Sleep Medicine 42 (2018) 83–89

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Somatosensory function is impaired in patients with idiopathic REM sleep behaviour disorder

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ARTICLE INFO

Article history:
Received 29 June 2017
Received in revised form
1 September 2017
Accepted 28 September 2017
Available online 28 October 2017

Keywords:
REM sleep behavior disorder
Parkinson's disease
Alpha-synucleinopathies
Quantitative sensory testing
Laser evoked potentials
Somatosensory function

ABSTRACT

Background: Idiopathic REM sleep behaviour disorder (iRBD) has been recognised as a significant biomarker for developing a neurodegenerative alpha-synucleinopathy, which is why iRBD is considered to be a prodromal state for alpha-synucleinopathies including Parkinson's disease (PD). Many patients with PD suffer from complaints of pain and present impaired somatosensory function. We hypothesized that pain perception and somatosensory function could be altered already in a preclinical stage of PD including iRBD. Hence, the objective of this study was to investigate pain perception and somatosensory function in patients with iRBD.

Methods: Quantitative sensory testing (QST), laser evoked potentials (LEPs), and conditioned pain modulation (CPM) testing were performed in 13 iRBD patients without any clinical signs of PD or narcolepsy (11 males, 2 females, mean age 65.2 years) and 15 gender- and age-matched healthy control subjects (12 males, 3 females, mean age 65.8 years).

Results: Thermal detection thresholds were higher in the iRBD group compared with the control group (cold detection threshold (CDT) $p = 0.020$, thermal sensory limen (TSL) $p = 0.001$), indicating an impaired temperature sensation in iRBD patients. The N2/P2 LEPs amplitude was smaller in iRBD patients than controls, but not statistically significant ($p = 0.053$).

Conclusions: This study found an impaired somatosensory function in iRBD patients, suggesting that somatosensory impairment might be an early feature in the neurodegenerative process of PD.

1. Introduction

REM sleep behaviour disorder (RBD) is characterized by loss of muscle atonia during rapid eye movement (REM) sleep (REM sleep without atonia, RSWA) documented by polysomnography (PSG) and presence of dream enactment (vocalizations and/or complex motor behaviour) [1,2]. Idiopathic RBD (iRBD) is an important predictor of neurodegenerative alpha-synucleinopathies including Parkinson's disease (PD), Lewy body dementia, and multiple system atrophy. Early reports have suggested that up to 80% of the iRBD patients develop a neurodegenerative disease [3–5]. RBD may be caused by involvement of the subcoeruleus nucleus and related structures thereby interfering with active REM inhibition of spinal motor neurons [6]. Thus, RBD may represent an early stage of an incipient synucleinopathy due to a dissemination of the alpha-synuclein pathology, starting in the medulla oblongata, pontine tegmentum, and olfactory bulb/anterior olfactory nucleus and then ascending to the mesencephalon, including substantia nigra and at last to the neocortex [7].

Patients with PD have preclinical symptoms for several years before the motor symptoms appear. The current treatment options for PD using dopaminergic drugs modify the symptoms, however they have no influence on the prognosis. Currently, no proven therapy modifies the neurodegenerative process when PD is clinically obvious. Preclinical diagnosis of PD would imply a potential for future neuroprotective agents. When PD is diagnosed, a

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https://doi.org/10.1016/j.sleep.2017.09.035

Abbreviations

CDT	cold detection threshold
CPM	conditioned pain modulation
CPT	cold pain threshold
DFNS	The German Research Network on Neuropathic Pain
HPT	heat pain threshold
IENFD	intraepidermal nerve fibre density
iRBD	idiopathic rapid eye movement sleep behaviour disorder
KSS	Karolinska Sleepiness Scale
LEPs	laser evoked potentials
MDI	Major Depression Inventory
MDT	mechanical detection threshold
MMSE	Mini-Mental State Examination
MPT	mechanical pain threshold
NRS	numerical rating scale
PD	Parkinson's disease
PPT	pressure pain threshold
PSQI	Pittsburgh Sleep Quality Index
QST	quantitative sensory testing
RBD	rapid eye movement sleep behaviour disorder
SFN	small fibre neuropathy
SIT-12	Sniffin' Sticks 12-identification test
TSL	thermal sensory limen
UPDRS-III	the motor part of the Unified Parkinson's Disease Rating Scale
VDT	vibration detection threshold
WDT	warm detection threshold
WUR	wind-up ratio

significant proportion of cellular destruction involving several parts of the brain stem including substantia nigra is apparent. Why any potential protective therapy should be presented years prior to onset of motor symptoms when the neural involvement is less certain. Therefore, early prodromal markers for PD are central. IRBD has the potential to provide a preclinical marker for alpha-synucleinopathy. Studies have found some other potential markers for incipient neurodegenerative synucleinopathy in patients with iRBD—for instance, as in PD, patients with iRBD have impaired olfaction [8–10] and autonomic disturbances [11].

Many patients with PD suffer from pain [12,13]. Studies in patients with PD have shown somatosensory abnormalities when examined with quantitative sensory testing (QST) [14]. PD patients present increased cold and warm detection thresholds compared with healthy control subjects, indicating that temperature sensation could be impaired in PD patients [15,16]. Studies examining cold and heat pain thresholds in PD patients are inconsistent; increased, decreased, and unaltered thresholds have been found [15–18]. A study with laser evoked potentials (LEPs) has found that patients with PD have lower N2/P2 amplitudes than healthy controls [19]. LEPs are the easiest and most reliable of the neurophysiological methods for assessing the function of nociceptive pathways [20]. It is unclear which parts of the nervous system and which mechanisms that are involved in PD patients' somatosensory deficits. One possible mechanism is that the dopaminergic denervation may lead to a loss of response specificity, resulting in transmission of less-differentiated and noisier information to cortical regions, thus causing increased thresholds [14]. Another potential mechanism is the degeneration of peripheral nerve endings. Moreover, a study analysing skin biopsies in patients with PD observed a reduced number of free and encapsulated nerve endings [16]. This suggests that a small fibre neuropathy could explain, at least in part, the sensory impairment in PD. Theoretically, a degenerative process in the brainstem could affect the descending pain inhibitory system, which can be experimentally measured with conditioned pain modulation (CPM) testing [21].

Furthermore, somatosensory function and pain perception could hypothetically be already changed in a preclinical stage of PD. Therefore, the objective of this study was to examine somatosensory function and pain perception, measured with QST, LEPs, and CPM, in patients with iRBD. If iRBD patients have an altered pain perception and sensory function compared with healthy control subjects, these parameters could be studied as potential prodromal diagnostic markers for later neurodegenerative disease. In addition, new knowledge about changed pain perception and sensory function in iRBD patients would contribute to a better pathophysiological understanding of pain and sensory impairment in PD.

2. Materials and methods

2.1. Subjects

Patients with a clinical diagnosis of iRBD were recruited from the Department of Neurology and Department of Clinical Neurophysiology, Aarhus University Hospital, the Department of Neurology, Viborg Regional Hospital, and Danish Center of Sleep Medicine, Glostrup Hospital, Denmark, between November 2015 and August 2016. The inclusion criteria were age between 40 and 80 years, history of dream-enacting behaviour, and REM sleep without atonia verified with video polysomnography in accordance to American Academy of Sleep Medicine [2]. Exclusion criteria, in both the patient and control group, were symptoms of Parkinson's disease (rigidity, rest tremor, bradykinesia, postural instability), any signs indicating peripheral neuropathy or a history of diabetes mellitus or alcoholism, severe psychiatric disorders, severe disease (cancer, cardiac/lung/renal insufficiency), narcolepsy, chronic pain (> 3 on the numerical rating scale (NRS), 0 = no pain, 10 = worst pain imaginable), and cognitive impairment (Mini-Mental State Examination (MMSE), cut-off score: <25).

Healthy sex- and age-matched subjects without a history of dream-enacting behaviour served as control group. By clinical history there was no evidence that the controls had RBD. All subjects gave their written informed consent prior to participation in the study. The study was approved by the Central Denmark Region Committees on Health Research Ethics (reference number: 1-10-72-180-15).

2.2. Sleep and neurological assessment

The day before the examination day, subjects completed two questionnaires: The Pittsburgh Sleep Quality Index (PSQI), which assesses sleep quality the preceding month, and the Major Depression Inventory (MDI). Immediately before the QST, the subjects rated their subjective level of sleepiness using the Karolinska Sleepiness Scale (KSS).

Neurological examination including the motor examination part of the Unified Parkinson's Disease Rating Scale from the International Parkinson and Movement Disorder Society (MDS-UPDRS Part III) was performed in both groups to ensure that the subjects did not have peripheral neuropathy or Parkinson's disease. The subjects' olfactory sense was examined with Sniffin' Sticks

12-identification test (SIT-12). Twelve common odours were presented, and then the subjects had to identify them by selecting from a list of four descriptors. Analgesics and pain, if any, were registered with pain localisation and rating of intensity (NRS 0–10).

2.3. Quantitative sensory testing

QST assesses and quantifies different nociceptive and non-nociceptive modalities of the somatosensory nervous system. Before testing, the subjects' reaction time was examined, as the reaction time may have an influence on thermal thresholds. The subjects let go of a button as soon as possible after the investigator activated a loud sound and a red light, and the reaction time was given in milliseconds. The averaged reaction time of three consecutive measurements was then calculated.

Testing was performed on the dorsum of the dominant hand using the QST protocol of the German Research Network on Neuropathic Pain (DFNS) [22]. The tests for vibration and thermal thresholds were also conducted on the dorsum of the dominant foot. The same investigator (AVS) conducted all the tests, which were always performed in the following order: cold detection threshold (CDT), warm detection threshold (WDT), thermal sensory limen (TSL), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), wind-up ratio (WUR), vibration detection threshold (VDT), and pressure pain threshold (PPT).

Standardised instructions to the subjects were used. Before testing in the test area, a demonstration of each test was performed at a practice area to ensure that the subjects were familiar with the testing procedure.

2.4. Laser evoked potentials

LEPs assess the function of nociceptive pathways. Cutaneous stimuli were delivered by a Nd:YAP laser (Neodimium:Yttrium-Aluminium-Perovskite; 1.34 μm wavelength, beam diameter 6 mm, 11 ms pulse duration (Stimul 1340, Electronic Engineering, Florence, Italy)) on the dorsum of the dominant hand. A red helium-neon laser confocal with the infrared beam visually indicated the irradiated area.

The subjects were asked to rate the pain after each stimulation using the NRS (0–10). The stimuli (a pinprick) elicited a moderately painful sensation; usually with a NRS score of 4–6. The energy intensities ranged from 13.26 to 18.57 J/cm^2. After each stimulus, the laser beam stimulation location was slightly shifted in a random direction to avoid skin damage and sensitization or fatigue of the nociceptors [23]. The interstimulus interval ranged from 20 to 30 s.

The subjects lay on a bed in a warm and silent room. They wore protective googles and were instructed to keep their eyes open and focus their attention on a spot on the wall and relax their facial muscles when the laser stimulation took place.

Laser evoked potentials were obtained using four surface recording electrodes placed over Cz, the temporal region contralateral to the stimulation site (T3 or T4), the frontoparietal region ipsilateral to the stimulation site (Fp1 or Fp2), and nasion. The N2 and P2 potentials were recorded by the Cz referred to the nasion electrode. Potential ocular artefacts were detected with an electrode located on the lower orbicularis oculi muscle and referred to an electrode on the cheek (electrooculogram). The software programme Keypoint.NET (Dantec, Skovlunde, Denmark) was used for the recordings.

Latencies of N2 and P2 and amplitudes of the N2/P2 complex were averaged from 15 artefact-free recordings. The analyses were done off-line. All examinations were first anonymized by the examiner (AVS), and then cursors were set in consensus by two specialists in clinical neurophysiology (MOT and HT), who were blinded about whether the recordings were from patients or healthy controls.

2.5. Conditioned pain modulation testing

CPM testing investigates the endogenous pain inhibitory pathway based on the "pain inhibits pain" phenomenon. The test stimulus is the term for the painful stimulus upon which the conditioning effect is tested. Mechanical pressure and heat were used as test stimuli [24]. Pressure pain threshold (PPT) was measured using a manual pressure algometer (Bridge amplifier, Somedic AB, Sweden) with a contact area of 1 cm^2. The testing was performed above the transverse part of the dominant trapezius muscle. During the pressure stimulation, subjects should press a button as soon as the pressure sensation became painful (PPT) whereby the pressure value was frozen on a digital display. The subjects were familiarised with the testing procedure with a demonstration on the non-dominant trapezius muscle. PPT was measured three times and a mean PPT was calculated. Heat pain threshold (HPT) was measured using a Thermal Sensory Analyser (TSA 2001-II, Medoc, Israel). The testing was done at the dominant volar forearm. The subjects were instructed to push a button as soon as the heat sensation became painful. HPT was measured three times and a mean HPT was calculated.

The conditioning stimulus is the term for the stimulus used to induce the change in pain perception. The conditioning stimulus was an ice water immersion (between −1 and 1 °C) of the non-dominant hand to wrist level. The subjects were instructed to keep the hand in the water for one minute or until the pain became unbearable. The duration of the water immersion was registered.

Immediately after the withdrawal of the hand from the ice water, PPT was measured on the dominant trapezius muscle using the same procedure as previously described. One minute after withdrawal of the hand, HPT was measured on the dominant volar forearm. Finally, PPT was measured two and three minutes after the end of the ice water immersion.

Conditioned pain modulation (CPM) is the term for the phenomenon through which the conditioning stimulus affects perception of the test stimuli. The calculation of the CPM response was conducted by subtracting the second test stimuli PPT and HPT from the first test stimuli PPT and HPT, thus the pain inhibition was denoted with a negative value [24].

After the CPM testing, subjects were asked to rate the maximum pain intensity and pain unpleasantness during the ice water bath on the NRS 0–10).

2.6. Statistical analysis

Statistical comparisons of continuous data between groups were performed using unpaired two-sample *t*-test (normal distribution) or Mann–Whitney *U* test (non-normal distribution) after testing for normal distribution using Q–Q plots. Categorical data were tested using Fisher's exact test. *p*-values below 0.05 were considered statistically significant. Statistical analysis was conducted using Stata version 13.2.

The raw QST data were via the programme eQuiSTA transformed into z-values based on a reference database of healthy controls, thus normalising for age, gender, and body location of testing [22]. The resulting z-scores are independent of the original units of measurements and are therefore useful for the creation of somatosensory profiles. The 95% confidence interval of z-values of reference controls is between −1.96 and +1.96. Z-scores above zero indicate hyperfunction (gain of function), which means that the subjects are more sensitive to the tested parameter than reference

controls (lower thresholds), whereas z-scores below zero indicate hypofunction (loss of function) and thereby lower sensitivity of the subjects compared with reference controls (higher thresholds) [25].

3. Results

3.1. Patients and controls

Thirteen patients (11 males, 2 females, mean age 65.2 years) with a clinical diagnosis of iRBD were included. In one patient, polysomnography had been performed without video. Fifteen healthy control subjects (12 males, 3 females, mean age 65.8 years) were included. None of the subjects showed signs of cognitive impairment using MMSE (cut-off score: <25 points). Demographic data did not differ significantly between the two groups (Table 1).

Four patients (two: unknown reasons; two: physical overload) and three controls (two: unknown reasons; one: physical overload) had experienced pain in the past 24 h. In this period, one subject from each group had taken mild analgesics (ibuprofen).

Six patients were treated with melatonin, and two patients were taking clonazepam. None of the patients received dopaminergic drugs, except for one patient who took a dopamine agonist for restless legs syndrome. Two of the iRBD patients were treated with selective serotonin reuptake inhibitors.

3.2. Clinical assessments and questionnaires

There was no significant difference in height between the two groups, although the iRBD patients weighed significantly more than the control subjects (Table 1).

Patients with iRBD had a higher UPDRS-III score compared with controls (Table 1). Patients scored lower than controls in the Sniffin' Sticks odour identification test (Table 1).

Sleep quality the preceding month (PSQI, Table 1) and subjective level of sleepiness (KSS, Table 1) did not differ significantly between iRBD patients and controls. There was no significant difference in the MDI score between the two groups (Table 1).

3.3. Quantitative sensory testing

Patients with iRBD had a significantly higher CDT and TSL on the dorsum of the hand compared with healthy controls (CDT $p = 0.020$, TSL $p = 0.001$, Fig. 1). 31% of the iRBD patients and none of the controls had abnormal low sensitivity to cold detection above the dorsal hand ($p = 0.035$). Abnormal low sensitivity to detection of temperature differences (thermal sensory limen (TSL)) above the hand was significantly more frequent in the patient group (62%) than in the control group (13%, $p = 0.016$). There was a tendency towards a higher CDT on the dorsum of the foot in the patients in comparison with the controls (p = 0.094, Fig. 2). CPT and HPT both on the hand and foot did not differ significantly between the two groups (Figs. 1 and 2). The reaction time was not significantly different in the patient group (250 ms ± 90 ms) compared with the control group (230 ms ± 60 ms (mean ± standard deviation), $p = 0.31$).

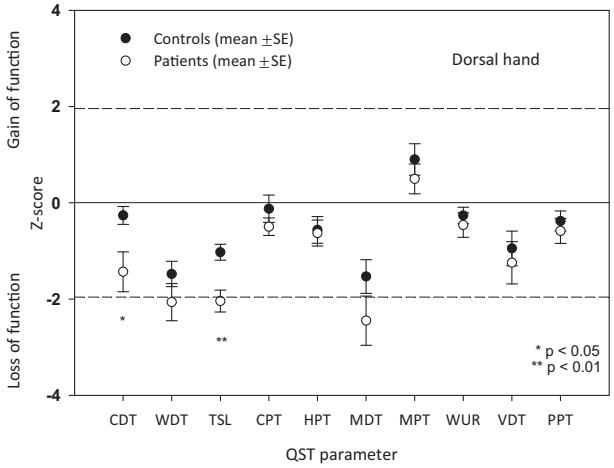

Fig. 1. Somatosensory profiles of the dorsal hand based on quantitative sensory testing (QST) in patients with idiopathic REM sleep behaviour disorder and healthy control subjects. Mean z-scores ± standard error of the mean. For further explanation, see the *Statistical analysis* section. CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold. $^{*}p < 0.05$; $^{**}p < 0.01$ for iRBD patients vs. healthy control subjects. Group comparisons were performed using two-sample *t*-test.

3.4. Laser evoked potentials

The amplitude of the N2/P2 complex tended to be smaller in the patients with iRBD (13.7 ± 12.8 μV) than in healthy controls (33.4 ± 18.6 μV (median ± interquartile range), $p = 0.053$, Fig. 3). N2 and P2 latencies did not significantly differ between the two groups

Table 1
Demographic data and clinical characteristics.

	Patients (n = 13)	Controls (n = 15)	*p* value
Sex (males/females)	11/2	12/3	1.0[a]
	Mean ± standard deviation		
Age (years)	65.2 ± 7.6 (range: 54–77)	65.8 ± 7.3 (range: 52–75)	0.84[b]
Height (cm)	179.2 ± 8.1	176.5 ± 9.0	0.42[b]
Weight (kg)	84.6 ± 14.4	72.7 ± 10.9	0.020[b]
PSQI score	6.2 ± 4.2	4.9 ± 2.1	0.33[b]
KSS score	3.0 ± 1.8	2.0 ± 1.0	0.096[b]
MMSE score	28.5 ± 1.5	29.3 ± 1.4	0.15[b]
SIT-12 score	5.9 ± 3.1	10.5 ± 1.4	<0.001[b]
	Median (minimum–maximum)		
UPDRS-III score	3 (1–14)	1 (0–4)	0.002[c]
MDI score	4 (0–27)	3 (0–12)	0.52[c]

Demographic and clinical characteristics in patients with idiopathic REM sleep behaviour disorder and healthy control subjects.
PSQI: Pittsburgh Sleep Quality Index; KKS: Karolinska Sleepiness Scale; MMSE: Mini-Mental State Examination; SIT-12: Sniffin' Sticks 12-identification test; UPDRS-III: The motor part of the Unified Parkinson's Disease Rating Scale; MDI: Major Depression Inventory.
[a] Fisher's exact test.
[b] Two-sample *t*-test.
[c] Mann–Whitney *U* test.

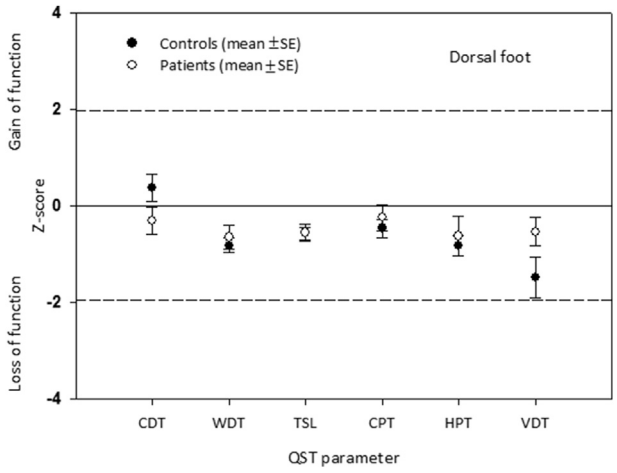

Fig. 2. Somatosensory profiles of the dorsal foot based on quantitative sensory testing (QST) in patients with idiopathic REM sleep behaviour disorder and healthy control subjects. Mean z-scores ± standard error of the mean. For further explanation, see the *Statistical analysis* section. CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; VDT: vibration detection threshold.

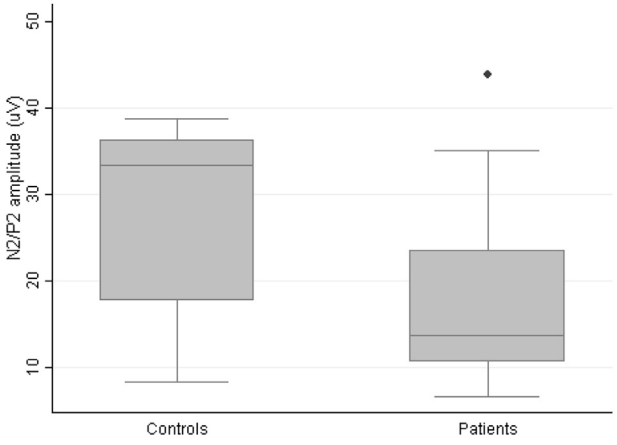

Fig. 3. Box plot showing amplitude of the N2/P2 complex in controls (n = 15) and patients (n = 13). The box plot displays the median, quartiles, interquartile range (the span of the box), and smallest and largest values in the data. "Extreme" values are plotted as isolated dots (lying farther from the box edge than 1.5 times the interquartile range).

(N2 latency: Patients 218 ± 27 ms; Controls 229 ± 29 ms (median ± interquartile range), $p = 0.39$. P2 latency: Patients 324 ± 65 ms; Controls 343 ± 28 ms (median ± interquartile range), $p = 0.73$).

3.5. Conditioned pain modulation testing

One patient did not undergo the CPM testing because of unstable angina. The CPM response regarding heat pain did not significantly differ between patients and controls (Table 2), whereas the pain inhibition response regarding pressure pain was larger in the patient group than the control group (Table 2).

The pain ratings during the hand in ice water immersion were the same in the two groups (Maximum pain intensity (NRS_{0-10}): Patients 7.4 ± 2.0; Controls 7.7 ± 1.8 (mean ± standard deviation), $p = 0.67$. Maximum pain unpleasantness (NRS_{0-10}): Patients 6.9 ± 1.4; Controls 7.3 ± 2.0 (mean ± standard deviation), $p = 0.54$).

Table 2
Results of the conditioned pain modulation (CPM) in patients and healthy controls.

	Patients (n = 12)	Controls (n = 15)	*p* value
	Absolute values (mean ± SD)		
CPM response HPT (°C)[a]	−2.1 ± 2.3	−1.6 ± 2.8	0.62
CPM response PPT (kPa)[b]	−147.8 ± 68.9	−60.3 ± 106.7	0.021
	Percent change		
CPM response HPT (%)	−5.0 ± 5.7	−3.6 ± 6.8	0.58
CPM response PPT (%)	−44.3 ± 28.2	−14.0 ± 24.0	0.006

CPM: conditioned pain modulation; HPT: heat pain threshold; PPT: pressure pain threshold.
The calculation of the CPM response was conducted by subtracting the second test stimuli PPT and HPT from the first test stimuli PPT and HPT, thus the pain inhibition was denoted with a negative value.
Group comparisons were performed using two-sample *t*-test.
[a] (mean of three HPT measurements before ice water)−(HPT measured one minute after ice water).
[b] (mean of three PPT measurements before ice water)−(PPT measured immediately after ice water).

4. Discussion

This study found impaired somatosensory function in iRBD patients in comparison with healthy controls, with increased thermal detection thresholds and a tendency towards lower LEPs amplitudes in iRBD.

These results are in accordance with former studies in PD patients, showing higher CDT and WDT in PD patients than in healthy controls [15,16]. This indicates that impaired thermal sensory function may occur early in the course of PD. The reduced ability to sense cold and warm stimuli in iRBD and PD may either be caused by changes in the central or in the peripheral nervous system. Alpha-synuclein aggregates have been detected in multipolar lamina I projection neurons in PD patients [26] and might be the cause for an impaired thermal detection in our patients, as the primary afferent thermal Aδ and C fibres synapse almost exclusively with multipolar projection neurons of lamina I.

Conversely, impaired thermal sensation may be due to dysfunction of peripheral small nerve fibres. Thus, cold detection is conveyed by thinly myelinated Aδ fibres, warm detection by unmyelinated C fibres, whereas TSL measures the function of both Aδ and C fibres. A recent study found a reduced intraepidermal nerve fibre density (IENFD) in skin biopsies of iRBD patients compared with healthy controls. 39% of the patients and 4.5% of the controls had small fibre neuropathy (SFN) [27]. SFN and decreased IENFD have also been shown in PD patients [16,28]. These findings suggest that SFN is an early feature in the neurodegenerative process and might be used as a prodromal biomarker for PD. Studies have demonstrated that IENFD is negatively correlated with CDT and WDT [29–31], and therefore the increased thermal detection thresholds found in our iRBD patients may reflect the affection of the small fibres. Furthermore, two recent studies demonstrated phosphorylated alpha-synuclein deposits in dermal nerve fibres including somatosensory fibres of patients with RBD [32,33]. No deposits were found in healthy controls. This provides evidence that somatosensory nerve fibres are involved at preclinical stages of PD and supports our findings of an impaired somatosensory function in iRBD patients. However, the association between functional and structural small fibre affection in iRBD needs to be further investigated because QST and skin biopsy methods may complement each other in the diagnosis of SFN [34].

Our study found a tendency towards lower N2/P2 amplitudes in iRBD patients than in controls. This is in accordance with a study that demonstrated smaller N2/P2 amplitudes in PD patients in comparison with controls [19]. These findings suggest an abnormal processing of the nociceptive laser input in both PD and iRBD

patients. This dysfunction may be located in the central nervous system or in the small peripheral nerve fibres, as LEPs is conveyed by thinly myelinated Aδ fibres. A previous study found a positive correlation between N2/P2 amplitude and IENFD and that patients with SFN had lower N2/P2 amplitude than healthy control subjects [35], suggesting that the lower N2/P2 amplitude in iRBD patients might be due to SFN.

Conflicting findings regarding CPT and HPT in PD have been published [15–17], which might reflect the unaltered thermal pain thresholds in PD patients. In our study we found no difference of the CPT and HPT between the iRBD patient and control group, suggesting that cold and heat pain perception are not altered in iRBD patients.

Patients with iRBD did not show decreased function of the descending pain inhibitory system using CPM testing – in fact, patients had a larger inhibition of PPT than controls, which is difficult to explain and may be a coincidental finding. A previous study has demonstrated that CPM responses did not differ between PD patients and healthy controls using a paradigm consisting of heat pain as the test stimulus and a cold pressor task as the conditioning stimulus [21]. Hence, these findings suggest that neither PD nor iRBD is related to general deficits of the descending pain inhibitory system.

It is unclear if these findings have clinical implications for individual patients. SFN may lead to neuropathic pain, yet, in this study, iRBD patients and healthy controls did not differ regarding clinical pain symptoms. However, the question if iRBD patients might suffer from more pain than the general population was not the aim of this study, and a bigger study group would be needed to answer this question.

A limitation of this study is the small sample size, and a larger sample of iRBD patients is necessary to confirm our results. Laboratory tests of vitamin B12, folic acid, and glucose were not performed in all patients. Consequently, metabolic causes of a subtle neuropathy might have been undetected. Electromyography (EMG) was not performed to rule out a potential SFN. Comorbidity, especially cardiovascular disease and obstructive sleep apnoea, was more frequent in iRBD patients than controls. UPDRS scores were higher in iRBD patients than controls, indicating a slightly higher motor impairment in this group. However, none of the patients fulfilled diagnostic criteria for PD [36]. We did not correct for multiple testing, and some of the significant results could therefore have been found by coincidence alone. Strength of this study is that the gender and age distribution was very similar among the patients and controls. Furthermore, we used a standardised QST protocol and transformed the QST data into z-values based on a normative reference database of healthy controls, so it is reasonable to compare our results with other standardised QST studies. The neurophysiologists, who placed the measurement cursors on the LEPs curves, were blinded regarding if the subject was a patient or control. As somatosensory function and pain perception in iRBD have not been investigated before, this study provides new insight into sensory processing in the early stage of synucleinopathy.

Future studies should address the predictive value of QST and LEPs measures in iRBD patients regarding time to disease conversion and type of evolving neurodegenerative alpha-synucleinopathy. Such studies could clarify if impaired somatosensory function might be used as a prodromal diagnostic biomarker for neurodegenerative disease. In addition, thermal detection thresholds and LEPs should be investigated together with IENFD in a larger sample of iRBD patients.

5. Conclusion

This study found thermal sensory impairment and reduced N2/P2 amplitude in patients with iRBD in comparison with controls, which might be due to functional affection of the small nerve fibres. Further studies are required to assess if impaired somatosensory function can be used as a marker for incipient alpha-synucleinopathy-mediated neurodegeneration.

Acknowledgements

This work was supported by the Graduate School of Health Aarhus University, Fonden til Lægevidenskabens Fremme, Aase og Ejnar Danielsens Fond, Grosserer L. F. Foghts Fond; and Murermester Jacob Johansen og Hustru Maren Johansens Legat.

Conflict of interest

The authors declare no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2017.09.035.

References

[1] Boeve BF. REM sleep behavior disorder. Updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. Ann N Y Acad Sci 2010;1184:15–54.
[2] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
[3] Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med Aug 2013;14(8):744–8.
[4] Iranzo A, Tolosa E, Gelpi E, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. Lancet Neurology 2013;12(5):443–53.
[5] Iranzo A, Fernandez-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 2014;9(2), e89741.
[6] Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain Nov 2007;130(Pt 11):2770–88.
[7] Braak H, Ghebremedhin E, Rub U, et al. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res Oct 2004;318(1):121–34.
[8] Fantini ML, Postuma RB, Montplaisir J, et al. Olfactory deficit in idiopathic rapid eye movements sleep behavior disorder. Brain Res Bull Oct 16 2006;70(4–6):386–90.
[9] Postuma RB, Gagnon JF, Vendette M, et al. Olfaction and color vision identify impending neurodegeneration in rapid eye movement sleep behavior disorder. Ann Neurol May 2011;69(5):811–8.
[10] Miyamoto T, Miyamoto M, Iwanami M, et al. Olfactory dysfunction in idiopathic REM sleep behavior disorder. Sleep Med May 2010;11(5):458–61.
[11] Ferini-Strambi L, Oertel W, Dauvilliers Y, et al. Autonomic symptoms in idiopathic REM behavior disorder: a multicentre case-control study. J Neurol Jun 2014;261(6):1112–8.
[12] Wasner G, Deuschl G. Pains in Parkinson disease – many syndromes under one umbrella. Nat Rev Neurol May 2012;8(5):284–94.
[13] Truini A, Frontoni M, Cruccu G. Parkinson's disease related pain: a review of recent findings. J Neurol Jan 2013;260(1):330–4.
[14] Conte A, Khan N, Defazio G, et al. Pathophysiology of somatosensory abnormalities in Parkinson disease. Nat Rev Neurol Dec 2013;9(12):687–97.
[15] Maruo T, Saitoh Y, Hosomi K, et al. Deep brain stimulation of the subthalamic nucleus improves temperature sensation in patients with Parkinson's disease. Pain Apr 2011;152(4):860–5.
[16] Nolano M, Provitera V, Estraneo A, et al. Sensory deficit in Parkinson's disease: evidence of a cutaneous denervation. Brain Jul 2008;131(Pt 7):1903–11.
[17] Djaldetti R, Shifrin A, Rogowski Z, et al. Quantitative measurement of pain sensation in patients with Parkinson disease. Neurology 2004;62(12):2171–5.
[18] Ciampi de Andrade D, Lefaucheur JP, Galhardoni R, et al. Subthalamic deep brain stimulation modulates small fiber-dependent sensory thresholds in Parkinson's disease. Pain May 2012;153(5):1107–13.
[19] Tinazzi M, Del Vesco C, Defazio G, et al. Abnormal processing of the nociceptive input in Parkinson's disease: a study with CO_2 laser evoked potentials. Pain May 2008;136(1–2):117–24.
[20] Cruccu G, Sommer C, Anand P, et al. EFNS guidelines on neuropathic pain assessment: revised 2009. Eur J Neurol Aug 2010;17(8):1010–8.
[21] Grashorn W, Schunke O, Buhmann C, et al. Influence of dopaminergic medication on conditioned pain modulation in Parkinson's disease patients. PLoS One 2015;10(8), e0135287.
[22] Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on neuropathic pain (DFNS): standardized protocol and reference values. Pain Aug 2006;123(3):231–43.

[23] Hu L, Valentini E, Zhang ZG, et al. The primary somatosensory cortex contributes to the latest part of the cortical response elicited by nociceptive somatosensory stimuli in humans. Neuroimage Jan 2014;84:383–93.
[24] Yarnitsky D, Bouhassira D, Drewes AM, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. Eur J Pain Jul 2015;19(6):805–6.
[25] Gierthmühlen J, Maier C, Baron R, et al. Sensory signs in complex regional pain syndrome and peripheral nerve injury. Pain Apr 2012;153(4):765–74.
[26] Braak H, Sastre M, Bohl JR, et al. Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre- and postganglionic neurons. Acta Neuropathol Apr 2007;113(4):421–9.
[27] Schrempf W, Katona I, Dogan I, et al. Reduced intraepidermal nerve fiber density in patients with REM sleep behavior disorder. Park Relat Disord Aug 2016;29:10–6.
[28] Doppler K, Ebert S, Uceyler N, et al. Cutaneous neuropathy in Parkinson's disease: a window into brain pathology. Acta Neuropathol 2014;28:99–109.
[29] Pittinger GL, Ray M, Burcus NI, et al. Intraepidermal nerve fibers are indicators of small-fiber neuropathy in both diabetic and nondiabetic patients. Diabetes Care 2004;27(8):1974–9.
[30] Shun CT, Chang YC, Wu HP, et al. Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments. Brain Jul 2004;127(Pt 7):1593–605.
[31] Quattrini C, Tavakoli M, Jeziorska M, et al. Surrogate markers of small fiber damage in human diabetic neuropathy. Diabetes Aug 2007;56(8):2148–54.
[32] Doppler K, Jentschke HM, Schulmeyer L, et al. Dermal phospho-alpha-synuclein deposits confirm REM sleep behaviour disorder as prodromal Parkinson's disease. Acta Neuropathol Apr 2017;133(4):535–45.
[33] Antelmi E, Donadio V, Incensi A, et al. Skin nerve phosphorylated α-synuclein deposits in idiopathic REM sleep behavior disorder. Neurology May 2017;88(22):2128–31.
[34] Devigili G, Tugnoli V, Penza P, et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. Brain 2008;131(7):1912–25.
[35] Casanova-Molla J, Grau-Junyent JM, Morales M, et al. On the relationship between nociceptive evoked potentials and intraepidermal nerve fiber density in painful sensory polyneuropathies. Pain Feb 2011;152(2):410–8.
[36] Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord Oct 2015;30(12):1591–601.