

Instantaneous Bispectral Analysis of Heartbeat Dynamics for the Assessment of Major Depression

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Abstract

Major depression (MD) is associated with increased cardiovascular risk. Although alterations in autonomic regulation have been proposed as one potential pathophysiological mechanism to explain this comorbidity, studies using standard HRV features in depressed subjects have been inconclusive. In this study, 48 patients with MD and 48 healthy controls (HC) were randomly assigned to an audio-visual task with two different versions: one emotionally neutral (N) and the other emotionally arousing (E). ECG signal (lead II) was collected at 250 Hz, and point process nonlinear analysis of heartbeat dynamics was performed to obtain instantaneous features from standard time-domain analysis, as well as spectral (LF, HF, LF/HF) and bispectral (LL, LH, and HH) analysis. Mean values of all features were computed over the 30s segment of the emotional elicitation session. Only bispectral parameters LH and HH were significantly different between patients and HC ($p < 0.02$). Our results suggest that time-varying nonlinear dynamics of parasympathetic activity are significantly reduced in MD compared to HC in response to emotional elicitation. We conclude that instantaneous bispectral analysis could be a promising tool for assessment of autonomic modulation in MD.

1. Introduction

Major depression (MD) has been associated with an increased risk of cardiovascular disease [1]. Although the exact mechanism of this relationship remains unknown, alterations in the regulation of cardiac autonomic tone have been proposed as one of the main contributing factors underlying this comorbidity [1]. It is well known that autonomic nervous system (ANS) outflow can be estimated non-invasively using Heart Rate Variability (HRV) analysis [2], and HRV measures have been

previously employed to explore ANS alterations in major depressed subjects by evaluating the modulatory effects of ANS dynamics on sinus node activity [3-5].

Although a reduced HRV has been consistently found in depressed patients with coronary heart disease [3], the evidence supporting an association between autonomic cardiac dysfunction and depression in otherwise healthy subjects is inconclusive. While some authors reported a reduced vagal tone and increased sympathetic modulation in depressed patients in response to emotional elicitation tasks [4], others have not observed significant differences when compared to healthy subjects [5]. One possible explanation for such conflicting results could be the limitations of HRV analysis by means of standard procedures when a high resolution in the time and frequency domains is needed [2].

To this extent, instantaneous bispectral analysis represents a recent development for HRV analysis, being able to identify underlying nonlinear interactions occurring between sympathetic and parasympathetic dynamics [6-9]. This analysis relies on nonlinear point-process models, which use Wiener-Volterra and Laguerre expansions to obtain reliable and effective estimates from heartbeat dynamics with a reduced number of parameters to be estimated [9]. This approach was recently applied in the field of mental health and psycho-physiology [6-8], and is particularly effective in performing instantaneous estimates within very short-time windows of, e.g., emotional elicitation [8].

In this paper we aim to evaluate alterations in heartbeat dynamics in response to negative affective stimuli in subjects with MD. To this end, we employ our nonlinear point-process framework [6-9], looking for significant differences between healthy controls (HC) and MD patients using standard ANS-related HRV metrics defined in the time and frequency domains, as well as features defined in the bispectral plain [6-9].

2. Materials and methods

2.1. Study population

We selected 48 subjects with MD (age: 22.6 ± 4.7 years) and 48 age- and gender-matched HC (age: 23.5 ± 4.9 years). A Structured Clinical Interview for DSM-IV Axis I disorders, Clinical version, was applied to confirm the MD diagnosis. All patients were experiencing their first depressive episode and had not received antidepressants. Exclusion criteria for both MD and HC subjects were known cardio-, cerebro-, or peripheral vascular disease, presence of neoplasm, diabetes mellitus, kidney or liver failure, infectious or systemic inflammatory disease and current neurological illness. All subjects gave written informed consent approved by an Institutional Review Board.

2.2. Experimental protocol

The task used in the study consisted on a set of eleven slides accompanied by a narrative with two different versions: one emotionally neutral (N) and the other emotionally arousing (E). Both set of slides show a mother taking her young son to see his father at a nearby hospital where he works. In the N version of the story, the mother and son witness a minor car accident, which attracts the attention of the child, whereas in the E version the child himself is critically injured and requires a surgical intervention at the hospital.

Subjects from each group (MD, HC) were randomly assigned to the N or E stimulus version, resulting in 4 experimental groups (MD-N, MD-E, HC-N, HC-E). All subjects were instructed to concentrate on each slide for the duration of its presentation and to watch the slide show as they would watch a movie. Continuous ECG monitoring (lead II) was collected at 250Hz using a Finometer device (Finapres Medical System, The Netherlands). Data were digitized and stored in a PC computer using a signal acquisition system DATAQ 720-WINDAQ PRO (DataQ Instruments, Akron, OH, USA). Subjects were initially asked to rest for 10 minutes in a reclining position. This acclimation period was followed by a 3-minute baseline period and the exposure to the emotional stimulus previously described, followed by a 3-minute recovery period, during which participants rested quietly.

2.3. Point-process model of the heartbeat

By using the inhomogeneous point-process framework [6-9], we model the unevenly sampled RR interval series through probability density functions (*pdf*) characterizing and predicting the time until the next event occurs as a function of the past history. Within this

framework, Laguerre expansions of the Wiener-Volterra linear and nonlinear autoregressive terms account for long-term nonlinear information [9]. As major advantages, instantaneous measures can be estimated without applying any interpolation techniques to the RR interval series, and are associated to effective goodness-of-fit measures.

The *pdf* characterizing the time of the next ventricular contraction is an inverse Gaussian function, parametrized in its first-order moment $\mu_{RR}(t)$ as a Nonlinear Autoregressive model with Laguerre expansions (NARL) of the Volterra terms [9]. We perform the Laguerre expansion on the derivative R-R series in order to improve stationarity within the sliding time window W (in this work we have chosen $W = 90$ s) [9]. Of note, the corresponding nonlinear autoregressive Volterra-Wiener model has (theoretically infinite) long-term memory [9].

As $\mu_{RR}(t)$ is defined in continuous time, it is possible to obtain an instantaneous R-R mean estimate at arbitrary timescales without interpolating between the arrival times of two consecutive heartbeats.

Concerning parameter estimation, we initialize the Newton-Raphson procedure at t with the previous local maximum-likelihood estimate at time $t - \Delta$, where Δ defines the time interval shift to compute the next parameter update. We determine the optimal model order based on the Kolmogorov-Smirnov (KS) test and associated KS statistics [9]. Autocorrelation plots are also visually inspected to ensure that all points of the plot are within the 95% of the confidence interval, hence guaranteeing the independence of the model-transformed intervals [6-9].

2.4. Instantaneous time, frequency, and higher-order spectral analysis

In order to provide quantitative tools related to standard measures defined in the time and frequency domains, as well as higher order spectral representations, it is necessary to link the NARL model to the traditional input-output Wiener-Volterra model [9]. Then, the time-domain characterization is based on the first and the second order moments of the underlying probability structure. Given the time-varying parameter set, instantaneous estimates of mean μ_{RR} , and R-R interval standard deviation σ_{RR} can be extracted at each moment in time [9].

Estimates in the frequency domain are obtained by integrating the instantaneous autospectrum [9] within low frequency (LF = 0.05-0.15 Hz), and high frequency (HF = 0.15-0.5 Hz) ranges, along with their ratio (LF/HF).

The higher-order spectral representation allows for the estimation of statistics beyond the second order, and phase relations between frequency components which would otherwise be suppressed. A detailed description of

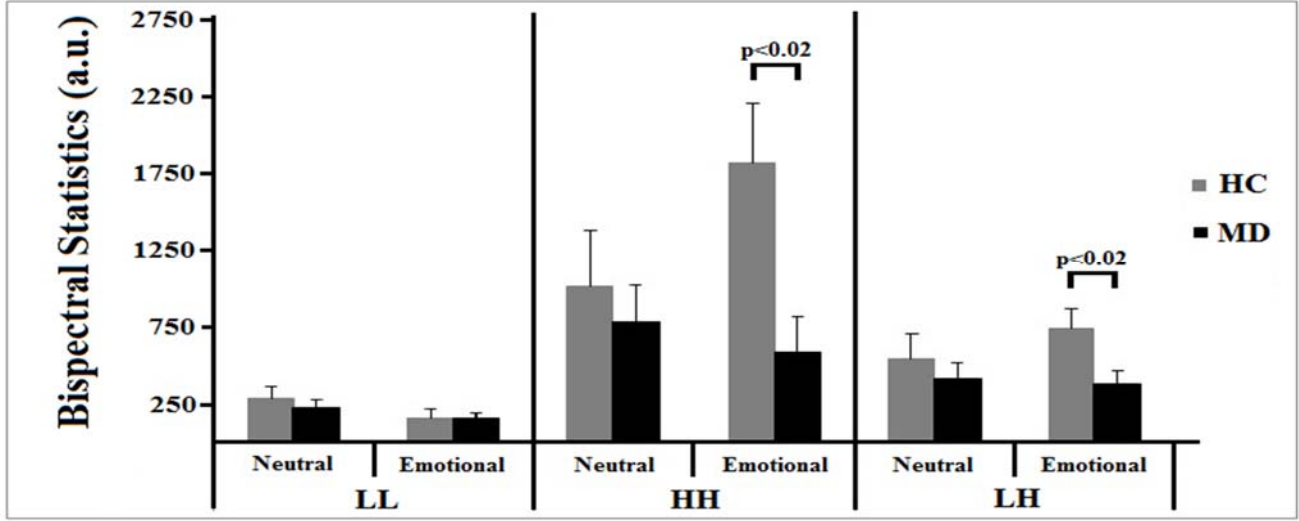


Figure 1. Point-process bispectral statistics during neutral- and emotional-eliciting task in 48 major depressed subjects and 48 age- and gender-matched healthy controls.

the instantaneous bispectrum derivation from point-process nonlinear models can be found in [6-8]. This tool allows to evaluate the instantaneous presence of nonlinearity in heartbeat series by calculating nonlinear sympatho-vagal interactions as low-freq.-low-freq. (LL), low-freq.-high-freq (LH), and high-freq.-high-freq. (HH) interactions [6-8].

2.5. Statistical analysis

All HRV features were instantaneously calculated with a $\Delta = 5$ ms temporal resolution. In order to build subject-specific feature vectors, for every subject and for every feature X , we condensed the information about the time-varying dynamics of X through its median across time. For each feature, we evaluated statistical differences between the two groups (MD vs HC), for each of the two elicitation conditions (N vs E), using bivariate non parametric statistics (Mann-Whitney test) under the null hypothesis that the between-subject medians of the two groups were equal. This choice was justified by the fact that The majority of the group samples resulted non-normally distributed (p-values gathered from Kolmogorov-Smirnov tests with null hypothesis of normality resulted <0.05 , i.e., data are not normally distributed).

Since we tested each feature taking two elicitation conditions into account, the threshold for statistical significance is here set to $\alpha=0.05/2=0.025$, according to a Bonferroni correction.

3. Results

Point-process goodness-of-fit analyses yielded optimal NARL orders of $p=4$ and $q=1$. In 88 out of a total

of 96 recordings, both KS plots and more than 98% of the autocorrelation samples fell within 95% confidence intervals. Results of group statistics for all features are shown in Table 1. Representative feature values for bispectral indices are depicted in Fig. 1.

No significant differences between HC and MD groups were observed for any of the considered standard features during the neutral task ($p>0.05$). MD patients and HC subjects exposed to the N version of the story were also comparable in relation to point-process bispectral features (Figure 1). Likewise, no significant differences between groups were observed for any of the considered standard features during the emotional task ($p>0.05$).

However in those subjects exposed to the E version of the story, LH and HH measures were able to significantly discern between MD patients and HC ($p<0.02$).

Table 1. Results of Point Process spectral analyses during the neutral and emotional elicitation test. Values are expressed as $\{\text{median}(X) \pm \text{MAD}(X)\}$, where $\{\text{MAD}(X) = |X - \text{median}(X)|\}$.

	HC-N	HC-E	MD-N	MD-E
μ_{RR} (ms)	762±150	823±205	807±117	793±190
σ_{RR} (ms)	343±667	681±941	504±906	423±766
LF (ms ²)	548±987	646±913	837±780	561±971
HF (ms ²)	318±505	578±722	358±852	437±569
LF/HF	1.8±2.9	0.9±2.1	2.1±2.6	1.7±2.1
LL (a.u.)	285.7±157.3	161.0±122.6	230.3±94.8	158.3±76.5
LH (a.u.)*	542.3±343.2	747.9±257.3	414.6±210.8	381.3±178.4
HH (a.u.)*	1022±723.6	1820±796.4	789.4±481.8	590.5±459.8

* $p<0.05$ between HC-E and MD-E

Finally, we report that a $p = 0.15$, given by the Mann-Whitney non-parametric test, was associated to the null hypothesis of having equal median age between the healthy and MD groups. This outcome confirms that our results are not affected by age differences between the groups.

4. Discussion

Our results reveal that instantaneous complex heart beat dynamics are modulated by emotional elicitation in patients with MD. These patients presented significant reductions in HH and LH bispectral indices compared to healthy subjects when exposed to negative affective stimuli. These results are in agreement with previous studies showing that mental disorders alter cardiovascular complexity [6,7,10]. Furthermore, this complexity modulation was only observed in response to emotionally-relevant stimuli, which is also concordant with literature linking mood disorders, and emotional reactivity to ANS dynamics [11].

Although the exact physiological mechanisms behind these complex dynamics have not been completely elucidated, it has been suggested that the inherent complexity and nonstationarity dynamics of heartbeat variations are associated to nonlinear neural interactions occurring at the neuron and receptor levels, so that the sinoatrial node responds in a nonlinear way to the changing levels of efferent autonomic inputs [12]. Just as the sympathovagal linear effects on HRV are mainly characterized by the LF and HF spectral powers [2], it is possible to identify underlying nonlinear interactions occurring between sympathetic and parasympathetic dynamics by using bispectral analysis in the appropriate frequency bands (LL, HH) [8]. Thus, our findings of a reduced HH could be interpreted as alterations in vagal complex dynamics of depressed subjects in response to negative emotional elicitation. We speculate that these alterations could be reflecting an abnormal regulation of cardiac vagal activity by the central autonomic network in response to psychological stress. This could be a key mechanism in explaining the association between depressed mood, chronic cardiac dysregulation and cardiovascular risk in MD, however further studies should be performed to confirm this hypothesis.

The linear instantaneous features defined in the time and frequency domain were no different between groups, suggesting that, although sympatho-vagal interactions might be affected by mood disorders, the inter-subject variability is too high to allow such changes to be revealed through linear analysis. On contrast, our statistical analysis of instantaneous complexity provided a much higher discriminating power. Furthermore, our model has the advantage of monitoring instantaneous heart-beat dynamics in response to fast emotional stimuli allowing a continuous evaluation of the disorder progression in experimental or clinical settings. Therefore we conclude that instantaneous bispectral analysis could be a promising tool for assessment of cardiovascular autonomic regulation in depressed patients.

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