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ORIGINAL ARTICLE

Neurophysiological and ultrasonographic comparative study of autonomous nervous system in patients suffering from fibromyalgia and generalized anxiety disorder

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Abstract

Background Fibromyalgia (FM) and generalized anxiety disorder (GAD) share common clinical features: they both affect women more than men, their diagnosis is based solely on clinical criteria, and some of the symptoms such as anxiety, aches and muscle tension, sleep disorders, and cognitive dysfunction occur in both diseases. For both conditions, an underlying dysregulation of the autonomic nervous system (ANS) has been proposed.

Objective The aims of this study were to investigate ANS dysfunction in FM and GAD and compare them with controls.

Methods Sympathetic skin response (SSR) from palm and sole and cross-sectional area (CSA) of bilateral vagus nerves (VN) were measured in 28 healthy controls, 21 FM patients, and 24 GAD patients.

Results CSA of VN was significantly smaller in FM patients (right: $1.97 \pm 0.74 mm^2$, left: 1.75 ± 0.65 mm2) and GAD patients (right: $2.12 \pm 0.97 mm^2$, left: 1.71 ± 0.86 mm^2) compared to controls (right: 3.21 ± 0.75 mm^2, left: 2.65 ± 1.13 mm^2, $p < 0.001$, but did not differ between the two patient groups. SSR parameters were similar between patients and controls. SSR latency correlated to clinical scales (FM Widespread Pain Index) in the FM group ($r = 0.515$, $p = 0.02$ and $r = 0.447$, $p = 0.05$) for the upper and lower limbs respectively, but no other correlation between clinical and neurophysiological parameters was identified.

Conclusion This study confirms similar ANS abnormalities in FM and GAD that fairly distinguish them from controls and support the hypothesis of a common pathophysiological substrate underlying both conditions.

Keywords Sympathetic skin response · Cross-sectional area · Vagus nerve · Fibromyalgia · Generalized anxiety disorder

Introduction

Fibromylagia (FM) is a multisystem disorder characterized mainly by chronic generalized pain. Other non-pain-associated symptoms like depression, fatigue, sleep disorders, and cognitive dysfunction should be taken into account in the final Symptom Severity Score (SSS), along with the Widespread Pain Index (WPI) for the diagnosis [1]. FM has a prevalence of 5.4% and a female to male ratio 2.3:1 [2].

Generalized anxiety disorder (GAD) is a psychiatric condition, affecting 6% of the population; has a chronic course; and produces a high health burden. GAD is characterized by at least 6 months of persistent and excessive anxiety, recurring worry about common events, and physical symptoms, such as muscle tension, aches and pains, insomnia, and fatigue combined with significant distress or impairment in personal, occupational, or other areas of function. The

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diagnostic criteria also include autonomic arousal symptoms [3].

FM and GAD share many common features. Both diseases affect women twice more often than men, produce severe distress in patients and lead them to overuse of health services, and occasionally might be indistinguishable since they present almost identical clinical symptoms. Both disorders, apart from their clinical similarity, are of unknown etiology, and therefore, common pathophysiological mechanisms may underlie both, as has already been suggested [4].

An abnormal pattern of stimulated hypothalamic–pituitary–adrenal axis activity has been noted in FM. Diminished autonomic regulation in FM may explain the reduced ability of patients to cope with environmental stressors. There are heart rate variability (HRV) studies that support the hypothesis of sympathetic hyperactivity [5]. Other studies have shown reduced parasympathetic activity and sympathetic reactivity to stress in FM patients [6].

Patients suffering from GAD show a decreased autonomous flexibility. Acute stress produces sympathetic reactivity in all persons, but GAD patients may show delay in returning to normal autonomic activity. Few studies concerning GAD show increased sympathetic tone in nonstress conditions but reduced flexibility in stress conditions [7, 8].

Other studies support the contrary, that GAD patients may exhibit a suppression of sympathetic responses [9]. There is evidence that noradrenergic dysregulation may be involved in GAD but no unified hypothesis has yet to be proposed. Other studies focus on the role of the parasympathetic nervous system and suggest that a reduced vagal tone, as expressed through HRV, may be responsible for reduced autonomic flexibility [10].

In conclusion, in both FM and GAD, an altered activation of sympathetic nervous system in stress conditions is reported, but existing data are insufficient to describe the baseline autonomous nervous system (ANS) function.

The aims of this study are to explore baseline ANS function in patients suffering from the above diseases and compare them with healthy controls. For the purpose of the study, two separate methods have been chosen: sympathetic skin response (SSR) to investigate the sympathetic nervous system (SNS) and the cross-sectional area (CSA) of the vagus nerve (VN), measured by ultrasonography, to investigate the parasympathetic nervous system (PNS). This particular choice was based on the fact that each method investigates each component of ANS exclusively in contrast to other methods such as HRV where SNS and PNS interact to produce measurements. SSR has only been used once in GAD patients in comparison to patients suffering from major depression [11] and in several studies investigating FM [12–15] but with inconsistent results. Review of the literature did not reveal any research of CSA of VN in any of the conditions.

Methods

Study design

A prospective study was carried out in one outpatient electrodiagnostic service of a tertiary care hospital (Department of Neurology, Attikon University Hospital) in Athens, Greece.

Study population

Patients with a diagnosis of FM or GAD were recruited. Diagnosis of FM was based on 2010 criteria [1]. A score of WPI $\geq$ 7 and SSS $\geq$ 5, or WPI 3–6 and SSS scale score $\geq$ 9 was considered as positive for FM diagnosis. The diagnosis of GAD was set through a clinical interview with an experienced psychiatrist using the DSM-5 criteria [3]. Exclusion criteria were the presence of diabetes mellitus, the treatment with neurotoxic agents such as chemotherapeutics, vitamin deficiency, endocrine disorders, rheumatologic disorders, or other chronic orthopedic diseases, such as osteoarthritis. Psychiatric exclusion criteria included the presence of concurrent major psychiatric conditions, including psychosis and major mood disorders; other anxiety disorders, e.g., panic disorder, currently in acute exacerbation; and substance abuse/alcoholism. Additionally, the FM patients did not meet criteria for GAD. All patients underwent psychiatric evaluation by attending physicians of the Department of Psychiatry of our Institution. Controls were recruited following an open invitation to participate in the research and they were interviewed for somatic and mental diseases.

Demographic and clinical data

The following data were collected: patient's personal data (age, sex, BMI, handedness) and laboratory test results that are associated with abnormal EDX results (TSH, HbA1c, B12, folic acid, Vit D).

Self-reported questionnaires

Patients were asked to complete WHODAS 2.0–12 item version and Hospital Anxiety and Depression Scale (HADS).

WHODAS 2.0–12 item

WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) is a self-rated health questionnaire; it is a direct derivative of International Classification of Functioning, Disability and Health (ICF) and is applicable to any health condition [16]. The WHODAS 2.0 was developed in order to

assess behavioral limitations and restrictions to participation experienced by an individual, independently from a medical diagnosis. WHODAS 2.0–12 item has excellent psychometric properties, is easy to use and score, and is available in the public domain in the form of self-report, proxy, and telephone-based versions that can be administered in around 5–10 min. WHODAS 2.0 assesses perceived disability associated with the health condition in the 30 days preceding its application. This instrument is divided into six domains: (i) cognition; (ii) mobility; (iii) self-care; (iv) inter-personal relationships; (v) activities of daily living; and (vi) participation. Scoring is based on "item-response-theory" (IRT). It takes into account multiple levels of difficulty for each WHODAS 2.0 item. It takes the coding for each item response as "none," "mild," "moderate," "severe," and "extreme" separately, and then uses an algorithm to determine the summary score by differentially weighing the items and the levels of severity. The SPSS algorithm is available from the WHO. WHODAS 2.0 generate an overall score ranging from 0 to 100 (0 = no disability; 100 = full disability). A disability score of equal or greater to 25% was considered to indicate disability (0–4% no disability, 5–24% mild disability, 25–49% moderate disability, 50–95% severe disability, and 96–100% complete disability).

HADS

The Hospital Anxiety and Depression Scale (HADS) was developed by Zigmond and Snaith in 1983 [17] and was validated in the Greek language in 2008 [18]. Its purpose is to provide clinicians with an acceptable, reliable, valid, and easy to use practical tool for identifying and quantifying depression and anxiety. The HADS is a self-report rating scale of 14 items on a 4-point Likert scale (range 0–3). It is designed to measure anxiety and depression (7 items for each subscale HADS-A, HADS-D). The total score is the sum of the 14 items, and for each subscale, the score is the sum of the respective seven items (ranging from 0 to 21). A score of 0 to 7 for either subscale could be regarded as being in the normal range, a score of 11 or higher indicating a probable presence of the mood disorder, and a score of 8 to 10 just being suggestive of the presence of the respective state. The HADS has demonstrated reliability and validity when used to assess medical patients and gives clinically meaningful results as a psychological screening tool and furthermore; HADS scores predict a psychosocial and, possibly, also a physical outcome.

Nerve conduction studies

Sural and radial nerve conduction studies were measured in all participants (antidromic method) using surface stimulating and recording electrodes. The study was judged as normal or abnormal based on standardized EDX criteria.

SSR

SSR examination was performed using Nihon Kohden Neuropack MEB-9400 EMG instrument, Nihon Kohden Corp., 1–31-4, Nishiochiai Shinjuku-ku, Tokyo 161–8560, Japan. The examination followed the standard protocol. All subjects were instructed to refrain from smoking and to have a light breakfast that did not include alcohol or caffeine. Room temperature was kept at 23–26 °C and limb temperature at 32–33 °C.

The active electrode surface circular-shaped disks were placed on the left palm and on the right sole. The reference electrodes were placed on the dorsum of the hand and of the foot. Electrical stimuli were delivered on the right wrist at 75 mA and 0.1-ms duration; the band pass was 0–5–2000 Hz. Five stimuli were delivered unexpectedly at random intervals of at least 30 s. Latency was measured from the onset of the stimulus artifact to the first deflection from baseline (seconds). Amplitude was measured peak to peak (negative peak to positive peak) (mV). The shortest of the 5 responses was used for statistical analysis. Measurements included in analysis were as follows: SSR upper limb latency (SSR UL LAT), SSR upper limb amplitude (SSR UL AMP), SSR lower limb latency (SSR LL LAT), SSR lower limb amplitude (SSR LL AMP).

CSA VN

The ultrasound study was performed using the ultrasound system Sonosite Edge (Sonosite Inc.), with a linear transducer at 6–15 Hz. Patients and controls were scanned by the same operator. The operator was blinded about the patient and the control group as well as was blinded about the results of the SSR study. Participants were asked to lie in the supine position and turn their head to the side opposite from the examiner. Bilateral vagus nerves (VNs) were scanned in axial view and the settings of the ultrasound system were individually optimized for each participant.

To capture the nerve, the transducer was initially placed at the level of the thyroid cartilage and then swept laterally to identify the nerve inside the carotid sheath. The carotid artery and the internal jugular vein were used as the anatomical landmarks which were identified through their anechoic appearance and their Doppler signal. The vagus nerve was located laterally to the common carotid artery and dorsally to the internal jugular vein into the carotid sheath with a small rounded hypoechoic or honeycomb structure. Whenever necessary, color Doppler was used to prevent misinterpreting a small vessel within this hypervascularized region for being the vagus nerve [19, 20]. Prior to measuring the

cross-sectional area, the examiner made sure that the pressure of the transducer was reduced until the lumen of the internal jugular vein was clearly inflated just so as to avoid compression of the vagus nerve. The cross-sectional area (CSA) of the vagus nerve was measured by following the contour of the nerve just inside its hyperechoic rim (in mm^2). The mean of 2 CSA's values was used for statistical analyses. CSA of both vagus nerves was included in the analysis.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS Inc., version 24.0 for Windows; IBM, Armonk, NY, USA). Descriptive statistics are given as the mean and standard deviation, frequency, and percentage. Statistical comparisons between different groups were performed using the chi-square test (or exact test) for binary outcomes, and Student's *t*-test or Mann–Whitney *U* test for continuous variables as appropriate. Correlations between variables were tested using Pearson's or Spearman's correlation coefficients (*r*) as appropriate. A two-tailed *p*-value of less than 0.05 was considered significant.

The inter- and intra-observer reproducibility of ultrasound measurement of vagus nerve CSA was evaluated in 10 pairs of measurements. The intraclass correlation coefficient (ICC) was computed to measure agreement between two raters (inter-observer reproducibility) and between two sets of measurements within the same rater (intra-observer reproducibility). The ICC was > 0.9 in all pairs of measurements indicating an excellent inter- and intra-observed reproducibility [21].

Informed consent was obtained from all subjects. The present study was approved by the local Ethics Committee of our Institution and followed the principles of the Helsinki Declaration and its later amendments [22].

Results

Demographic, biochemical, psychometric, clinical, and neurophysiological characteristics

A total of 28 healthy subjects (13 women, 15 men) and 45 patients were included (Table 1): 21 with FM (16 women, 5 men) and 24 with GAD (15 women, 9 men). The mean age of controls was 50 years, ranging between 34 and 74 years; the mean age of FM patients was 57 years, ranging between 34 and 74 years; the mean age of GAD patients was 51 years, ranging between 23 and 67 years. The three groups did not differ in age ($p = 0.113$) and sex ($p = 0.102$). Ninety percent of the participants were right-handed. Mean BMI was 25.36 kg/m^2, with a range of 17.9–44.9 kg/m^2 for controls; 26.90 kg/m^2, with a range of 24.13–29.68 kg/m^2 for FM patients; and 26.3 kg/m^2, with a range of 23.78–28.83 kg/m^2 for GAD patients. BMI did not differ between groups ($p = 0.620$).

Psychometric properties measured by HADS-A and HADS-D were marginally elevated in both groups of patients (scores over 7) but did not differ between groups; similarly, there were no differences in WHODAS between groups. There was a statistically significant difference in all FM scales, where FM patients scored higher than GAD patients ($p < 0.001$ and $p = 0.023$, for FM WPI and FM SSS respectively).

Sural and radial nerve conduction studies and SRAR (sural to radial ratio) were within normal limits in all patients and did not differ between groups; all biochemical parameters were similar between groups including the measurements for the thyroid-stimulating hormone (TSH), hemoglobin A1c (HbA1c), vitamin B12, folic acid, vitamin D, and the rheumatoid factor (RF).

Table 1 Comparison of demographic, psychometric, and neurophysiological characteristics between patient groups

Characteristic	FM ($n = 21$)	GAD ($n = 24$)	*p*
Sex (females%)	76	62.5	0.105
Age mean (SD) (years)	56.6 (10.03)	51.2 (13.74)	0.113
BMI mean (SD)	26.9 (6.09)	26.3 (5.84)	0.620
WHODAS mean (SD)	26.24 (18.07)	17.99 (20.07)	0.171
HADS-A mean (SD)	8.35 (4.42)	9.63 (5.56)	0.415
HADS-D mean (SD)	7.25 (4.66)	7.13 (3.75)	0.931
FM WPI mean (SD)	11.1 (3.75)	3.35 (3.18)	**< 0.001**
FM SSS mean (SD)	5.85 (2.66)	3.35 (3.69)	**0.023**
FM SUM mean (SD)	16.95 (5.50)	5.42 (5.78)	**< 0.001**
Radial amplitude mean (SD) (mV)	26.57 (10.64)	29.57 99.36)	0.349
Sural amplitude mean (SD) (μV)	17.57 (7.96)	20.97 (8.320	0.187
SRAR mean (SD)	0.71 (0.27)	0.75 (0.44)	0.730

Abbreviations: *BMI*, Body Mass Index; *WHODAS*, World Health Organisation Disability Assessment Schedule 2.0 12-item version; *HADS*, Hospital Anxiety and Depression Scale; *WPI*, Widespread Pain Index; *SSS*, Symptom Severity Score; *SRAR*, sural to radial ratio

Bold values show statistical significance

Table 2 Comparison of SSR measurements and CSA VN values between groups

Characteristic	Controls ($n=28$)	FM ($n=21$)	GAD ($n=24$)	p
SSR UL LAT mean (SD) (ms)	1.23 (0.25)	1.21 (0.24)	1.25 (0.26)	0.986
SSR UL AMP mean (SD) (mV)	2.90 (2.24)	3.26 (2.31)	2.60 (1.96)	0.759
SSR LL LAT mean (SD) (ms)	1.67 (0.39)	1.72 (0.23)	1.82 (0.52)	0.701
SSR LL AMP mean (SD) (mV)	1.39 (1.18)	1.44 (1.27)	1.29 (1.46)	0.966
CSA VN R mean (SD) (mm^2)	3.21 (0.75)	1.97 (0.74)	2.12 (0.97)	**< 0.001**
CSA VN L mean (SD) (mm^2)	2.65 (1.13)	1.75 (0.65)	1.71 (0.86)	**< 0.001**

Abbreviations: *SSR*, sympathetic skin response; *UL*, upper limb; *LL*, lower limb; *LAT*, latency; *AMP*, amplitude; *CSA*, cross-sectional area; *VN*, vagus nerve; *R*, right; *L*, left

Bold values show statistical significance

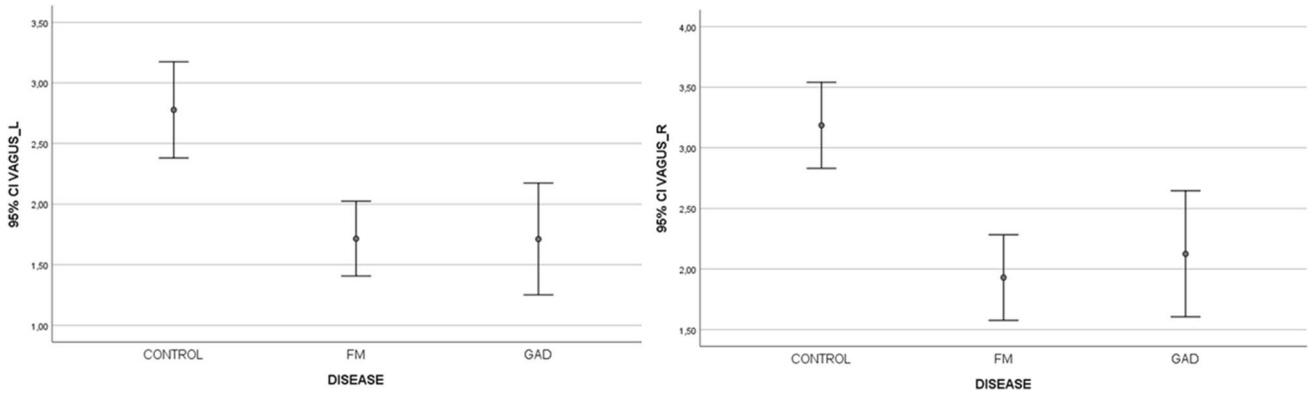

Fig. 1 Error bars showing means/standard error of CSA VN (right and left) in the three groups

SSR measurements

SSR were elicited in all controls and patients. Amplitudes and latencies were similar between groups (Table 2).

CSA VN

CSA of both the right and the left vagus nerves were significantly smaller in FM ($p=0.001$) and GAD ($p=0.001$) patients compared to controls, but did not differ between the two patient groups ($p>0.999$) (Table 2). It is noteworthy that values on the right VN (mean 2.50, SD 1.03) were significantly larger than those on the left VN (mean 2.15, SD 0.99) in all participants ($p<0.001$) (Fig. 1).

Correlations between SSR measurements and clinical-psychometric characteristics

There was no correlation between age and SSR measurements (Table 3). In FM patients, there was a correlation of FM WPI and SSR UL LAT ($p=0.020$, $r=0.515$) and marginally with SSR LL LAT ($p=0.055$, $r=0.447$). No other correlation was observed (Table 4).

Table 3 Correlations between age, SSR, and CSA

Variable	Pearson's correlation (r)	p
SSR UL LAT vs age	0.217	0.077
SSR UL AMP vs age	−0.125	0.312
SSR LL LAT vs age	0.035	0.791
SSR LL AMP vs age	0.102	0.434
CSA VN R vs age	−0.155	0.234
CSA VN L vs age	−0.125	0.336
SSR UL LAT vs CSA VN R	−0.123	0.368
SSR UL AMP vs CSA VN R	0.145	0.286
SSR LL LAT vs CSA VN R	−0.40	0.779
SSR LL AMP vs CSA VN R	−0.271	0.127
SSR UL LAT vs CSA VN L	−0.96	0.481
SSR UL AMP vs CSA VN L	0.96	0.480
SSR LL LAT vs CSA VN L	−0.35	0.807
SSR LL AMP vs CSA VN L	−0.215	0.130

Abbreviations: *SSR*, sympathetic skin response; *UL*, upper limb; *LL*, lower limb; *LAT*, latency; *AMP*, amplitude; *CSA*, cross-sectional area; *VN*, vagus nerve; *R*, right; *L*, left

Table 4 Correlations among SSR, clinical and psychometric characteristics

Variable	Pearson's correlation (*r*)	*p*
SSR UL LAT vs FM WPI (FM patients)	0.515	**0.020**
SSR UL LAT vs FM SSS (FM patients)	0.191	0.420
SSR LL LAT vs FM WPI (FM patients)	0.447	**0.055**
SSR LL LAT vs FM SSS (FM patients)	0.109	0.657
SSR UL LAT vs FM WPI (GAD patients)	0.084	0.747
SSR UL LAT vs FM SSS (GAD patients)	−0.153	0.557
SSR LL LAT vs FM WPI (GAD patients)	−0.268	0.298
SSR LL LAT vs FM SSS (GAD patients)	−0.352	0.166
HADS A vs WHODAS (FM patients)	0.427	0.06
HADS D vs WHODAS (FM patients)	0.324	0.164
HADS A vs FM WPI (FM patients)	−0.066	0.784
HADS D vs FM WPI (FM patients)	−0.140	0.557
HADS A vs FM SSS (FM patients)	0.286	0.221
HADS D vs FM SSS (FM patients)	0.094	0.694
HADS A vs WHODAS (GAD patients)	0.493	**0.020**
HADS D vs WHODAS (GAD patients)	0.673	**0.001**
HADS A vs FM WPI (GAD patients)	0.351	0.167
HADS D vs FM WPI (GAD patients)	0.331	0.194
HADS A vs FM SSS (GAD patients)	0.597	**0.011**
HADS D vs FM SSS (GAD patients)	0.657	**0.004**

Abbreviations: *SSR*, sympathetic skin response; *UL*, upper limb; *LL*, lower limb; *LAT*, latency; *AMP*, amplitude; *FM*, fibromyalgia; *GAD*, generalized anxiety disorder; *WPI*, Widespread Pain Index; *SSS*, Symptom Severity Score; *HADS*, Hospital Anxiety and Depression Scale

Bold values show statistical significance

Correlations between CSA measurements and clinical-psychometric characteristics

There was no correlation between age and bilateral CSA vagus measurements (nor with any other clinical or psychometric characteristic in any patient group or controls) (Table 3).

Correlations between SSR measurements-CSA

No correlation was observed in any group (Table 3).

Correlations between clinical and psychometric characteristics

GAD patients showed a significant correlation in both HADS scales (HADS-A, HADS-D) with WHODAS ($p=0.020$, $r=0.493$ and $p=0.001$, $r=0.673$ respectively) and in FM_SSS ($p=0.011$, $r=0.597$ and $p=0.004$, $r=0.657$ respectively) (Table 4).

Discussion

The objectives of this study were to distinguish the sympathetic nervous system and the parasympathetic nervous system abnormalities in GAD and FM patients and to compare them to controls, by using SSR and CSA of VN for the estimation of each branch of ANS. The study demonstrates (a) ANS abnormalities both in FM and GAD patients compared to controls and (b) similarities in PNS dysregulation between FM and GAD, when compared to each other.

The most prominent finding was the smaller CSA of VN in both patient groups compared to controls. It is worth noting that CSA did not differ between FM and GAD patients, rending them indistinguishable on this basis. On the other hand, no significant difference was observed regarding SSR parameters between patient groups and controls. SSR latencies correlated to the severity of symptoms in FM patients. No other correlation of clinical and psychometric characteristics with ANS evaluation was observed. SSR parameters, latency and amplitude, did not correlate to CSA of VN in neither the patient group nor the control group. Both GAD and FM patients demonstrated high scores in HADS, confirming similarities in clinical presentation, yet still, specific FM severity scales differentiate them. Notably, FM patients included in the present study did not meet DSM-5 criteria for GAD.

The activation of the stress system leads to behavioral and peripheral adjustments that enable the organism to withstand adversities and survive. The ANS maintains homeostasis through its two branches, SNS and PNS; thus, the ANS can be viewed as a complex adaptive system and disease may occur as a maladaptation of ANS to a hostile environment. For these reasons, distinct exploration of SNS and PNS and their interaction might give insight into understanding symptom generator in FM and GAD. The findings of the present study come to add in the poor until now literature on ANS dysfunction in these diseases.

Several studies have focused on possible dysregulation of ANS in FM that may alter central pain processing. The most commonly used method, HRV, shows a persistent sympathetic hyperactivity but with a decreased reactivity to stressors [23]. In a review of ANS dysfunction in FM, several methods have been reported and the summarized conclusion favors sympathetic hyperactivity, while there are other studies that propose the opposite, parasympathetic predominance [24]. The authors of the review conclude that SNS dysregulation may play a role in the pathogenesis of FM and explain some of the symptoms, such as pain and sleeping problems, but this association may not necessarily imply causative association.

SSR is a slow wave recorded from skin surface and represents sudomotor activity. It is a result of a polysynaptic

reflex and is used to evaluate SNS lesions in thin unmyelinated fibers and central sympathetic pathways. In healthy subjects, latency from the hands is shorter than that from the legs, and amplitude is higher. No side differences in amplitude or latency of SSR are observed [25] since central pathways are common and peripheral nerves are symmetrical. It is stated that SSR best correlates with disorders of unmyelinated axons and not generally with clinical evidence of dysautonomia. SSR may be absent in cases of dying back neuropathy without any clinical evidence of dysautonomia. Alternatively, in diseases where dysautonomia is suspected, like FM and GAD, but without evidence of small fiber neuropathy, SSR might be normal.

SSR is only rarely used in studies investigating anxiety disorders. SSR was used in a comparison study between patients with a major depressive disorder, GAD patients, and controls. It is reported that SSR latency was significantly shorter, and the amplitude was significantly higher in GAD patients vs. controls. The opposite results were found for patients with major depression [11]. The authors proposed that these significant differences between the two diseases can be used to distinguish them.

SSR has been scarcely used to investigate autonomic dysfunction in FM and the results of these studies remain controversial. In one study, SSR was elicited in all patients [13]; in two studies, SSR failed to emerge in only one patient of the 50 recruited [12] and of the 28 recruited [26], while on the Ulas et al. paper, SSR was absent in 15% of patients in the sole and 6% from the palm [27]. Regarding SSR parameters, latency and amplitude, results are inconsistent too. In two studies, SSR latencies were reported increased in FM patients while SSR amplitude did not differ significantly from that of the control group [12, 27]. In the other two studies, SSR latencies of FM patients were not found to differ from controls [13, 26]. One study focuses on SSR amplitude that is reported to be lower in FM patients compared to controls [26], a result that is not confirmed by others [12, 27]. In two studies, SSR latency was correlated to anxiety [12, 13].

In a previous study, using SSR to investigate ANS dysregulation in FM and GAD, similar results were elicited [28]: marginal prolonged latencies in patients compared to controls, a finding that was not reproduced in the present study. It seems that SSR is not a sensitive method to elucidate SNS pathology in FM and GAD, since some studies reach a positive result while others do not, although small nerve fiber pathology is well documented in skin biopsies [29] and should have affected SSR parameters.

The VN, the tenth cranial nerve, is the main contributor of the parasympathetic nervous system. The VN has a very long route, extending from its origin in the medulla through the neck and thorax to the abdomen. VN owes its name to the Latin word vague, meaning indefinite, wandering, due to the long circuit and the excess of sensory information, somatic and visceral, that it transfers. The vagal efferents account for only 10–20% of all fibers while the vagal afferents account for 80–90% of all fibers designating VN as a major sensory conveyer for the brain, bringing information of the inner organs of the thorax and abdomen. The gut has the largest surface toward the outer world, making it one of the major sources of sensory information to the brain [30]. An interesting finding is that VN CSA is consistently smaller on the left than on the right, in both controls and patients. This finding has been observed by other researchers in the past [20, 31–33]. One possible explanation for this finding is that VN innervates internal organs in an asymmetric manner. The left VN innervates the gastrointestinal tract up to the duodenum while the right VN contributes to the innervation further in the small intestine and colon. Thus, the right VN contains more fibers and therefore has a larger CSA [34].

Visceral sensory signals delivered by afferent cell bodies in nodose ganglia arrive at the nucleus tractus solitarii (NTS) that centrally projects to the locus coeruleus, the rostral ventrolateral medulla, the amygdala, and the thalamus, which are considered mood-regulating limbic areas [30]. The bidirectional connection between the brain and gut, the gut-brain axis attained by VN, links emotional and cognitive centers with environmental stimuli. Moreover, it is suggested that VN is involved in the activation/regulation of the hypothalamic–pituitary–adrenal (HPA) axis, which coordinates the adaptive responses of the organism to stressors of any kind [35].

Based on the above, an emerging interest of the role of VN in the pathogenesis of mood disorders has risen and research is conducted for its implication in therapeutic management. On these grounds, VN stimulation has been proposed for the treatment of those that do not respond to conventional therapies for major depression, although the underlying mechanism remains unclear [36]. In the case of post-traumatic stress disorder, it is considered that symptoms are due to a diminished parasympathetic function of VN [37], and therefore, VN stimulation has been proposed as a therapeutic option to treat anxiety disorders [38].

CSA of VN has been used to investigate diseases with known dysautonomia such as Parkinson's disease. Most studies report VN atrophy attributed to dorsal nuclei degeneration [31, 32, 39, 40], while others do not find any difference in CSA between patients and controls [41, 42]. Two recent studies utilized CSA of VN to investigate dysautonomia in patients suffering from diabetes mellitus [19] and bulbar amyotrophic lateral sclerosis [43]. Both studies reported atrophy of VN as documented by ultrasonography, attributed to vagus neuropathy in the case of diabetes

mellitus and to degeneration of nucleus ambiguous in the case of bulbar ALS. In the present study investigating FM and GAD, vagus atrophy could be attributed to dying back neuropathy, consistent with findings in skin biopsy and EDX studies [29, 44].

The present study has certain limitations. The number of patients recruited is moderate. The heterogeneity of clinical forms of FM might have affected not only scores in the clinical scales but also measurements of SSR and CSA in an unpredictable way. In addition, some patients were treated with antidepressant and anti-anxiety medications. A larger cohort of patients, matched for symptoms and medication, would help surpass the above limitations and further strengthen the findings of this pilot study.

Conclusion

To the best of our knowledge, this is the first study to utilize CSA of VN as an additional tool to SSR for the investigation of ANS abnormalities in FM and GAD. Our study suggests that in both clinical entities, CSA VN values are significantly lower compared to those of normal controls. These reductions were similar between FM and GAD. Both diseases share common clinical features, like anxiety and aches. Since both are of unknown etiology, it is justified to hypothesize that a common pathogenic mechanism for at least some of the symptoms may underlie both conditions. There is cumulative evidence in the literature of ANS dysregulation in FM and GAD, but it is not conclusive of the role of each branch of ANS. The present study further supports the above knowledge and adds a new perspective to the investigation of ANS dysregulation using CSA of VN.

Author contribution **Papadopoulou** Marianna: conceptualization, investigation, writing original draft.
Papapostolou Apostolos: conceptualization, investigation.
Bakola Eleni: investigation.
Masdrakis G. Vasilios: methodology.
Moschovos Christos: investigation.
Chroni Elisabeth: review and editing.
Tsivgoulis Georgios: methodology, review and editing.
Michopoulos Ioannis: methodology, formal analysis, review and editing.

Declarations

Ethical approval The research was approved by the Local Ethics Committee of our Institution (A1/19.02.2020).

Informed consent Informed consent was obtained from all participants.

Conflict of interest The authors declare no competing interests.

References

1. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Katz RS, Mease P et al (2010) The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 62(5):600–610
2. Jones GT, Atzeni F, Beasley M, Flüß E, Sarzi-Puttini P, Macfarlane GJ (2015) The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis Rheumatol 67(2):568–575
3. APA - Diagnostic and Statistical Manual of Mental Disorders DSM-5 Fifth Edition [Internet]. [cited 2021 Apr 17]. Available from: https://www.appi.org/Diagnostic_and_Statistical_Manual_of_Mental_Disorders_DSM-5_Fifth_Edition
4. Arnold LM, Hudson JI, Keck PE, Auchenbach MB, Javaras KN, Hess EV (2006) Comorbidity of fibromyalgia and psychiatric disorders. J Clin Psychiatry 67(8):1219–1225
5. Martínez-Lavín M, Hermosillo AG, Rosas M, Soto ME (1998) Circadian studies of autonomic nervous balance in patients with fibromyalgia: a heart rate variability analysis. Arthritis Rheum 41(11):1966–1971
6. Reyes Del Paso GA, de la Coba P (2020) Reduced activity, reactivity and functionality of the sympathetic nervous system in fibromyalgia: an electrodermal study. PLoS One. 15(10):e0241154
7. Hoehn-Saric R, McLeod DR (1988) The peripheral sympathetic nervous system. Its role in normal and pathologic anxiety. Psychiatr Clin N Am 11(2):375–86
8. Kang JH, Kim JK, Hong SH, Lee CH, Choi BY (2016) Heart rate variability for quantification of autonomic dysfunction in fibromyalgia. Ann Rehabil Med 40(2):301
9. Fisher AJ, Newman MG (2013) Heart rate and autonomic response to stress after experimental induction of worry versus relaxation in healthy, high-worry, and generalized anxiety disorder individuals. Biol Psychol 93(1):65–74
10. Friedman BH (2007) An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. Biol Psychol 74(2):185–199
11. Jiang H, Wang L, Wang X, Feng R, Zhang Y, Tu L et al (2013) Comparison of skin sympathetic reaction in patients with generalized anxiety disorder and with major depression disorder. Zhejiang Da Xue Xue Bao Yi Xue Ban 42(2):192–196
12. de Tommaso M, Ricci K, Libro G, Vecchio E, Delussi M, Montemurno A et al (2017) Pain processing and vegetative dysfunction in fibromyalgia: a study by sympathetic skin response and laser evoked potentials. Pain Res Treat 2017:9747148
13. Ozgocmen S, Yoldas T, Yigiter R, Kaya A, Ardicoglu O (2006) R-R interval variation and sympathetic skin response in fibromyalgia. Arch Med Res 37(5):630–634
14. Ozkan O, Yildiz M, Köklükaya E (2012) The correlation of laboratory tests and sympathetic skin response parameters by using artificial neural networks in fibromyalgia patients. J Med Syst 36(3):1841–1848
15. Ozkan O, Yildiz M, Arslan E, Yildiz S, Bilgin S, Akkus S et al (2016) A Study on the Effects of sympathetic skin response parameters in diagnosis of fibromyalgia using artificial neural networks. J Med Syst 40(3):54
16 Ustün TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J et al (2010) Developing the World Health Organization Disability Assessment Schedule 2.0. Bull World Health Organ 88(11):815–23
17. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6):361–370
18. Michopoulos I, Douzenis A, Kalkavoura C, Christodoulou C, Michalopoulou P, Kalemi G et al (2008) Hospital Anxiety and

Depression Scale (HADS): validation in a Greek general hospital sample. Ann Gen Psychiatry 6(7):4
19. Tawfik EA, Walker FO, Cartwright MS, El-Hilaly RA (2017) Diagnostic ultrasound of the vagus nerve in patients with diabetes. J Neuroimaging 27(6):589–593
20. Pelz JO, Belau E, Henn P, Hammer N, Classen J, Weise D (2018) Sonographic evaluation of the vagus nerves: protocol, reference values, and side-to-side differences. Muscle Nerve 57(5):766–771
21. Koo TK, Li MY (2016) A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 15(2):155–163
22. World Medical Association (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310(20):2191–2194
23 Martinez-Lavin M (2007) Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. Arthritis Res Ther 9(4):216
24. Martínez-Martínez L-A, Mora T, Vargas A, Fuentes-Iniestra M, Martínez-Lavín M (2014) Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. J Clin Rheumatol 20(3):146–150
25. Kucera P, Goldenberg Z, Kurca E (2004) Sympathetic skin response: review of the method and its clinical use. Bratisl Lek Listy 105(3):108–116
26. Unlü E, Ulaş UH, Gürçay E, Tuncay R, Berber S, Cakçi A et al (2006) Genital sympathetic skin responses in fibromyalgia syndrome. Rheumatol Int 26(11):1025–1030
27. Ulas UH, Unlu E, Hamamcioglu K, Odabasi Z, Cakci A, Vural O (2006) Dysautonomia in fibromyalgia syndrome: sympathetic skin responses and RR interval analysis. Rheumatol Int 26(5):383–387
28. Papadopoulou M, Papapostolou A, Michopoulos I, Palaiodimou L, Theodorou A, Bregianni M et al (2020) Fibromyalgia and generalized anxiety disorder; common neurophysiological findings may be related to common clinical signs. In: EUROPEAN JOURNAL OF NEUROLOGY. WILEY 111 RIVER ST, HOBOKEN 07030–5774, NJ USA, p 537–8
29. Doppler K, Rittner HL, Deckart M, Sommer C (2015) Reduced dermal nerve fiber diameter in skin biopsies of patients with fibromyalgia. Pain 156(11):2319–2325
30. Breit S, Kupferberg A, Rogler G, Hasler G (2018) Vagus nerve as modulator of the brain–gut axis in psychiatric and inflammatory disorders. Front Psychiatry [Internet]. [cited 2021 Apr 30];9. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00044/full
31. Pelz JO, Belau E, Fricke C, Classen J, Weise D (2018) Axonal degeneration of the vagus nerve in Parkinson's disease-a high-resolution ultrasound study. Front Neurol 9:951
32. Walter U, Tsiberidou P, Kersten M, Storch A, Löhle M (2018) Atrophy of the vagus nerve in parkinson's disease revealed by high-resolution ultrasonography. Front Neurol 9:805
33. Curcean AD, Rusu GM, Dudea SM (2020) Ultrasound appearance of peripheral nerves in the neck: vagus, hypoglossal and greater auricular. Med Pharm Rep 93(1):39–46
34. Al-Kureischi K (1979) Topographic anatomy and fiber diameter of the human vagal trunk. Acta Anat (Basel) 103(3):252–258
35. Tsigos C, Chrousos GP (2002) Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res 53(4):865–871
36. Schlaepfer TE, Frick C, Zobel A, Maier W, Heuser I, Bajbouj M et al (2008) Vagus nerve stimulation for depression: efficacy and safety in a European study. Psychol Med 38(5):651–661
37. Agorastos A, Boel JA, Heppner PS, Hager T, Moeller-Bertram T, Haji U et al (2013) Diminished vagal activity and blunted diurnal variation of heart rate dynamics in posttraumatic stress disorder. Stress 16(3):300–310
38. George MS, Ward HE, Ninan PT, Pollack M, Nahas Z, Anderson B et al (2008) A pilot study of vagus nerve stimulation (VNS) for treatment-resistant anxiety disorders. Brain Stimul 1(2):112–121
39. Sartucci F, Bocci T, Santin M, Bongioanni P, Orlandi G (2021) High-resolution ultrasound changes of the vagus nerve in idiopathic Parkinson's disease (IPD): a possible additional index of disease. Neurol Sci
40. Tsukita K, Taguchi T, Sakamaki-Tsukita H, Tanaka K, Suenaga T (2018) The vagus nerve becomes smaller in patients with Parkinson's disease: a preliminary cross-sectional study using ultrasonography. Parkinsonism Relat Disord 55:148–149
41. Fedtke N, Witte OW, Prell T (2018) Ultrasonography of the vagus nerve in Parkinson's disease. Front Neurol 9:525
42. Laucius O, Balnytė R, Petrikonis K, Matijošaitis V, Jucevičiūtė N, Vanagas T et al (2020) Ultrasonography of the vagus nerve in the diagnosis of Parkinson's disease. Parkinsons Dis 2020:2627471
43. Holzapfel K, Naumann M (2020) Ultrasound detection of vagus nerve atrophy in bulbar amyotrophic lateral sclerosis. J Neuroimaging 30(6):762–765
44. Hulens M, Bruyninckx F, Rasschaert R, Vansant G, De Mulder P, Stalmans I et al (2020) Electrodiagnostic abnormalities associated with fibromyalgia. J Pain Res 9(13):737–744