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Autonomic nervous system functioning associated with psychogenic nonepileptic seizures: Analysis of heart rate variability

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ABSTRACT

Objective: Psychogenic nonepileptic seizures (PNESs) resemble epileptic seizures but originate from psychogenic rather than organic causes. Patients with PNESs are often unable or unwilling to reflect on underlying emotions. To gain more insight into the internal states of patients during PNES episodes, this study explored the time course of heart rate variability (HRV) measures, which provide information about autonomic nervous system functioning and arousal.

Methods: Heart rate variability measures were extracted from double-lead electrocardiography data collected during 1–7 days of video-electroencephalography monitoring of 20 patients with PNESs, in whom a total number of 118 PNESs was recorded. Heart rate (HR) and HRV measures in time and frequency domains (standard deviation of average beat-to-beat intervals (SDANN), root mean square of successive differences (RMSSD), high-frequency (HF) power, low-frequency (LF) power, and very low-frequency (VLF) power) were averaged over consecutive five-minute intervals. Additionally, quantitative analyses of Poincaré plot parameters (SD1, SD2, and SD1/SD2 ratio) were performed.

Results: In the five-minute interval before PNES, HR significantly ($p < 0.05$) increased ($d = 2.5$), whereas SDANN ($d = -0.03$) and VLF power ($d = -0.05$) significantly decreased. During PNES, significant increases in HF power ($d = 0.0006$), SD1 ($d = 0.031$), and SD2 ($d = 0.016$) were observed. In the five-minute interval immediately following PNES, SDANN ($d = 0.046$) and VLF power ($d = 0.073$) significantly increased, and HR ($d = -5.1$) and SD1/SD2 ratio ($d = -0.14$) decreased, compared to the interval preceding PNES.

Conclusion: The results suggest that PNES episodes are preceded by increased sympathetic functioning, which is followed by an increase in parasympathetic functioning during and after PNES. Future research needs to identify the exact nature of the increased arousal that precedes PNES.

1. Introduction

Psychogenic nonepileptic seizures (PNESs) are episodes of movement, behavior, or sensations that resemble epileptic seizures but are not accompanied by epileptiform brain activity on electroencephalogram (EEG). The underlying cause is assumed to be of psychogenic origin. The current diagnostic manuals (DSM-IV-TR, ICD-10) classify PNESs as dissociative or conversion symptoms. Hence, PNESs are considered as involuntary somatic manifestations of emotional distress [1,2]. However, patients often do not report the feelings (e.g., stress, anxiety) that are associated with an episode as well as possible stressors. Nevertheless, some patients describe a "warning" uncomfortable feeling that can last up to hours, followed by a relief from this feeling by the PNES [3].

Investigation of more objective physiological parameters that reflect arousal, which possibly reflects (negative) emotional well-being, could elucidate the circumstances of the episodes, which would facilitate diagnosis and treatment in patients with PNESs [4]. Specifically, measures of heart rate variability (HRV) have often been applied in behavioral science and medicine. Changes in HRV measures reflect changes in (co)activation of the sympathetic and parasympathetic branches of the autonomic nervous system [5]. Stress and anxiety – which elicit

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the sympathetic branch of the autonomic nervous system to initiate a fight or flight response – counteract the parasympathetic (vagal) branch that is considered important for reacting appropriately to external stressors [6,7]. Patients with PNESs are expected to demonstrate decreased vagal functioning, as is found in patients with posttraumatic stress disorder [8], major depression [9], panic disorder [10], and schizophrenia [11]. Indeed, between-group analyses of patients with PNESs and healthy controls indicate a reduced resting vagal tone in patients with PNESs [12–14]. In addition, vagal tone is demonstrated to decrease during PNES episodes compared to rest [14].

Ictal changes in HRV have been described in some detail by Ponnusamy et al. [14] who compared two 3-minute ECG samples, one ictal ECG interval and one interictal ECG interval that was chosen regardless of its occurrence in time in relation to the seizure, in order to elucidate differences in autonomic functioning between patients with epilepsy and patients with PNESs. They identified decreased vagal tone during PNES episodes and an even larger decrease of vagal tone during epileptic seizures. However, based on their study design, no conclusions can be drawn about the periictal pattern of autonomic nervous system functioning that accompanies a PNES episode. Examination over consecutive recording periods may provide more information about gradual changes in measures of HRV. The current study used a within-subject design to investigate the relationship between gradual changes in HRV and the occurrence of PNESs.

2. Materials and methods

2.1. Study population

The study population consisted of twenty patients (2 M/18 F) with a confirmed diagnosis of PNESs. All patients who had been previously monitored with video-EEG for 1–7 consecutive days between July 2010 and February 2012 in the Reference Centre for Refractory Epilepsy of Ghent University Hospital in Belgium for differential diagnosis of PNESs and epilepsy were considered for inclusion. The diagnosis of PNESs was based on the analysis of at least two episodes captured on video-EEG by two epileptologists with extensive experience in this field (KEV and PAB, >10 years experience). Patients with dual pathology (epilepsy and PNESs) were also included when epileptic seizures were controlled and when the PNESs were confirmed by video-EEG monitoring. Exclusion criteria were uncertainty about the diagnosis of PNESs and comorbid psychiatric disorders (e.g., mood and anxiety disorders, schizophrenia and psychosis, and substance-related disorders). The investigation received ethical approval from the Medical Ethical Committee of Ghent University.

2.2. Electrocardiogram recordings

The ECG was recorded via precordial electrode positions V1–V4 throughout the video-EEG monitoring period (1–7 days) with a two-lead channel of the Micromed EEG system (Micromed S.p.A., Mogliano Veneto, Treviso, Italy). The incidence of artifacts was limited by asking the patients to stay in supine position in bed or on a chair during the day and lying down in bed during the night. The start and end of a PNES were defined by the associated motor symptoms (verified by the video recordings), which were often accompanied by unresponsiveness.

2.3. Heart rate variability analysis

Heart rate variability measures were derived according to the recommendations of the task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [5]. Electrocardiogram data were exported from the Micromed reporting system and imported in Matlab (Mathworks Inc., Natick, MA, USA). Custom-built Matlab scripts were used to subsequently carry out R-peak detection, model-based validation, and – if necessary – correction of the list of subsequent RR intervals (tachogram) and HRV parameter calculation over consecutive five-minute intervals.

Two time-domain measures of HRV were calculated: SDANN (standard deviation of the average beat-to-beat intervals) and RMSSD (square root of the mean squared difference of successive beat-to-beat intervals). Standard deviation of average beat-to-beat intervals, in general, reflects the overall cyclic nature of HRV (the more sinusoidal the tachogram is, the higher the SDANN) and is considered to be a measure of overall variability. The square root of the mean squared difference of successive beat-to-beat intervals is considered to be a measure for vagal control of heart rate but also includes respiratory sinus arrhythmia, i.e., the local, intrathoracic effect in HR fluctuations caused by respiratory pressure change during breathing.

Frequency-domain measures of HRV were calculated, using fast Fourier transformation to derive the spectral distribution. Indices included high-frequency (HF) power (.15–.40 Hz), low-frequency (LF) power (.04–.15 Hz), and very low-frequency (VLF) power (3–30 mHz). Efferent vagal activity is a major contributor to the HF component, as has been consistently demonstrated by clinical and experimental observations [15–17]. Consequently, HF power can be seen as a reliable index of parasympathetic nervous system activity. The interpretation of the LF component is more controversial; some studies suggest LF power to be a marker of sympathetic modulation [17–20], while others conclude LF power to be a parameter that includes both sympathetic and vagal influences [15,21]. As a result, it is unclear whether the ratio of the latter two indices (LF/HF) can be regarded as a measure of sympathovagal balance or of sympathetic modulations. The physiological correlates of lower frequency components (VLF) of HRV are still unknown [5].

Quantitative analyses of Poincaré plot parameters were also performed. The Poincaré plot (Fig. 1) is a plot of RR (n) on the *x*-axis versus RR (n + 1) on the *y*-axis; it plots the duration of each RR interval against the duration of the next RR interval. The technique most commonly used to quantify a Poincaré plot is fitting an ellipse to the plot [22–25]. We obtained the standard deviation of instantaneous inter-beat interval (IBI) variability, SD1 (which measures the width of the Poincaré cloud) [25–28], the standard deviation of continuous long-term IBI variability, SD2 (which measures the length of the Poincaré cloud) [25–28], as well as the SD1/SD2 ratio. As a measure of instantaneous changes in IBI, SD1

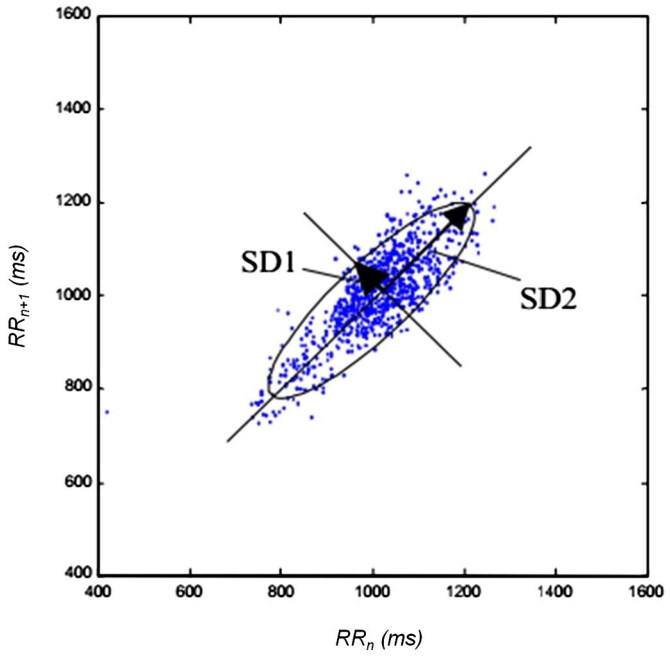

Fig. 1. An example Poincaré plot.

is assumed to reflect vagal efferent activity [25], whereas SD2 expresses the overall variability in heart rate [29].

2.4. Statistical analysis

Our focus was on changes within the time window from approximately 1 h before the occurrence of a PNES until 1 h after the PNES. Therefore, samples of 12 intervals (of 5 min each) that preceded and followed the episodes were selected. Since it was not possible to select 25–26 intervals in total for all PNESs (12 intervals before the PNES (represented as −12 to −1), 1–2 intervals during the PNES (i1 and i2), and 12 intervals after the PNES (+1 to +12)) because of the occurrence of another PNES in a short time window or the removal of intervals which were disturbed by artifacts, N differed per interval. Therefore, confidence intervals were calculated, and nonparametric tests were used. To prevent patients with a high number of seizures from dominating the average, the intervals were first averaged per patient before being entered in the within-subject analysis, resulting in an N of 20. After visual inspection of the plotted averages of the HRV parameters, related-samples Wilcoxon signed-rank tests were used to test for statistical differences between all selected intervals. p-Values < 0.05 were considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

The study population included 20 patients with PNESs (18 women, 2 men, ages: 35.7 ± 10.4 years, number of seizures during registration: 5.9 ± 5.7) who had a total number of 118 PNES episodes during video-EEG monitoring. All the patients had motor signs during the PNES episodes; none of the patients only experienced unresponsiveness during the episodes, although unresponsiveness frequently co-occurred. Information about medication and comorbidity is summarized in Table 1.

3.2. Heart rate and linear heart rate variability parameters

The average heart rate and linear heart rate variability measures are summarized in Table 2 and Fig. 2. Nonparametric related-samples testing demonstrated significant changes in the intervals directly preceding and following a PNES. Between intervals −2 and −1 (the two intervals preceding a PNES), there was a significant increase in HR and a significant decrease in SDANN and VLF. Between interval −1 and PNES interval i1 (the first interval of a PNES episode), there was a significant increase in HF. Between interval −1 and interval +1 (the interval following a PNES), there was a significant increase in SDANN and VLF and a significant decrease in HR.

3.3. Poincaré plot parameters

Nonparametric related-samples tests indicated significant increases in SD1 ($p = 0.010$) and SD2 ($p = 0.019$) between interval −1 and PNES interval i1. The SD1/SD2 ratio significantly decreased between interval −1 and interval +1 ($p = 0.044$). Example Poincaré plots for interval −1 and interval +1 are shown in Fig. 3.

4. Discussion

The current study examined differences in cardiac autonomic functioning associated with the occurrence of PNESs. Cardiac measures were recorded during video-EEG monitoring. Significant changes in HRV measures were identified only shortly before a PNES occurred: In the five-minute interval before a PNES, an average increase in heart rate and decreases in SDANN and VLF power were observed. During a PNES, there was a significant increase in HF power, SD1, and SD2. In the five minutes directly after a PNES, SDANN and VLF power were significantly increased, and the heart rate and SD1/SD2 ratio decreased significantly, compared to the interval preceding a PNES. No significant changes were identified between intervals longer away from the PNES.

Table 1
Participant demographics and characteristics.

ID	Age	Gender	Number of attacks during registration	Medication	Comorbidity
1	40	F	14	Levetiracetam, carbamazepine, interferon beta-1b, paracetamol, and omeprazole	Multiple sclerosis
2	41	F	6	Valproate, venlafaxine, escitalopram, clorazepate, and alprazolam	
3	26	F	2	Levetiracetam and paroxetine	
4	52	F	4	Levetiracetam, topiramate, lorazepam, glucosamine sulfate, and levothyroxine	
5	50	F	2	Acetylsalicylic acid, bisoprolol, oxcarbazepine, pregabalin, ticlopidine, diltiazem, omeprazole, and escitalopram	CREST syndrome and temporal lobe epilepsy (seizure-free with oxcarbazepine)
6	23	F	3	Mirtazapine and salmeterol/fluticasone	
7	51	F	3	Trazodone, duloxetine, tramadol, metformin, alprazolam, fentanyl, pantoprazole, topiramate, and paracetamol	Fibromyalgia and migraine
8	39	F	2	Paracetamol	Narcolepsy (attack-free)
9	37	M	16	Lacosamide and pregabalin	
10	24	M	19	Clonazepam	Posttraumatic brain damage (left hemisphere)
11	34	F	2	Levetiracetam and clonazepam	Juvenile myoclonic epilepsy (seizure-free) and mental retardation
12	23	F	5	Levetiracetam, carbamazepine, lacosamide, clonazepam, and methylphenidate	Generalized tonic–clonic epilepsy
13	48	F	3	Levetiracetam, lamotrigine, baclofen, sertraline, paracetamol, and clonazepam	
14	22	F	5	Aldactazine, levetiracetam, lamotrigine, sodium bicarbonate, escitalopram, tetrazepam, lorazepam, and paracetamol	Interictal epileptic spikes
15	34	F	18	Valproate, levetiracetam, lacosamide, lormetazepam, prazepam, clorazepate, and venlafaxine	Insomnia
16	45	F	2	Pantoprazol, hydroxychloroquine, piroxicam, and prednisone	
17	22	F	3	Propanolol and carbamazepine	Migraine and trigeminal neuralgia
18	42	F	3	Levetiracetam, phenytoin, lacosamide, venlafaxine, simvastatin, phenprocoumon, and nadroparin	
19	35	F	3	Valproate, benzodiazepine, montelukast, omeprazole, metoprolol, and escitalopram	Migraine
20	26	F	3	Escitalopram, pantoprazole, clobazam, and pregabalin	

Table 2
Descriptive statistics of heart rate and heart rate variability parameters. Results are reported as mean (SD) [95% CI]. Abbreviations: HR = heart rate, RMSSD = root mean square of successive differences, SDANN = standard deviation of average beat-to-beat intervals, VLF = very low frequency, LF = low frequency, HF = high frequency, and SD = standard deviation.

	Interval −2	Interval −1	Interval i1	Interval i2	Interval +1
Linear HR(V) measures					
HR	75.1 (8.2) [71.25–78.91]	77.6 (8.6) [73.62–81.64]	78.2 (8.7) [74.18–82.30]	79.4 (11.0) [74.06–84.69]	74.3 (6.9) [71.05–77.48]
RMSSD	0.074 (0.05) [0.05–0.10]	0.066 (0.05) [0.04–0.09]	0.081 (0.05) [0.06–0.10]	0.085 (0.06) [0.06–0.11]	0.068 (0.06) [0.04–0.09]
SDANN	0.817 (0.09) [0.77–0.86]	0.787 (0.08) [0.75–0.82]	0.797 (0.09) [0.75–0.84]	0.789 (0.11) [0.74–0.84]	0.835 (0.11) [0.78–0.89]
VLF power	0.685 (0.15) [0.61–0.76]	0.634 (0.12) [0.58–0.69]	0.655 (0.16) [0.58–0.73]	0.649 (0.17) [0.57–0.73]	0.722 (0.20) [0.63–0.82]
LF power	0.0010 (0.001) [0.00047–0.00184]	0.0015 (0.002) [0.00025–0.00157]	0.0012 (0.001) [−0.00064–0.00319]	0.0013 (0.001) [0.00069–0.00153]	0.0011 (0.001) [0.00070–0.00144]
HF power	0.0026 (0.004) [0.00066–0.00446]	0.0026 (0.004) [0.00077–0.00443]	0.0032 (0.003) [0.00194–0.00452]	0.0033 (0.004) [0.00158–0.00497]	0.0024 (0.003) [0.00109–0.00361]
LF/HF ratio	1.549 (1.32) [0.93–2.17]	1.711 (1.47) [1.02–2.40]	1.298 (1.14) [0.77–1.83]	1.150 (0.73) [0.80–1.50]	1.504 (1.31) [0.89–2.12]
Quantitative Poincaré parameters					
SD1	0.120 (0.06) [0.09–0.15]	0.132 (0.07) [0.10–0.16]	0.163 (0.05) [0.14–0.19]	0.152 (0.06) [0.12–0.18]	0.127 (0.06) [0.10–0.16]
SD2	0.079 (0.06) [0.05–0.11]	0.083 (0.06) [0.05–0.11]	0.099 (0.05) [0.07–0.12]	0.097 (0.06) [0.07–0.13]	0.082 (0.06) [0.05–0.11]
SD1/SD2 ratio	2.306 (1.05) [1.81–2.80]	2.484 (1.29) [1.88–3.09]	2.722 (1.91) [1.83–3.62]	2.356 (1.55) [1.61–3.10]	2.216 (1.10) [1.70–2.73]

4.1. Clinical interpretation

The increase in heart rate and decrease in SDANN in the interval before a PNES suggest an increase in sympathetic functioning and therewith an increase in arousal, shortly before a PNES episode. These findings are consistent with the hypothesis that PNESs are caused by – and are the somatic manifestation of – increased (emotional) discomfort [1,3]. The discomfort can result from internal or external sources of stress but could also be caused by "prodromal" feelings that an episode is coming which may cause uncomfortableness [3]. Another explanation of the increased sympathetic functioning which precedes PNES episodes is the body's anticipation to movement, which could either be conscious or subconscious.

The significant increases in HF power and SD1 during an episode suggest increased vagal influence, which implies that PNES occur in a state of relative relaxation. The significant decreases in HR and SDANN in the interval following a PNES, when compared with the values in the interval before the episode, suggest a decrease in sympathetic functioning resulting from the episodes. Based on this apparent calming effect of PNES episodes, a plausible function of a PNES may be to serve as a coping mechanism to deal with tension. These findings correspond well with patients reporting that tension is alleviated after a PNES [3].

The significant increase in SD2 during the episode and the decrease in SD1/SD2 ratio following a PNES, when compared with the interval before the episode, are more difficult to explain since SD2 reflects total variability [29]. Similarly, the physiological nature of VLF power, which decreased in the interval before the PNES and then increased after the PNES, is still unclear [5].

Our findings are contradictory to the results of Ponnusamy et al. [14] who found significant decreases of RMSSD and HF power during PNES episodes when compared to interictal intervals. An important factor that may explain this discrepancy may be the differences in study design (in the study of Ponnusamy et al., the interictal ECG samples differed in occurrence in time relative to the PNES episode).

4.2. Implications for treatment

Our findings of increased arousal before, and alleviation by, PNES episodes could have important implications for the psychological treatment of PNESs. These findings suggest that PNES episodes are adopted as a coping style to decrease (emotional) arousal. In patients with PNESs with similar HRV patterns, therapy should focus on showing the patients insight into their behavior and on replacing invalidating coping styles with other means for stress reduction and relaxation techniques. However, if the increased sympathetic functioning is caused by an aroused feeling because the patient feels that an episode is coming, the implication for treatment is different, and therapy should focus on means to avoid the attack.

In the future, after consistent replication of our findings in individual patients also, heart rate variability measurements themselves could also be valuable for treatment: If the occurrence of a PNES could eventually be predicted by HRV measures within individual patients, it would be possible to design an ambulatory device that monitors these physiological characteristics. Ambulatory monitoring during everyday life, in the subject's own environment (naturalistic settings), could be of additional value in the course of psychological treatment, providing information about individual (reactivity to) (socio)emotional stressors (tracked by diary keeping). It would be particularly important for the examination of the situations which elicit PNESs in the individual patient. This knowledge could eventually improve the psychological treatment of patients with PNESs. However, therapists should consider the feelings of stress which might be elicited by the handling of a device and diary keeping in some patients, which might adversely affect the treatment. Finding a relationship between HRV parameters and PNESs could also offer options for treatment in the form of biofeedback, although

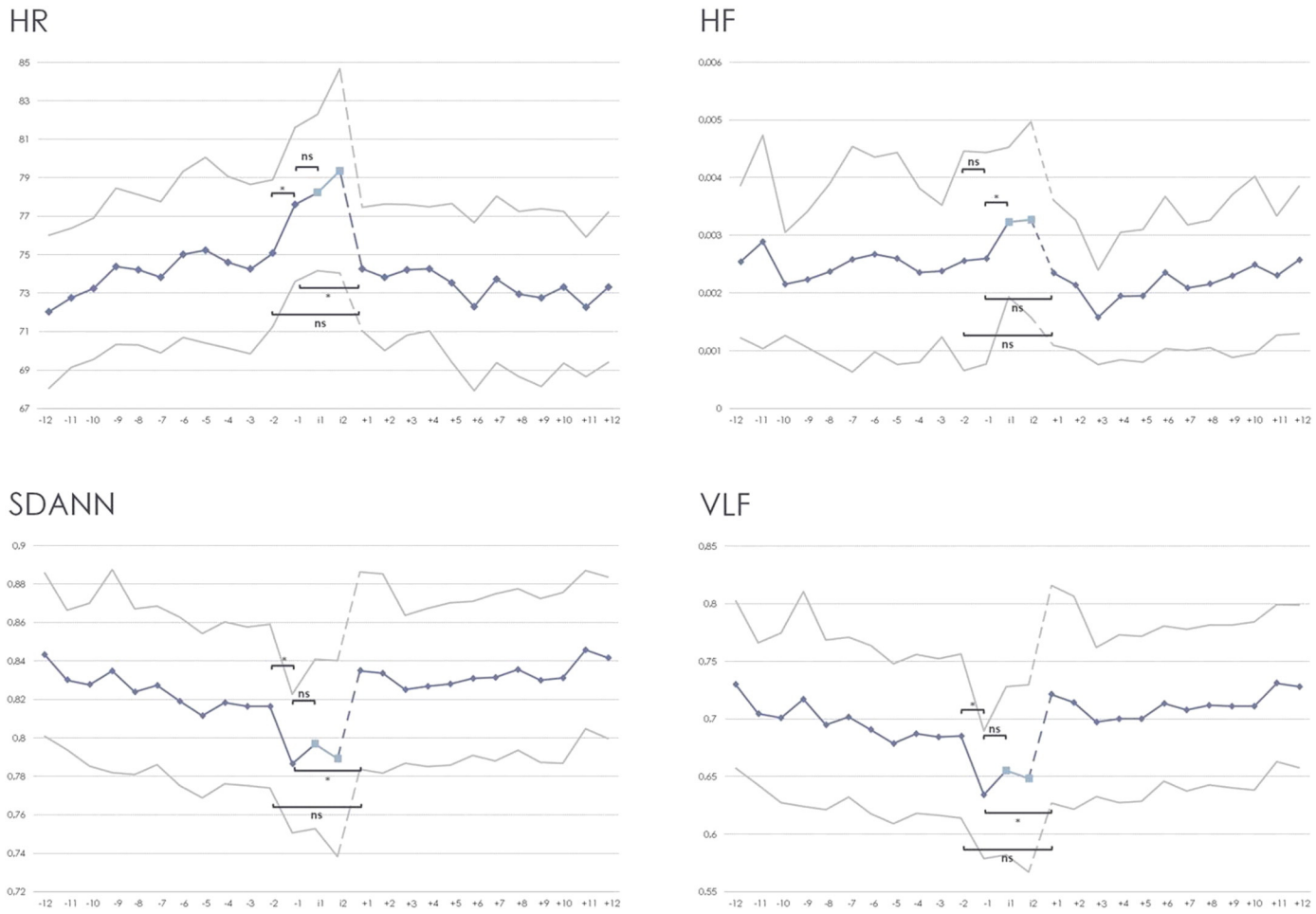

Fig. 2. Average pattern of heart rate and linear heart rate variability indices which demonstrated significant changes before, during, and after PNES episodes. The blue line represents the average HR/HRV characteristic, with 95% confidence intervals in gray. Each interval lasted approximately 5 min: Intervals −12 to −1 comprise the hour preceding a PNES, the intervals i1 and i2 cover the PNES, and the hour following the PNES consists of the intervals +1 to +12. The line between interval i2 and +1 is dashed because not all patients had episodes consisting of exactly 2 intervals. * = $p < 0.05$ and ns = not significant. HR = heart rate, HF = high-frequency power, SDANN = standard deviation of average NN intervals, and VLF = very low-frequency power. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

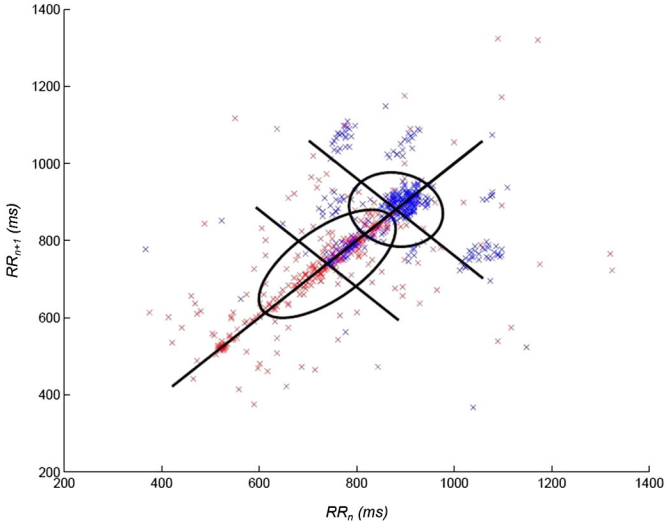

Fig. 3. Example Poincaré plots of the 5-minute intervals directly before and after a PNES episode. The preseizure interval is depicted in red and the postseizure interval is depicted in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

sensitivity (avoidance of false-positive warnings) and unobtrusiveness of the device are important concerns.

4.3. Limitations

This study had an exploratory character and therewith included a relatively small study population. The small study population may have led to type I errors (false negatives) due to lack of power, while the relatively large amount of comparisons may have resulted in type II errors (false positives). Also, only patients with major motor symptoms were studied, and none of the patients experienced PNES episodes only characterized by unresponsiveness. Future research should include both patient types, although the duration of episodes of unresponsiveness could be difficult to determine. Related to the previous point is the fact that possible nonmotor stadia of a PNES (consisting of behavioral, sensory, perceptual, and cognitive components) are difficult to determine and are not considered in the current study. As a result, what we consider as preictal and postictal changes in HR(V) metrics may in fact be ictal changes.

Also, many patients were on (antiepileptic) medication, of which the effects on the autonomic outcome measures are not exactly known. Ponnusamy at al. [14] reported no significant differences in the majority of the HRV measures between patients with PNESs on antiepileptic medication and patients with PNESs not on antiepileptic medication. However, in view of conflicting reports of other studies of the influence

of antiepileptic medication on heart rate variability [30–32], we do not know to what extent our findings are influenced by these medications.

Furthermore, we emphasize that the physiological interpretation of most HRV parameters is mainly based upon experimental findings in various clinical studies. The understanding of the complex physiological processes that govern HRV and their intricate interrelations is still in its infancy. We admit that the concept of "overall variability", in fact, is poorly defined and, when associated with different HRV parameters, may lead to seemingly conflicting results.

4.4. Conclusions

Our study suggests that PNES episodes are preceded by increased sympathetic functioning, which is followed by an increase in parasympathetic functioning during and after a PNES. Future research is needed to identify the exact cause of the increased arousal that precedes PNES episodes: Do PNESs serve as a coping mechanism in dealing with increased (emotional) arousal or is the increased arousal caused by the prodromal feeling that the attack is coming?

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose.

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