

# Lower Instantaneous Entropy of Heartbeat Dynamics Characterizes Cognitive Impairment in Parkinson's Disease

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## Abstract

*It has been estimated that the incidence of cognitive deficits in Parkinson's disease (PD), ranging from Mild Cognitive Impairment (MCI) to frank dementia, is six-fold compared to that in the general population. Also, PD involves postganglionic sympathetic failure and, in 25% of patients, autonomic failure. PD patients commonly present a range of ANS-dysfunction related symptoms. Since cognitive impairment has been previously linked with cardiovascular dysautonomia in PD, in this paper we investigate whether a link exists between autonomic complexity and MCI in PD. To this end, we employ our recently developed instantaneous measures of complexity, which have been explicitly designed for stochastic time series with binary events that occur in continuous time: the inhomogeneous point-process approximate and sample entropy (ipApEn and ipSampEn, respectively). Experimental results obtained by comparing 8 cognitively preserved (PD-NC) to 8 PD-MCI subjects during resting state demonstrate that grand average values of ipSampEn are able to differentiate the two groups. This suggests that a significant loss of time-varying cardiovascular complexity is associated with MCI in PD. Importantly, no other heart rate variability (HRV) measures differed significantly between groups, possibly pointing toward subtle autonomic changes (not detectable through conventional HRV analysis) which accompany the initial stage of cognitive impairment in PD.*

## 1. Introduction

Parkinson's disease (PD), a common neurological disorder in aging people, is classically associated with

motor symptoms including tremor, balance problems, limb rigidity, bradykinesia and gait abnormalities. However, PD patients frequently present Autonomic Nervous System (ANS) dysfunctions such as cardiovascular alterations, constipation, abnormal salivation and sweating, urinary leakage, and sexual dysfunctions, even in the early stages of the disease. Accordingly, Lewy bodies (the pathological hallmark of PD), have been found in a number of ANS regions such as the hypothalamus and the sympathetic/parasympathetic systems. Additionally, it has been estimated that the incidence of cognitive deficits in PD, ranging from Mild Cognitive Impairment (MCI) to frank dementia, is six-fold compared to that in the general population. Over the course of their lifetime, up to 80% of PD patients will eventually develop dementia [11]. While MRI studies have investigated central correlates of motor/non-motor symptoms of PD [12,13] and the mechanisms underlying differential modulation of cognition in PD [14], the brain areas involved in PD-related dysautonomia are unknown. Also, some studies have documented an association between cognitive dysfunction and neurocirculatory abnormalities [6] such as cardiovascular autonomic failure [8].

It has been widely accepted that the quantification of ANS complexity can provide useful information on psychophysiological and pathological states [2-5,7,9,10]. Accordingly, we have previously demonstrated how the stability and complexity of autonomic dynamics is altered in PD patients when compared to healthy controls [2]. In this study, we hypothesize that the complex behavior of ANS activity is further modulated by the presence of MCI in PD. We investigate ANS dynamics through analysis of the series obtained by computing the time intervals between two consecutive R-waves detected from the

Electrocardiogram, i.e. the R-R intervals, whose variability is defined as Heart Rate Variability (HRV) [3]. In particular, we employed recently proposed definitions of approximate and sample entropy based on the inhomogeneous point-process theory: the inhomogeneous point-process approximate and sample entropy (ipApEn and ipSampEn, respectively) [4]. To this end, the unevenly sampled RR interval series is modeled through probability density functions, which characterize and predict the time until the next event occurs as a function of the past history. Within this framework, Laguerre expansions of the Wiener-Volterra autoregressive terms account for long-term nonlinear information [4,5,9]. As the proposed measures of entropy are instantaneously defined through probability functions, these novel indices are able to provide instantaneous tracking of complexity [4,9].

In a previous study [2], we demonstrated the application of these concepts to the estimation of instantaneous linear and nonlinear heartbeat dynamics from PD patients vs. healthy controls. In this paper, these measures are tested on data gathered in sixteen PD patients, of which 8 are cognitively preserved (PD-NC) and 8 affected by MCI (PD-MCI).

## 2. Materials and methods

### 2.1. Point-process nonlinear modeling of heartbeat dynamics

We assume history dependence and an inverse Gaussian probability distribution of the waiting time indicating the probability of having an event at time  $t$  given that a previous event has occurred. The mean of the probability function  $\mu_{RR}(t)$  can be interpreted as signifying the most probable moment when the next event could occur [1]. In order to compute the ipApEn and ipSampEn indices, which are described in the next paragraph, we apply a specific model formulation based on a Nonlinear Autoregressive Model with Laguerre expansions (NARL) [4,5,9]. Of note, we process the derivative R-R series to improve on the achievement of stationarity within the sliding time window  $W$  (in this study  $W=90$  s.) [4,5,9].

As major advantage, the Laguerre filtering allows for a parsimonious number of unknown parameters that need be estimated, and the implementation of a nonlinear autoregressive Volterra-Wiener model with degree of nonlinearity 2 and long-term memory [4,5,9]. Since  $\mu_{RR}(t)$  is defined in continuous time, it is possible to obtain instantaneous estimates at an arbitrarily fine timescale, requiring no interpolation between the arrival times of two beats. Given a time-varying local observation interval of duration  $W$ , we find the unknown time-varying parameter vector that maximizes the local

log-likelihood through the well-known Newton-Raphson procedure [1,5]. The model and all its parameters are recursively updated at each iteration without priors. We determine the optimal model order based on the Akaike Information Criterion and the model goodness-of-fit (obtained by prefitting the model to a subset of the data), which is based on the Kolmogorov-Smirnov (KS) test and associated KS statistics [1,5]. Autocorrelation plots are also considered to test the independence of the model-transformed intervals [1,5]. Once the order is determined, the initial NARL coefficients are estimated by the method of least squares [5].

### 2.2. The inhomogeneous point-process entropy measures

While traditional algorithms estimating measures of entropy provide a single value (or a set of values) within a predetermined time window, in this study we use a new recently introduced definition of approximate and sample entropy as instantaneous entropy measures of the discrete cardiovascular system complexity. The originality of the new definition relies in the fact that they are fully embedded in the probabilistic framework of the inhomogeneous point-process theory and introduce important differences on the mathematical formulation of the phase-space vectors and on the definition of the distance between phase-space vectors.

In the mathematical formulation,  $m$  and  $r(t)$  are the embedding dimension and time delay of the phase space, respectively, that are as  $r(t) = 0.2\sigma_{RR}(t)$  and  $m=2$  [4]. According to the point-process theory, the ipApEn and ipSampEn measures take advantage by defining the vector distance in the phase space as the KS distance (i.e. the maximum value of the absolute difference between two cumulative distribution functions) between two Inverse Gaussian (IG) probability density function, for each pair of vectors [4]. Then, the standard ApEn and SampEn algorithm are considered for the final calculation [4].

As the definition of the proposed entropy measure is fully embedded into the inhomogeneous point-process nonlinear framework, it is possible to obtain instantaneous tracking of the system's complexity as  $ipApEn(m,r,N,t)$ . Of note, the definition of the  $ipSampEn(m,r,N,t)$  is slightly different [4]. Here we also mention that our instantaneous assessment opens the possibility of analyzing the proposed measures also in terms of variability of their evolution along time, which we refer to as *complexity variability framework* [4,9].

## 3. Experimental protocol and results

Pulse-oximeter signals were recorded from 16 PD patients, of which 8 were cognitively preserved (PD-NC,

4M/4F, age 68.7 +/- 3.1 years, of which 4 were *de novo*), and 8 were MCI (PD-MCI, 6M/2F, age 64.1 +/- 5.9 years, of which 4 were *de novo*). The two patient populations did not differ significantly in UPDRS-II ( $p=0.48$ ), UPDRS-III ( $p=0.55$ ) or Hoehn and Yahr ( $p=0.69$ ) scores (Mann-Whitney U Test). During the acquisition, subjects were placed horizontally in a supine position during the entire recording (600 s).

We computed mean values (over the whole recording period) of conventional heart rate variability (HRV) features, namely instantaneous time-domain estimation (first, i.e.,  $\mu_{RR}$ , and the second order moments, i.e., the RR and HR variance:  $\sigma_{RR}$  and  $\sigma_{HR}$  respectively [1]) and linear power spectrum estimation (low frequency, LF=0.04-0.15Hz, and high frequency, HF=0.15-0.4Hz, along with their ratio [1]), as well as standard and ipApEn and ipSampEn measures [4]. We tested for significant group effects (PD-MCI vs. PD-NC) using nonparametric statistics based on the Mann-Whitney test after globally regressing out the effects of age and gender using a general linear model (GLM). Results, expressed as “median  $\pm$  median absolute deviation” are reported in Table 1.

Table 1: Instantaneous and standard statistics from the PD-MCI and PD-NC dataset.

Index	PD-MCI	PD-NC	p-value
$\mu_{RR}$	1005 $\pm$ 95	912 $\pm$ 86	0.505
$\sigma_{RR}$	415 $\pm$ 328	527 $\pm$ 217	0.878
$\sigma_{HR}$	1.57 $\pm$ 1.08	1.56 $\pm$ 0.45	0.645
LF	189 $\pm$ 152	399 $\pm$ 250	0.645
HF	235 $\pm$ 204	466 $\pm$ 367	0.721
LF/HF	0.93 $\pm$ 0.72	0.79 $\pm$ 0.24	0.959
ApEn	1.38 $\pm$ 0.05	1.47 $\pm$ 0.17	0.234
ipApEn	0.21 $\pm$ 0.08	0.40 $\pm$ 0.03	0.065
SampEn	1.58 $\pm$ 0.09	1.67 $\pm$ 0.17	0.505
<b>ipSampEn</b>	<b>0.13<math>\pm</math>0.09</b>	<b>0.37<math>\pm</math>0.04</b>	<b>0.049</b>

Bold indicates statistically significant indices.  
p-values from the Mann-Whitney non-parametric test with null hypothesis of equal medians

All conventional HRV features were found to be statistically equal between the PD-MCI and PD-NC groups. Differences in standard ApEn and SampEn were also non-significant. Conversely, ipSampEn was significantly lower ( $p<0.05$ ) in PD\_MCI when compared to PD\_NC.

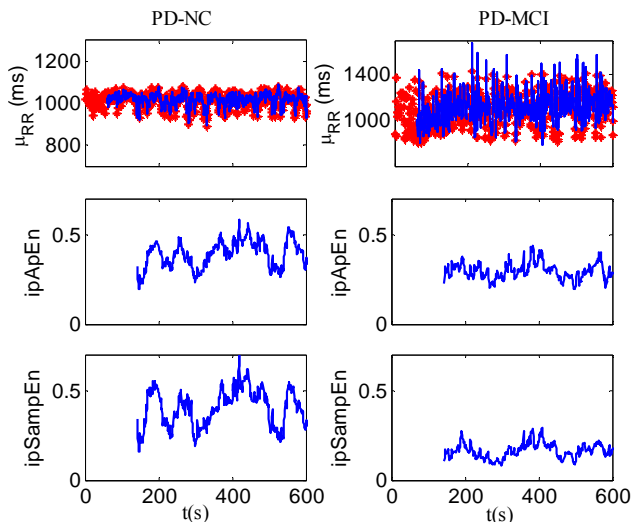


Fig. 1: Instantaneous statistics from exemplary PD patients. From the top, the instantaneous mean (blue line) is superimposed to the RR interval series (red asterisks) of a PD-NC patient (left column) and of a PD-MCI patient (right column). Below, the instantaneous entropy measures are shown.

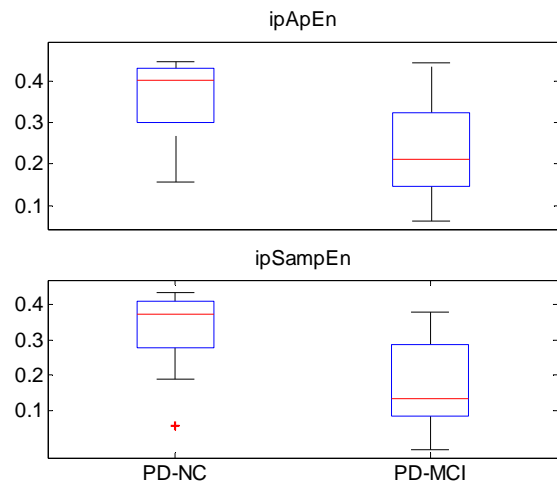


Fig. 2: Box plot statistics of the recently introduced ipApEn and ipSampEn indices in the PD-NC (left) and PD-MCI (right) groups.

#### 4. Discussion and conclusion

In this study, we demonstrate that complex cardiovascular dynamics is modulated by the presence of MCI in PD. It has been previously shown that cardiovascular autonomic failure has potentially negative effects on cardiovascular, cerebrovascular, and cognitive outcomes in subjects affected by all alpha-synucleinopathies, and that this effect was not due to antiparkinsonian treatment [8]. In particular, one

study demonstrated an association between cognitive impairment and cardiovascular dysautonomia in PD, where cognitive symptoms were seen to be associated with orthostatic hypertension (OH) as well as supine hypertension (SH) [6]. Additionally, dementia and white matter hyperintensities were more common in the latter group - a finding which could be explained through the multiple episodes of cerebral hypo- and hyperperfusion related to both SH and OH. It is therefore plausible that our instantaneous complexity measures are sensitive to cognitive changes through associated alterations in cardiovascular regulation. Importantly, since we only included patients which presented at most small non-specific and non-confluent hyperintense foci in the cerebral white matter, we hypothesize that this association is largely independent of white matter alterations. On a more general level, our results are in agreement with our previous findings showing that complex heartbeat dynamics is altered in mental disorders like major depression and bipolar disorders [10]. A physiological justification of this results is related to dysfunctions on the recruitment of the so-called Central Autonomic Network (CAN) [7,10] and other central circuits.

We studied complex cardiovascular dynamics through recently defined, instantaneous estimators of approximate and sample entropy (ipApEn and ipSampEn, respectively). The originality of the new definitions lies in the fact that they are fully embedded in the probabilistic framework of the inhomogeneous point-process theory, and that they introduce important differences to the mathematical formulation of the phase-space vectors and to the definition of the distance between phase-space vectors. Moreover, these measures are not affected by the statistical properties of the physiological noise behind the observed dynamics. This ensures that, when performing group comparisons like the one presented in this study, lower values of ipSampEn (which we found in PD-MCI group as compared to the PD-NC group) are actually associated with a lower instantaneous complexity as opposed to possible alterations in the noise statistics (e.g. a transition from 1/f noise to Gaussian noise).

In summary, our results suggest that cognitive impairment in PD is associated with a decrease in heartbeat complexity, possibly pointing toward subtle autonomic changes (not detected by conventional HRV) which accompany the initial stage of cognitive impairment in PD.

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