart rate with a Finometer MIDI (Finapres Medical Systems B.V., Enschede, Netherlands) and fan 4.1.0 (BioSign GmbH, Ottenhofen, Germany). Heart rate variability was measured during deep breathing, consisting of 6 inspirations per minute, and the means of the differences between the maximum and minimum heart rate at rest (coefficient of variation), in an upright position (Ewing coefficient), and during a Valsalva maneuver (Valsalva coefficient) were documented. After 5 minutes in the supine position, the tilt table was tilted up at 70° for at least 15 minutes. Maximum and mean systolic and diastolic blood pressure and heart rate changes were measured by the difference in the medium blood pressure or heart rate in the supine position and the minimum/mean blood pressure or maximum/mean heart rate during 10 minutes in the standing position. NE levels were measured after at least 10 minutes in the supine position (NE supine) and 10 minutes of active standing (NE standing) to measure any orthostatic NE increase.

Skin biopsies of at least 3 mm diameter were taken from the right distal leg 10 cm above the lateral malleolus.^{12,13} The intraepithelial nerve fiber density was analyzed using standard PGP9.5 immunofluorescence.^{13,14} Local anesthesia was applied for the skin biopsy with up to 0.5 mL prilocaine and epinephrine (Xylonest; Aspen Germany GmbH, Munich, Germany). An rIENFD was defined by a value below the normal range adjusted for age and sex.¹³

For QST, a panel of 11 tests with calibrated thermal or mechanical stimuli imitating natural ones was performed⁹ on one hand and foot.¹² The data were diagnosed as pathologic if they were not within the normal range (95% confidence range), and they were analyzed as described previously.¹² The results of the QST were compared with age- and sex-matched standard values of 30 HC (age: 34.20 ± 10.5 years, n = 6 male) derived from the clinic internal database.

Figure QST in POTS (n = 30, except for CDT, WDT, TSL, CPT, HPT n = 29)

At the hand and foot, the z-profile in QST shows a generalized and combined large fiber neuropathy and small fiber neuropathy for nonpainful thermal and mechanical stimuli (CDT, WDT, TSL, and MDT) and thermal pain thresholds, which were transmitted by combined C- and Aδ-fibers. CDT = cold detection threshold; CPT = cold pain threshold; DMA = dynamic mechanical allodynia; HPT = heat pain threshold; MDT = mechanical detection threshold; MPS = mechanical pain sensitivity; MPT = mechanical pain threshold; PHS = paradoxical heat sensation; POTS = postural orthostatic tachycardia syndrome; PPT = pressure pain threshold; QST = quantitative sensory testing; TSL = thermal sensory limen; VDT = vibration detection threshold; WDT = warm detection threshold; WUR = wind-up ratio.

According to previously proposed definitions,⁵ the diagnosis of SFN required at least 2 of the following 3 conditions, thus indicating impairment of Aδ and C fibers:

1. Clinical signs, such as distal sensory loss, reduced temperature or pinprick sensitivity in clinical examination, and/or pain or tingling in the distal extremities
2. An rIENFD on skin biopsy compared with age-dependent normative values^{13,15}
3. A pathologic QST in which the values of the patients with POTS deviated from the standard of HC with the same age and sex.

Correlations of IENFD with NE levels and other cardiovascular parameters were assessed using the Spearman rank correlation coefficient with IENFD as the determining factor. The non-parametric group differences between rIENFD vs nIENFD were compared using a Mann-Whitney *U* test. QST parameters were normally distributed in logspace and transformed logarithmically before statistical analysis.¹⁶ QST data were compared with sex and age corresponding normative values (POTS: 34.03 vs HC: 34.20, both: 6 male; *t* test: 0.95). We converted QST data into z-scores and conducted analysis of variance with the Fisher *least significant difference* post hoc test. All data are

displayed in the text as the mean $\pm$ SD. Sensitivity, specificity, and diagnostic efficiency for diagnosing SFN in POTS according to the abovementioned gold standard criteria⁵ with QST, IENFD, and/or clinical abnormalities were calculated.

Statistical analyses were performed using the software application IBM SPSS Statistics Version 25.0 and Statistica software for Windows 7.1 (StatSoft, Inc) with a p value of ≤ 0.05 set as the threshold for statistical significance.

Standard protocol approvals, registrations, and patient consents

All patients were able to understand the instructions. This investigation was performed in accordance with the Declaration of Helsinki and good clinical practice and approved by the Institutional Review Board of RWTH Aachen University (EK 101/15, EK 101/17, and EK101/18).

Data availability

The data that support the findings of this article are available within the article. Raw data were generated at RWTH Aachen University. Derived anonymized raw data supporting the findings of this study will be shared by request from the corresponding author.

Results

Of the 30 included patients with POTS, 56.67% ($n = 17$, 4 male) had an rIENFD (in fiber/mm), 36.67% had

The evaluation of all QST parameters in POTS compared with HC aimed to recognize a pattern of symptoms in somatosensory dysfunction of small fibers ($A\delta$ and C fibers) and large fibers ($A\beta$).

a pathologic QST ($n = 11$, 1 male), and 56.67% ($n = 17$, 3 male) had clinical signs of SFN. There were no correlations between IENFD and autonomic or clinical parameters, as shown in table 1. Patients with rIENFD did not differ from nIENFD with regard to age, sex, or laboratory values, as presented in table 1. Patients with POTS with rIENFD had an increased heart rate variability in the supine position (in ms, 8.67 ± 3.22 ; $p < 0.05$; Mann-Whitney U), but the other parameters did not differ between groups.

The evaluation of all QST parameters in POTS compared with HC aimed to recognize a pattern of symptoms in somatosensory dysfunction of small fibers ($A\delta$ and C fibers) and large fibers ($A\beta$). Findings yielded differences in all thermal parameters (cold detection threshold: $p < 0.05$,

Table 2 Somatosensory profile of patients with POTS ($n = 30$ for all parameters but CDT, WDT, TSL, CPT, HPT [only $n=29$]) vs HCs ($n = 30$): evaluation of all QST parameters in POTS vs HC indicated a generalized small fiber neuropathy (hand > foot), a large fiber neuropathy, and a non-region-specific thermal hypalgesia without interactions in POTS

Parameters in QST	POTS vs HC					
	(1) Main factor group ("between factor")		(2) Main factor region (hand vs foot; "within factor")		(1) + (2) Interaction	
	F Value	p Value	F Value	p Value	F Value	p Value
Cold detection threshold	5.69	<0.05	<0.001	n.s.	<0.001	n.s.
Warm detection threshold	15.3	<0.001	0.89	n.s.	0.89	n.s.
Thermal sensory limen	12.3	<0.001	1.43	n.s.	1.43	n.s.
Cold pain threshold	7.53	<0.05	1.27	n.s.	1.27	n.s.
Heat pain threshold	15.52	<0.001	0.99	n.s.	0.98	n.s.
Pressure pain threshold	0.14	n.s.	<0.001	n.s.	<0.001	n.s.
Mechanical pain threshold	0.34	n.s.	0.97	n.s.	0.98	n.s.
Mechanical pain sensitivity	0.86	n.s.	1.23	n.s.	1.23	n.s.
Wind-up ratio	1.22	n.s.	1.17	n.s.	1.18	n.s.
Mechanical detection threshold	5.27	<0.05	0.91	n.s.	0.92	n.s.
Vibration detection threshold	14.68	<0.001	1.49	n.s.	1.47	n.s.

Abbreviations: CDT = cold detection threshold; CPT = cold pain threshold; HC = healthy control; HPT = heat pain threshold; n.s. = not significant; QST = quantitative sensory testing; TSL = thermal sensory limen; WDT = warm detection threshold.

* $p < 0.05$, ** $p < 0.001$.

Table 3 QST data of patients with POTS (n = 30, except for CDT, WDT, TSL, CPT, HPT n = 29) vs HCs (n = 30)

QST parameter (expressed in log ^a)	POTS vs HC			
	Hand		Foot	
	POTS	HC	POTS	HC
Cold detection threshold (°C in log from BL)	0.22 ± 0.23*	0.08 ± 0.28*	0.48 ± 0.30*	0.35 ± 0.25*
Warm detection threshold (°C in log from BL)	0.45 ± 0.30*	0.22 ± 0.24*	0.81 ± 0.23*	0.66 ± 0.22*
Thermal sensory limen (°C log)	0.62 ± 0.27*	0.47 ± 0.26*	1.03 ± 0.27*	0.83 ± 0.23*
Pressure pain threshold (kPa log)	2.58 ± 0.14	2.59 ± 0.14	2.69 ± 0.17	2.70 ± 0.16
Mechanical pain threshold (mN log)	1.86 ± 0.41	1.89 ± 0.40	1.75 ± 0.42	1.86 ± 0.40
Mechanical pain sensitivity (pain rating 0–100 log)	−0.18 ± 0.45	−0.02 ± 0.39	−0.15 ± 0.49	−0.07 ± 0.41
Wind-up ratio (ratio log)	0.42 ± 0.29	0.37 ± 0.25	0.58 ± 0.29	0.44 ± 0.27
Mechanical detection threshold (mN log)	0.06 ± 0.39*	−0.14 ± 0.35*	0.59 ± 0.58*	0.11 ± 0.54*
Dynamic mechanical allodynia (pain rating 0–100 log)	−0.99 ± 0.11	−0.98 ± 0.11	−0.99 ± 0.05	−0.99 ± 0.05

QST parameter (expressed in original units ^b)	POTS vs HC			
	Hand		Foot	
	POTS	HC	POTS	HC
Cold detection threshold (°C from BL)	−1.65	−1.20	−3.00	−2.25
Warm detection threshold (°C from BL)	2.80	1.65	6.5	4.56
Thermal sensory limen (°C)	4.18	2.93	10.74	6.75
Cold pain threshold (°C)	8.61 ± 8.65*	14.66 ± 9.19*	10.53 ± 9.74	15.05 ± 9.98*
Heat pain threshold (°C)	46.45 ± 4.04*	42.52 ± 3.57*	47.22 ± 3.29*	44.44 ± 3.13*
Pressure pain threshold (kPa)	382.54	393.28	485.33	503.72
Mechanical pain threshold (mN)	73.18	77.17	56.75	72.51
Mechanical pain sensitivity (pain rating 0–100)	0.67	0.9	0.72	0.86
Wind-up ratio (ratio)	2.62	2.33	3.76	2.73
Mechanical detection threshold (mN)	1.15	0.72	3.91	1.30
Vibration detection threshold (×/8)	7.27 ± 0.40	7.82 ± 0.37	6.51 ± 1.02	7.37 ± 0.80
Paradoxical heat sensations (×/3)	0.27 ± 0.51	0.00 ± 0.00	0.70 ± 0.74	0.17 ± 0.53
Dynamic mechanical allodynia (pain rating 0–100)	0.10	0.10	0.10	0.10

Abbreviations: BL = baseline; CDT = cold detection threshold; CPT = cold pain threshold; HC = healthy control; HPT = heat pain threshold; QST = quantitative sensory testing; TSL = thermal sensory limen; WDT = warm detection threshold.

Data are presented as the mean ± SD.

Patient data (POTS) and HC were measured at the hand and foot. BL temperature was 32°C; thermal detection thresholds are expressed as the derivation from this baseline temperature, where heat or cold was detected.

* $p < 0.05$.

^a No log-transformed data (CPT, WPT, VDT, and PHS) because of a normal distribution.

^b Retransformed mean for log-normally distributed data.

warm detection threshold: $p < 0.001$, thermal sensory limen: $p < 0.001$, cold pain threshold: $p < 0.05$, and heat pain threshold: $p < 0.001$) and in paradoxical heat sensations ($p < 0.05$ Fisher LSD post hoc test). Differences in nonpainful stimuli (mechanical detection threshold: $p < 0.05$ and vibration detection threshold: $p < 0.001$ in the Fisher LSD post hoc test) were also detected, as shown in the figure and tables 2 and 3.

Furthermore, 46.67% ($n = 14$, 3 male) were diagnosed as having an SFN. Of these 14 patients, this diagnosis was based on clinical signs of SFN in combination with an rIENFD in 50.0% ($n = 7$, 3 male), an rIENFD combined with a pathologic QST in 14.3% ($n = 2$, 0 male), or a combination of these 3 criteria in 35.7% ($n = 5$, 0 male). All patients with a pathologic QST combined with clinical symptoms of SFN had an rIENFD (16.7%, $n = 5/30$, 0 male; sensitivity = 35.7%,

POTS often coexists in combination with SFN, but its diagnosis and clinical relevance are still under investigation.

specificity = 100.0%, diagnostic efficiency = 70.0%). IENFD had the highest sensitivity (100.0%), specificity (81.3%), and diagnostic efficiency (90.00%), followed by clinical signs (85.7%, 68.8%, and 76.7%) and QST (53.9%, 75.0%, and 63.3%) for diagnosing an SFN in POTS.

Discussion

In this cohort, POTS predominantly affected women (4:1 ratio) with a mean age of 34 years, which is in line with other studies.^{2,6} The universal criteria for POTS classification are still not established. POTS often coexists in combination with SFN, but its diagnosis and clinical relevance are still under investigation. SFN can be diagnosed by a combination of clinical signs together with QST and an rIENFD on an invasive skin biopsy. In this sample, 56.7% of the patients had an rIENFD. This is slightly increased relative to the reported findings of an rIENFD in a skin biopsy taken from the same position in approximately 38%–45% of patients with POTS.^{4,7} Comparing patients with rIENFD vs nIENFD, only the increased heart rate variability in a supine position was different between groups, whereas other parameters were not conspicuously different.

In this report, QST was performed on the hands and feet, whereas others tested QST only on the feet.⁷ We detected differences in the somatosensory profile between POTS and HC. The thresholds of nonpainful stimuli and thermal pain thresholds were increased, confirming previous results.⁷ These results combined with noticeable differences in nonpainful stimuli are suggestive of an SFN rather than a large fiber neuropathy in POTS and indicate small fiber impairment in both hands and feet (table 2). In contrast, the mechanical pain thresholds transmitted by A β fibers did not differ from controls. As described above, the exact pathophysiology of POTS remains to be determined. POTS could be caused by an autoimmune process affecting small fibers in the hands, the feet, and even the heart.^{2,8,17,18} Antibodies may attach to different structures, such as adrenergic and muscarinic receptors, and result in various pathomechanisms, as already suspected.⁷ QST results in this analysis indicate a generalized SFN of the A δ nerves in the hands and feet, thus supporting these assumptions.

The distribution of SFN can be patchy; thus, IENFD may be normal because the specific biopsy side did not show rIENFD. In agreement with previous researchers⁵ who investigated IENFD clinical signs and QST in patients with

TAKE-HOME POINTS

- The evaluation of all QST parameters in POTS compared with healthy controls yielded differences in all thermal parameters.
- Differences in nonpainful stimuli were also detected.
- All patients who had clinical signs of SFN in combination with the impairment of small fibers in QST also had SFN on skin biopsy.
- A non-region-specific SFN in POTS compared with controls may be detected by noninvasive QST predicting histologic small fiber pathology.

SFN, IENFD has the best sensitivity for diagnosing SFN in POTS, followed by clinical symptoms and QST. Although rIENFD has the highest sensitivity, specificity, and diagnostic efficiency for diagnosing SFN in POTS, we suggest using noninvasive QST in combination with clinical signs in clinical practice for patients with POTS suspected to have SFN before performing invasive skin testing because in our POTS cohort, a pathologic QST in combination with clinical signs of SFN always predicted an rIENFD. Nonetheless, the lack of availability of specialized testing, such as QST and skin biopsies, limits their use in clinical practice.

Important limitations of this analysis are its retrospective character and small sample size, which do not allow the generalization of these data. Moreover, possible effects of drug treatment of POTS on small fibers were not considered.

Thus, larger prospective studies should examine whether QST is suitable for the noninvasive diagnosis of SFN in POTS, as it might predict histologic SFN. In further prospective studies aiming to understand the pathophysiology of POTS, it may be useful to investigate both distal and proximal skin biopsies as well as QST from the hands and feet combined with a screening for autoantibodies in a larger POTS cohort.

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Appendix Authors

Name	Location	Contribution
Sophia C.I. Billig	Department of Neurology, RWTH Aachen University, Germany	Designed and conceptualized the study; data collection; analyzed and interpreted the data; and wrote the original draft and revised the manuscript
Joana C. Schauermann	Department of Neurology, RWTH Aachen University, Germany	Data collection and revised the manuscript for intellectual content
Roman Rolke, MD	Department of Palliative Care, RWTH Aachen University, Germany	Analyzed and interpreted the data; administrative support; and revised the manuscript for intellectual content
Istvan Katona, MD	Department of Neuropathology, RWTH Aachen University, Germany	Analyzed the data
Jörg B. Schulz, MD	Department of Neurology, RWTH Aachen University, Germany; JARA-Brain Institute Molecular Neuroscience and Neuroimaging, Forschungszentrum Jülich GmbH/RWTH Aachen University, Germany; Research Training Group 2416 MultiSenses-MultiScales, RWTH Aachen University, Germany	Performed review of results; interpreted the data; revised the manuscript for intellectual content; and personal and administrative support

Appendix (continued)

Name	Location	Contribution
Andrea Maier, MD	Department of Neurology, RWTH Aachen University, Germany	Designed and conceptualized the study; data collection; analyzed and interpreted the data; and revised and edited the manuscript

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