Complex Correlation Measure as a Sensitive Indicator of Risk for Sudden Cardiac Death in Patients with Depression

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Abstract

Heart rate variability (HRV) is reduced in patients with Major Depressive Disorder (MDD). We examined the sensitivity of a new nonlinear parameter, the Complex Correlation Measure (CCM) in patients with depression. Two-minute ECG recordings at rest with eyes-closed were analyzed. CCM was higher (0.36±0.1) in control participants compared to MDD (0.29±0.1), indicating a decrease in temporal variability associated with decreased parasympathetic function (Cohen's d = 0.7, p=0.0008). CCM also demonstrated a larger effect size than SD1 (Cohen's d = 0.5, p =0.0005) and SD2 (Cohen's d = 0.2, p = 0.015). These results highlight that depressed patients display a dampening of oscillations between parasympathetic and sympathetic input indicative of reduced functionality and increased risk of sudden cardiac death. CCM is a more sensitive measure of HRV, which provides additional information on HRV dynamics compared to SD1 and SD2 of the Poincaré plot distribution.

1. Introduction

Heart rate variability has been shown to be a good indicator of pathological conditions including heart disease, diabetes and neurological disorders [1-3]. Depression increases the risk of cardiac arrest and mortality, which may, in part, relate to reductions in heart rate variability (HRV) [4]. Heart rate variability has been shown to predict future mortality even in relatively healthy individuals without physical illness but does not provide dynamic changes of the heart-beat intervals over time [5].

Previous studies on otherwise healthy patients with MDD have reported decreases, increases and no differences in HRV. Using meta-analysis, we previously reported that such patients display reductions in HRV and that HRV is not improved following successful treatment [6]. Reductions in the non-linear domain of HRV in these patients using detrended fluctuation analysis (DFA) were particularly prominent.

Here we investigate whether the complex correlation method CCM, a new measure of non-linear HRV that measures the beat-to-beat dynamics, is more sensitive than a widely utilised non-linear measure obtained from the Poincaré plot distribution.

2. Methods and materials

2.1. Participant recruitment

All potential participants were reviewed for the presence of psychiatric and cardiovascular disease and other pathology. Otherwise healthy patients with MDD (n= 73) and age and sex-matched non-MDD controls (n= 94) were recruited from the general community. All participants completed the Mini-International Neuropsychiatric Interview (MINI) and ratings of severity were made using the structured Interview Guide for the Hamilton Depression rating scale (SIGH-D) [7, 8]. The study was approved by the University of Sydney Human Ethics Committee and all participants provided written consent.

2.2. ECG recording

Participants were seated in a sound and light controlled room at 24°C and electrocardiogram (ECG) recordings were collected under resting-state conditions, as part of a standardised psychophysiological recording protocol. The data was sampled at 500Hz, with 22-bit resolution digitization.

2.3. HRV analysis

HRV was analysed using custom developed software

that performs semi-automated pre-processing to remove noise and ectopics from the ECG and allows for the identification of the R peaks based on established methods [9].

2.4. Poincaré plot analysis

The Poincaré plot of the ECG signal is constructed by plotting consecutive points of the RR interval time series (i.e., lag-1 plot). It is a representation of the HRV signal on phase space or Cartesian plane, which is commonly used to asses the dynamics of the HRV signal, describing the sympathetic and parasympathetic modulation of heart rate [10]. Quantifying the Poincaré plot requires fitting an ellipse to the shape of the Poincaré plot and measuring the dispersion along the major and minor axis of the ellipse defined as SD1 and SD2 respectively [11, 12].
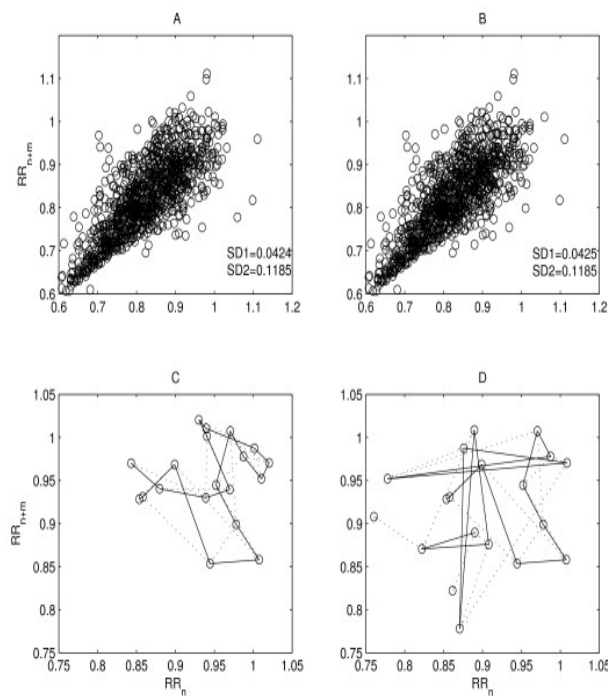

Figure 1. Poincare plots of almost similar shape but with different temporal structures [13].

Poincaré plots with similar $SD1$ and $SD2$ values with different temporal structure are shown (Fig 1). Top panel (A and B) shows the Poincaré plots (*lag-m* = 2) of two different RR intervals series of length N (N = 1000) with $SD1$ (0.0424 and 0.0425) and $SD2$ (0.1185 and 0.1185) values. The underlying temporal dynamics of the first 20 points of the same RR intervals are shown in the bottom panel (C and D), which shows the visible difference among them.

The dynamic nature of consecutive beat-to beat differences represent the dynamics of the system and is clearly identified in the lower panels.

2.5. Complex correlation method

The complex correlation method is computed in a windowed manner, which embeds the temporal information of the signal. A moving window of three consecutive points from the Poincaré plot are considered and the temporal variation of the points measured. If Poincaré plot is composed of N points then the temporal variation of the plot provides the complex correlation measure (CCM), which is composed of all overlapping three point windows and can be calculated as:

$$CCM(m) = \frac{1}{Cn(N-2)} \sum_{i=1}^{N-2} \|A(i)\|$$

where m represents lag of Poincaré plot and C_n is the normalizing constant which is defined as, $C_n = \pi * SD1 * SD2$, represents the area of the fitted ellipse over Poincaré plot. The length of major and minor axis of the ellipse are $2*SD1$, $2*SD2$, where SD1, SD2 are the dispersion perpendicular to the line of identity (minor axis) and along the line of identity (major axis) respectively. *A* represents the area of the triangle formed by the three points and *i* is the number of windows.

3. Statistical analysis

Statistical analysis was conducted using PASW (Predictive Analytics SoftWare) Statistics, Release Version 18.0.0 (SPSS, Inc., 2009, Chicago, IL). Independent samples t-tests were conducted on non-linear domain measures of HRV. Measures of Cohen's *d* are also reported to determine effect size, such that 0.2 to 0.3 is a small effect, 0.5 is a medium effect and greater than 0.8 is a large effect.

4. Results

Seventy-three patients with a primary diagnosis of MDD, and age and sex-matched controls were recruited for this study Table 1.

Table 1. Demographics of study population

	Control	MDD	P[**]
Age range (yrs)	19-60	18-64	0.47
Age (yrs) (mean±sd[*])	35.69±11.18	36.52±11.52	0.64

[*] standard deviation; [**] significance set at p=0.05

Figure 2 compares results for SD1, SD2 and CCM between control and MDD participants, indicating a difference in the HRV dynamics between control and depression.

Variation of SD1 between Control and MDD group

Variation of SD2 between Control and MDD group

Variation of CCM between Control and MDD group
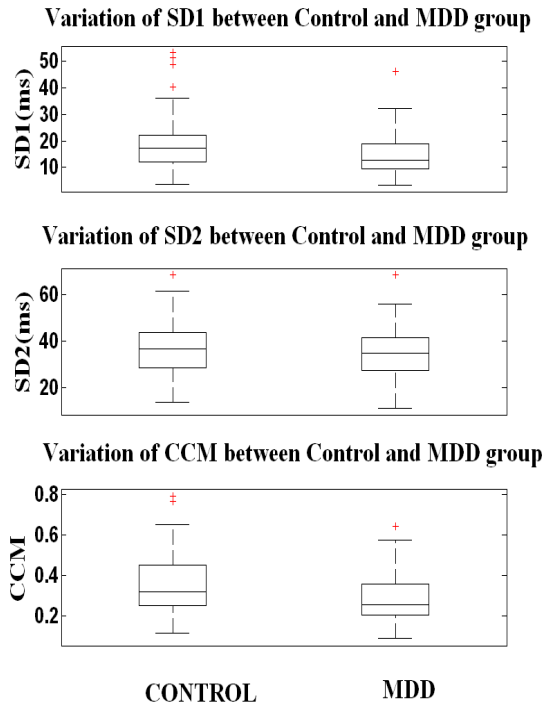
CONTROL   MDD

Figure 2: Nonlinear HRV measures. The central line represents distribution median, each box spans from 25 to 75 percentile points, and error bars extend from 10 to 90 percentile points.

The complex correlation measure provided the highest sensitivity for categorizing MDD in addition to a measure of the dynamic changes associated with depressive disorder (Table 2).

Table 2. Comparison of SD1, SD2 and CCM.

Extracted Features	Control(93)	Depressed(73)	P value
SD1(ms)	19.15 ± 10.07	14.37 ± 7.61	5.21E-04
SD2(ms)	36.57 ± 10.39	34.54 ± 11.20	2.30E-01
CCM	0.36 ± 0.14	0.29 ± 0.12	8.01E-04

CCM values were found to be 0.36 ± 0.14 in control and 0.29 ± 0.12 in depressed patients indicating a decrease in the temporal variability associated with a decrease in parasympathetic function (Cohen's $d = 0.7$, $p=0.0008$). CCM also demonstrated a larger effect size or greater sensitivity than SD1 (Cohen's $d = 0.5$, $p = 0.0005$) and SD2 (Cohen's $d = 0.2$, $p = 0.015$).

5.   Discussion

Nonlinear measures of HRV may be more sensitive to group differences than time and frequency domain measures [6]. Although the Poincaré analysis method provides information about heart rate variability that is not detected by conventional time domain methods it is limited by the standard descriptors (SD1 and SD2) and lacks information on the embedded temporal characteristics of the heart rate variability.

CCM in contrast to SD1 and SD2 shows the dynamics of HRV. The CCM algorithm quantifies the variability in the temporal structure of Poincaré plots, and is thus able to distinguish between Poincaré plots with similar shapes (see Fig 1). The dynamic behaviour of the heart rate variability is a function of multiple lag correlations of the heart rate variability signal. Thus CCM measures the point-to-point variation of the HRV signal rather than a gross description of the Poincaré plot [10]. The results in this paper highlight the difference between control and people with major depressive disorder, where both short (SD1) and long (SD2) term correlation of the heart rate variability is decreased. In addition the dynamics of the temporal signal is lower in the MDD group of patients. The decrease especially in the complex correlation measure indicates increased regularity and decreased variability, and provides further evidence of a greater risk of sudden cardiac death in people with MDD. Physiological complexity is reflected in the dynamic changes as a function of the point-to-point changes in the HRV and related to the adaptive capacity of the system. A decrease indicates pathological dynamics, which, in order to identify this, requires a multiscale analysis such as CCM. The reduced dynamics of the system in MDD suggests a reduction in the responsiveness of the cardiac system to changes in the internal and external environment and an increase in the risk of sudden cardiac death.

6.   Conclusion

These results highlight that depressed patients display a dampening of oscillations between parasympathetic and sympathetic input indicative of reduced functionality and increased risk of sudden cardiac death. CCM appears to be a more sensitive nonlinear measure of HRV, which provides additional information to SD1 and SD2 of the Poincaré plot distribution. CCM is also more sensitive to the parasympathetic nervous system activity as compared to SD1 and SD2 [10].

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