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Disruption of the Cortical-Vagal Communication Network in Parkinson's Disease

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Abstract— **Parkinson's disease (PD) is a neuropathy characterized by motor disorders, but it has also been associated with the presence of autonomic alterations as a result of degradation of the dopaminergic system. Studying the relation between Band Power time series (BPts) and Heart Rate Variability (HRV), has been proposed as a tool to explore the bidirectional communication pathways between cortex and autonomic control. This work presents a primer analysis on study brain ↔ heart interaction on a databse of PD patients under two conditions: without and after levadopa (L-dopa) intake. Additionally a healthy control population was also analyzed, and used as comparison level between both conditions. Results show PD affects pathways by reducing the number of connections, specially association of beta and power and the second faster component of HRV seems to be more sensitive to L-dopa administration.**

I. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative process that reduces the number of dopaminergic neurons [1]. It is mainly related with motor symptoms like body tremor and gait alterations [2]. Electroencephalographic (EEG) signal analysis has been explored to find useful biomarkers that can be used as diagnostic tool on early symptoms, evaluate disease progression or to increase knowledge about alterations related to PD evolution. Quantitative EEG analysis has shown that PD alters beta band. For example, He et al. [3] observe an increase on the interhemispheric coherence on early onset patients. Spay et al. [4], study a PD population with impulse control disorder observing an alteration on beta and gamma bands over the supplementary motor area and therefore the authors propose the power over beta band as a predictor of the impulse control disorder. Piña-Fuentes et al. [5], offer a literature review and meta–analysis of studies related to PD and dystonia patients, and also note that beta band was used as a descriptor on the selected eight studies. On the other hand, Geraedts et al. [6] conclude, after a literature review, that EEG presents a slower pattern tending to larger value on theta band.

Several publications have used network analysis to explore changes in the EEG dynamics over PD patients. Utianski et al. [7], show that the network integration is different between cognitively normal patients and those with dementia. Evangelisti et al. [1] analyze, using functional magnetic resonance images and EEG signals, the effect of levadopa (L-dopa) administration on PD patients. Their work show no significant change of the intramotor area connection network, but an increased interaction with the rest of the brain regions.

Heart ↔ brain interactions have been observed while in resting state in healthy subjects [8]. They have been associated with emotional valence [9], further, their distribution changes during the realization of a controlled breathing task [10], [11] and depends also on the EEG band being analyzed. PD could be associated with alterations on Autonomic Nervous System (ANS), modifying heart rate [12]. In 2013, Liou et al. [13] showed correlations between HRV and EEG power over different bands and that this correlation changes depending on a breathing task.

Extending these ideas this work explores the interactions between HRV signal and Band Power time series (**BPts**) of the EEG on recordings from a publicly available PD database [14]. Our results confirm that the network structure is altered on PD compared with a healthy control group, but also that L-dopa administration produces differential changes on networks associated with different spectral components of the HRV signal.

II. MATERIALS AND METHODS

A. Database

For this work, data was obtained from the "Resting State EEG Data from Patients with Parkinson's Disease" public dataset collected at the University of San Diego and curated by Alex Rockhill at the University of Oregon [14]. All participants provided written consent in accordance to the Institutional Review Board of the University of California, San Diego and the Declaration of Helsinki [15]. EEG and ECG from 14 subjects with PD and 16 healthy subjects, all right handed, 17 female, ages 50 through 82, sampled at 512 Hz was analyzed. Data from Parkinson's subjects was obtained on two sessions, "**On**" and "**Off**" their medication, while healthy subjects (**HC**) just went through one session, no tasks were performed during sessions. Following the handedness test, BDI, MMSE and NAART evaluations the EEG setup and recordings began, each with a duration of three minutes. Subjects were instructed to relax, keep their eyes open and maintain fixation on a white cross at the center of the screen.

B. Signal processing and analysis

The ECG signal was filtered with a 4^{th} order Butterworth [0.7-20]Hz filter and processed with a modified Pan and Tompkins QRS detection method, to obtain the temporal

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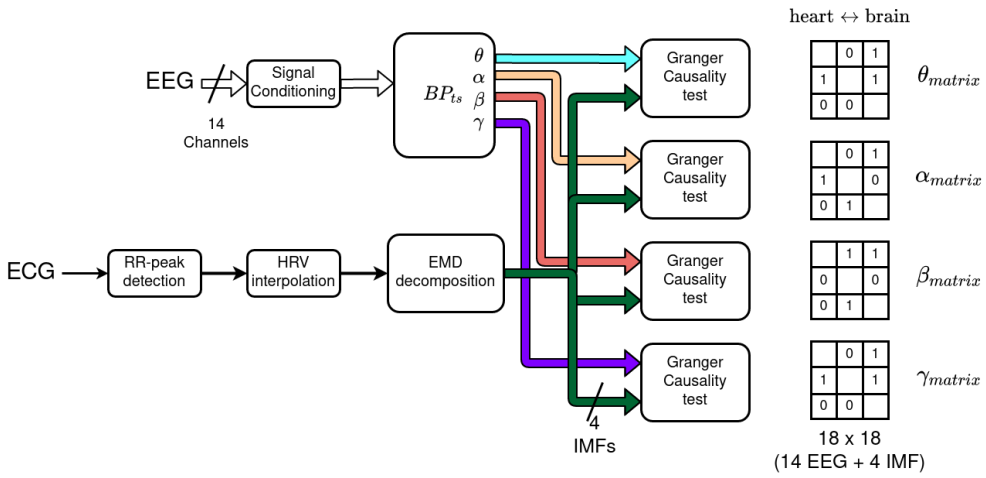

Fig. 1. Signal processing pipeline. EEG is conditioned and band-filtered to compute **BPts** for each band. R peaks are detected from ECG and the HRV series is interpolated from this data, and further decomposed using EMD. Granger causality tests are run among the processed signals (details in text).

indices of the R peaks [16]. The HRV signal was then interpolated at a sampling frequency of 10 sps using a cubic spline. Lastly the HRV signal was decomposed into intrinsic mode functions (IMF) using the Empirical Mode Decomposition (EMD) method, and obtaining up to four IMFs, being IMF1 the fastest and IMF4 the slowest. The band power time series **BPts** were estimated for alpha (**BPts**$_\alpha$, [8-12]Hz), beta (**BPts**$_\beta$, [14-30]Hz), gamma (**BPts**$_\gamma$, [30-100]Hz) and theta (**BPts**$_\theta$, [4-8]Hz) bands with a sliding window of two seconds and a sliding step of 0.1 seconds using the Welch periodogram estimator.

Finally, a Granger causality test, on both directions, was run between the **BPts** of each EEG frequency band and channel (Fp1, Fp2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, and O2) and the HRV IMFs. A total of 306 possible connections were tested per each subject. A causal correlation found between two signals does not imply a physical connection, but detects causality relationship from the first signal to the second. This method is based on a linear regression model of stochastic processes and was obtained using Seth's Matlab toolbox [17], [18]. The signal processing pipeline is summarized in Fig. 1.

III. RESULTS

Fig. 2 shows the total number of G-caused connections by EEG band, HRV component and direction. Data shown on these heatmaps correspond to the total sum of positive connections regardless of channel or subject. The upper panels correspond to the information pathway from **BPts** $\rightarrow$ IMF and it is larger than in the opposite direction (IMF $\rightarrow$ **BPts**). Both results are in accordance to previous studies on healthy population [8], [9], [10], [11], [19]. Analyzing by EEG band power, **BPts**$_\theta$ presents larger number of connections than **BPts**$_\gamma$, **BPts**$_\beta$ and **BPts**$_\alpha$, this order is quite similar for both directions and also agrees with previous reports. IMF3 and IMF4 components show the larger number of connections on **BPts** $\rightarrow$ IMF direction, nevertheless this could be an artifact associated with the short recording durations, so their analysis will not be considered herein. Comparison between the groups show that in general HC presents larger connection numbers than the other two groups in both directions, except for HRV$\rightarrow$**BPts**$_\alpha$, indicating that presence of PD has effect on the cortical-ANS network. In general **On** group achieves lower number of connections than **Off** group; additional details will be listed in the following.

The **BPts** $\rightarrow$ IMF direction shows that:

- **On** group achieves the second shorter number of connections for **BPts**$_\alpha$ and IMF1. For this pair the **Off** achieves larger number than the remaining groups.
- For **BPts**$_\beta$ $\rightarrow$ IMF2 **On** group recovers a similar number of connections. This is an interesting result, because the dynamics of such HRV component is useful to discriminate between groups.
- Also for **BPts**$_\beta$ and **BPts**$_\alpha$ the number of connections for IMF1 is close to half of those achieved for IMF2.
- **BPts**$_\gamma$ $\rightarrow$ IMF1 association evidences that **On** condition reduces the number of connections, perhaps given the L-dopa intake. This was the minimum value achieved for all the comparisons and is significantly reduced (three versus 21) when compared with the **Off** group.
- From **BPts**$_\theta$ analysis the general order of connection numbers follows: **HC**, **Off** and **On**. With larger connections related with IMF2 component.

The IMF $\rightarrow$ **BPts** direction shows that:

- In **BPts**$_\alpha$, the number of connections is reduced for **HC** on IMF1, and has apparently no effect associated with L-dopa administration on IMF2.
- For **BPts**$_\beta$ **On** and **Off** groups, have exactly the same number of connections (four), on IMF1 and IMF2. This is about two fifths and one third the number of connections observed for **HC** group.
- **BPts**$_\gamma$ and **BPts**$_\theta$ analysis observe the overall tendency,

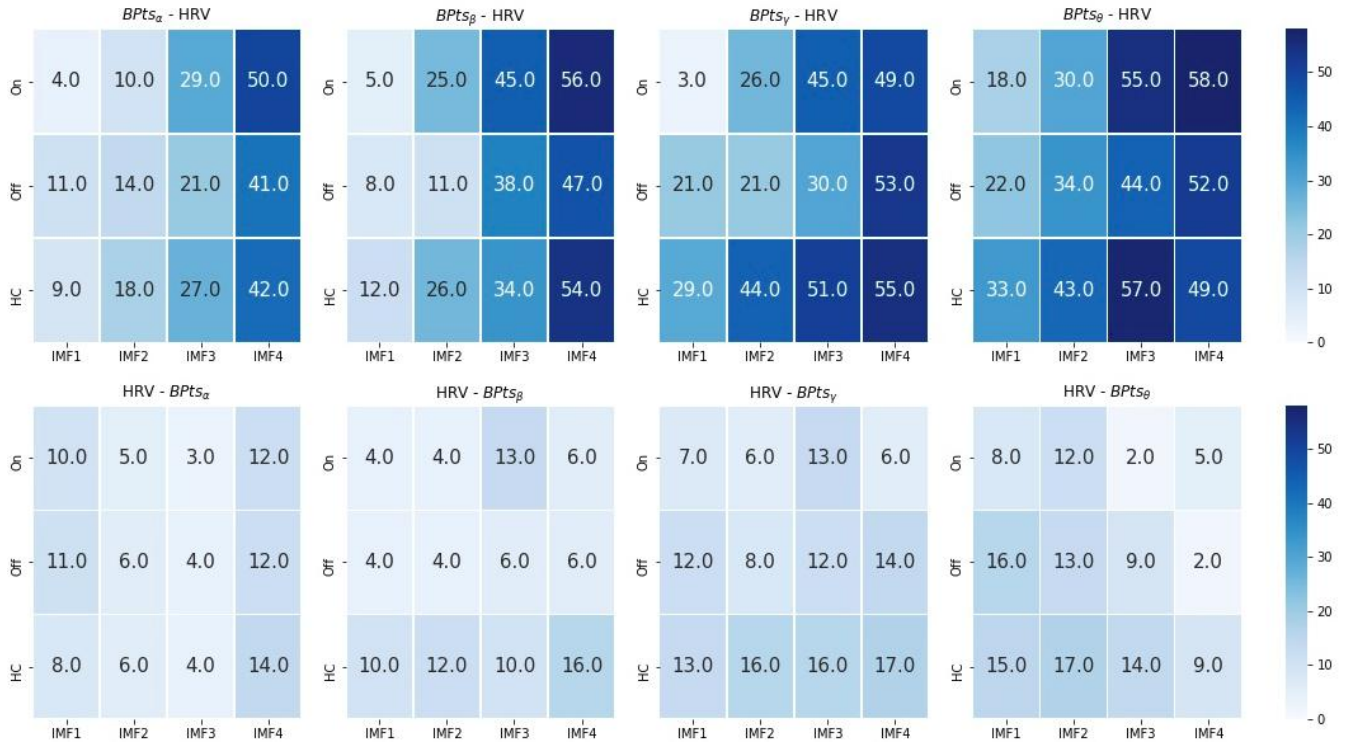

Fig. 2. Cumulative sums expressed in total numbers of G-positive relationships. The first row corresponds to the **BPts** $\rightarrow$ HRV direction and the second to the HRV $\rightarrow$ **BPts** direction, on both the columns correspond to alpha, beta, gamma and theta bands respectively. On each panel rows correspond to **On**, **Off** and **HC** and columns to IMFs 1 through 4 respectively.

a gradient from **On**, **Off** and **HC** groups.

- For this direction the number of counts, over IMF1 and IMF2, were: $\mathbf{BPts}_\alpha$- 46, $\mathbf{BPts}_\beta$- 38, $\mathbf{BPts}_\gamma$- 62 and $\mathbf{BPts}_\gamma$- 81. Leaving beta band with the lowest number of connections.

IV. DISCUSSION

The results reported in this work suggest that PD affects the cortical-ANS network and that L-dopa intake does not reestablish the network conditions. In both directions, the number of connections follows an overall ascending gradient with this order: **On**, **Off** and **HC**. This result could indicate that PD reduces the network integrity, settling it on a new architecture with a reduced number of connections, and L-dopa intake also reduces this network integrity overall but for beta band connections. Studies related with L-dopa intake [20] have shown an increase in beta power, but combined with the results presented here this increase is not necessarily related with an efficient communication. This hypothesis must be confirmed or discarded by first extending the number of subjects and performing longer studies that allow to clearly observe the effects over sympathetic and parasympathetic ANS branches.

The number of connections in terms of band and IMF component agrees with results already reported on healthy subjects by the same work group [19]. However, the larger numbers that were associated with theta band could be related to aging effects not previously observed. Another interesting point analyzing this band is that the difference between **HC** and **Off** is the lowest for any other comparison. PD patients are characterized by a slower EEG signal or increased theta power, suggesting that in this band the cortical-ANS communication is not affected and is possibly used as preferred pathway instead of the usual beta and alpha tracks. All these results suggest that PD affects the ANS or its communication with cortical levels, at least at a sub–clinical level. Network analysis over bidirectional **BPts** $\leftrightarrow$ HRV causal relationships should be used as a tool to evidence this lack of communication.

If PD affects communication with far long nodes like vagal outflow, possibly this altered communication is also associated with some other cognitive disorders commonly present on these patients. Future work to fully understand the implications of PD over ANS should be addressed using Holter recordings, pupil dilation, galvanic response or some other variable that conveys ANS outflow.

The principal shortcoming of this work corresponds to the recording duration. A three minute length is not enough time to fully address sympathetic or parasympathetic contribution to the HRV signal, so, the presented results must be considered cautiously. Nonetheless, the results shown agree with the knowledge about these networks interaction, pinpointing to the use of these analysis tools to fully assess PD.

V. CONCLUSIONS

Cortical–ANS network analysis suggests that PD could affect communication pathways between cortical centers and vagal effectors that control heart rate. For the four EEG

bands analyzed, a reduction in the number of connections was observed for the **On** and **Off** groups compared with **HC**. $\mathbf{BPts}_{\beta} \rightarrow$ IMF2 communication was the only one that achieved similar number between **HC** and **On**, suggesting that only beta band is sensitive to L-dopa intake. The overall tendency shows that **On** group evidences the lowest number of G-causal connections, and this interesting finding suggests L-dopa administration could recover EEG band power level, but does not necessary means an efficient network communication is reestablished. Finally, analysis of **BPts** $\leftrightarrow$ HRV interactions has shown again that it could be a complementary tool for highlighting sub–clinical effects associated with PD.

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