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Freezing of gait in Parkinson's disease increases sympathetic and parasympathetic indices

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Abstract— The assessment of autonomic activity in various clinical contexts relies on the analysis of heart rate variability (HRV). Standard HRV analyses often fall short in effectively disentangling sympathetic and parasympathetic activations. Recently, we introduced an HRV methodology based on Poincaré plot analysis. This approach provides time-resolved estimations of the primary HRV rhythms, separately from the changes in the baseline interbeat interval duration. It utilizes a robust covariance matrix estimation technique grounded in the Ledoit-Wolf approach. Through this method, we derived the Cardiac Sympathetic and Parasympathetic Indices (CSI, CPI) and compared them to the pre and post freezing of gait (FOG) episodes in patients with Parkinson's disease. Our method outperforms standard spectral counterparts of HRV in monitoring autonomic activity. This highlights their value for future development in wearables for real-time monitoring of FOG episodes through HRV analysis.

Keywords— Parkinson's disease, heart rate variability, freezing of gait, autonomic dysregulation.

I. INTRODUCTION

Autonomic dysfunction is a common manifestation of Parkinson's disease (PD), affecting various bodily functions[1]. One prominent symptom is freezing of gait (FOG), characterized by sudden, temporary episodes of immobility while walking. Recent research suggests a potential connection between autonomic dysfunction and FOG in PD[2], implicating autonomic dysregulation in its pathophysiology. Heart rate has revealed its potential to signal an ongoing FOG[3], but the role of heart rate variability (HRV) still remains unclear. We recently developed robust estimator of cardiac sympathetic and parasympathetic activities [4]. Our approach separates heart rate and HRV components of cardiac sympathetic and parasympathetic activities, building upon a time-resolved estimation of the eigenvalues of the covariance matrices of successive changes in the inter beat intervals. In this study we show how these cardiac indices successfully depict the physiological response triggered by FOG events and compare it to standard heart rate, low and high-frequency approaches.

II. MATERIALS AND METHODS

A. Dataset description

Ten adults with PD and history of FOG (5 males and 5 females, aged 69.1 years with 9.3 years since diagnosis, on average) were recruited under suspended dopaminergic therapy for at least 12 hours. The task started from a sitting state, they had to stand up and walk following a circuit of corridors, with obstacles and changes in direction. ECG was measured using MOVE system (Brain Products GmbH, Gilching, Germany) with a sampling frequency of 1000 Hz.

FOG events were detected by a specialist based on behavior, and considered in this study if they had a minimum

duration of 20 s and, previous the event onset, there were no other FOG events for at least 60 s. All events that fulfilled the criteria were considered as individual measurements. To assess the prediction capacity of the autonomic markers, the onset of the FOG events was considered 5 s before the one manually marked. Trials were considered in the -10 to 10 s with respect the onset of the defined event. A total of 46 FOG events fulfilling the above-mentioned criteria were identified among all participants.

The study was approved by the local ethical committee (Beijing Xuanwu Hospital, China, n° 2019-014). All participants signed informed consent to participate in the study as required by the Declaration of Helsinki. For further detail on the experimental procedures, please refer to the original study [5].

B. Cardiac sympathetic and parasympathetic indices

The ECGs' R-peaks were automatically identified [6] and subsequently adjusted manually to correct any misidentifications or ectopic beats. Following this, interbeat interval series (IBI) were generated based on the durations between successive R-peaks.

To accurately gauge the fluctuating properties of the changes in IBI time series, a robust and time-resolved estimation of the cardiac sympathetic and parasympathetic indices was conducted [4]. Three features were quantified from the successive changes in the IBI duration, as typically depicted in the Poincaré plot [7]. These features included R, indicating the distance to the origin of Poincaré ellipsoid, SD_1 and SD_2 , representing the short and long-term fluctuations of HRV. These metrics were combined into the cardiac sympathetic (CSI) and parasympathetic indices (CPI):

$$R(t) = \sqrt{\text{mean}(IBI_{i,\dots,n-1})^2 + \text{mean}(IBI_{i+1,\dots,n})^2} \quad (1)$$

$$[SD_1(t), SD_2(t)] = [\sqrt{\lambda_1}, \sqrt{\lambda_2}] \quad (2)$$

$$CSI(t) = SD_2(t) + \tilde{R}(t) \quad (3)$$

$$CPI(t) = SD_1(t) \cdot 10 + R(t) \quad (4)$$

where λ_1 and λ_2 are the shorter and larger eigenvalues of the covariance matrix of $IBI_{i,\dots,n-1}$ and $IBI_{i+1,\dots,n}$, and n is the length of the IBI array in the current time window. A robust estimator of the covariance matrix was obtained using a shrinkage covariance estimator based on the Ledoit-Wolf approach for the analytic calculation of the optimal shrinkage intensity [8]. The means were computed using a robust mean algorithm that excludes the 5% of outliers. Before CSI and CPI computation, R, SD_1 and SD_2 means were recentered, based on their computation through the whole recording, and

\tilde{R} is the flipped R with respect the mean. The computations were done using a sliding time window with a length of 15 s [9], and a step defined by each heartbeat.

CSI and CPI values were averaged for the conditions pre vs post FOG events, in an interval of 10 seconds, and compared to those markers obtained from mean IBI, low (LF) and high-frequency (HF) HRV. LF and HF were computed using a smoothed pseudo-Wigner–Ville distribution, based on a Fourier transform performing a filtering in time and frequency [10].

C. Statistical analysis

To evaluate the performance of the markers in discerning the conditions pre and post FOG, we used a non-parametric signed-rank test for paired samples. Time series were z-score normalized per trial. The group-wise descriptive measures are expressed as medians and median absolute deviations (MAD).

III. RESULTS

We investigated autonomic dynamics in patients with PD experiencing FOG. Using our proposed methodological approach based on the Poincaré plot, we computed cardiac sympathetic and parasympathetic activities (CSI, CPI). Table I shows the statistical comparisons between pre-FOG and post-FOG conditions, demonstrating the effectiveness of CSI and CPI in distinguishing between the two states. Furthermore, comparisons of standard markers such as mean IBI, low frequency (LF), and high frequency (HF) support the reliability of CSI and CPI in characterizing autonomic dynamics.

TABLE I. SIGNED-RANK TEST ON HEART RATE VARIABILITY MARKERS COMPARING PRE- VS POST-FREEZING OF GAIT EPISODES

Marker	Median (MAD) pre vs post freezing	p-value ^a	Z-value
CSI	-0.767(0.109) vs 0.783(0.111)	$2 \cdot 10^{-7}$	-5.1950
CPI	-0.699(0.168) vs 0.713(0.171)	$7 \cdot 10^{-6}$	-4.4849
LF	-0.731(0.144) vs 0.746(0.147)	0.0011	-3.2721
HF	-0.756(0.127) vs 0.771(0.130)	$6 \cdot 10^{-5}$	-4.1353
IBI	0.024(0.381) vs -0.025(0.389)	0.2491	1.1526

^a. Significance based on Bonferroni correction defined at $p < 0.01$.

Fig. 1 shows that 5 seconds prior to the onset of a FOG event, both CSI and CPI start to rise, maintaining this elevation throughout the FOG episode. These observations indicate that CSI and CPI exhibit a significantly increased ability to differentiate between pre and post-FOG periods.

IV. DISCUSSION

We have investigated the physiological responses associated with FOG events in PD patients through a precise and time-resolved estimation of cardiac sympathetic and parasympathetic activities [4]. Our approach effectively captures the alterations in autonomic activity expected during FOG events. Grounded in the Poincaré plot, our method proficiently captures beat-to-beat variations in heart rate and short- and long-term fluctuations in HRV. Our proposal provides a time-resolved estimation method, facilitating a thorough exploration of dynamic shifts in autonomic regulations. This study underscores the effectiveness of CSI and CPI particularly in accurately monitoring the

physiological response to FOG, surpassing the capabilities of standard heart rate and HRV[3].

The significance of this research includes its cost-effective nature, which paves the way for a routine monitoring of autonomic function in neurodegenerative conditions. Wearables offer a promising avenue for monitoring and potentially preventing falls in patients experiencing FOG. By continuously tracking autonomic and gait patterns in real-time, these devices could provide timely interventions to mitigate the risk of falls [11]. Providing a reliable method for estimating cardiac autonomic activity, this research could also advance our comprehension of the underlying pathophysiology of PD.

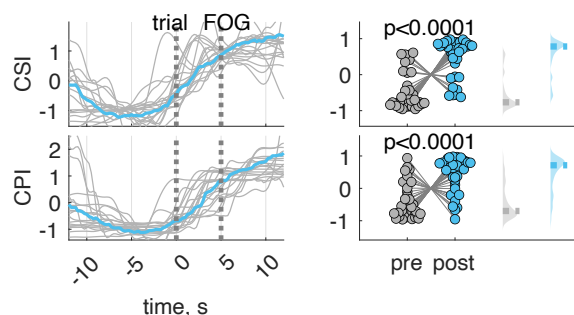


Fig. 1. Cardiac sympathetic and parasympathetic indices (CSI, CPI) under freezing of gait (FOG) episodes. CSI and CPI values were used to quantify the autonomic changes triggered instants (5 s) before the observed by the FOG event. Thick blue signals indicate the group median and light gray ones individual trials (one third for visualization purposes). The right panel displays the distribution of the average pre and post-FOG within a 10 s latency. All amplitude units are arbitrary units.

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