

Quantification of Cardiorespiratory Coupling in Acute Schizophrenia Applying High Resolution Joint Symbolic Dynamics

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Abstract

Schizophrenia is one of the most serious mental illnesses in the world. For schizophrenia an impaired cardiac autonomic function could be demonstrated in different studies. However, respiration as an important part in body's homeostatic control mechanisms in order to maintain a constant internal environment was given little attention especially to the corresponding cardiorespiratory regulation. The aim of this study was to quantify short-term cardiorespiratory couplings (CRC) in acute schizophrenia applying the high resolution joint symbolic dynamics (HRJSD) analysis approach. In this study, 23 unmedicated patients with acute schizophrenia (SZO; 12 male; 30.4±10.3 years) and 23 age- and gender matched healthy controls (CON, 13 male; 30.3±9.5 years) were investigated. HRJSD revealed for SZO in comparison to CON a significantly altered and widely distributed CRC ($p < 0.01$) that was mainly characterized by a larger amount of increased short-term alternating and fluctuating patterns. Further on, the respiratory regulation seems to be more complex in SZO and dominates the CRC. These results indicate to an impairment of short-term respiratory regulation probably due to an impaired or suppressed interplay of the brainstem and higher regulatory centres in SZO.

1. Introduction

Schizophrenia is one of the most serious mental illnesses in the world with a lifetime prevalence rate of approximately 1% (US: 2.2 million people, Germany: 800,000) [1]. For those patients it is known that they have a relative risk to suffer from cardiovascular disease that is up to three-times higher and an approximately 20% reduced life expectancy in comparison to the general population [2].

Different studies [3, 4] could demonstrated that cardiac autonomic dysregulation is associated with a decreased vagal and an increased sympathetic modulation for patients suffering from schizophrenia, and also partly for their healthy first-degree relatives. However, less information is available regarding whether respiration is known to be important in maintaining physiological homeostasis as a result of a complex interaction between the brainstem and higher centres for those patients. There are only a few studies which have investigated cardiorespiratory coupling (CRC) in patients with schizophrenia [5, 6].

The bivariate coupling analysis of heart rate (HR) and respiratory frequency (RESP) time series, respectively, might provide further information about the complex system of autonomic regulation in schizophrenia than univariate approaches can do.

For the characterization of linear and nonlinear CRC several concepts are available based on Granger causality; nonlinear prediction; entropies; symbolization and phase synchronization that are able to detect direct and indirect couplings between time series [7]. For the characterization of the beat-to-beat changes between HR and RESP time series the new High Resolution Joint Symbolic Dynamics (HRJSD) analysis approach was applied [8]. HRJSD based on a redundancy reduction strategy and is characterised by three symbols, a threshold (individual dynamic variability, physiological) for time series transformation, and 8 coupling pattern families (resulting in 64 different coupling patterns) which quantifying patterns of the autonomic regulation.

The aim of this study was to quantify short-term nonlinear cardiorespiratory couplings in acute schizophrenia applying HRJSD analysis approach. In this study we applied for the symbol transformation a threshold based on the individual physiological dynamic variability of the heart rate- and respiratory frequency time series.

2. Materials and methods

2.1. Patients

In this study, twenty-three unmedicated patients suffering from acute schizophrenia (SZO; 12 male; 30.4 ± 10.3 years) and twenty-three age-gender matched healthy controls (CON, 13 male; 30.3 ± 9.5 years) were enrolled for cardiorespiratory coupling (CRC) analysis. Schizophrenia was diagnosed by experienced psychiatrists when symptoms of patients fulfilled DSM-IV criteria as assessed by the Structured Clinical Interview for DSM-IV (SCID). The Structured Clinical Interview SCID II and additionally a personality inventory (Freiburger Persönlichkeitsinventar) were applied to CON to detect possible personality traits or mental disorders which might influence autonomic regulation (cardiorespiratory coupling). All participants were asked to refrain from drinking coffee, heavy eating or exercising, smoking at least two hours prior to the investigation. This study complied with the Declaration of Helsinki. All participants gave written informed consent to a protocol approved by the Ethics Committee of the University Hospital, Jena.

2.2. Data recordings and data preprocessing

For cardiorespiratory coupling analysis a high resolution short-term ECG (1000 Hz sampling frequency) and synchronized respiratory inductive plethysmography signal (LifeShirt®, Vivometrics, Inc., Ventura, CA, U.S.A.) were recorded for 30 minutes. All measurements were performed under resting conditions (supine position, quiet environment, same time of day and location).

From each record following time series were automatically extracted using in-house software (programming environment Delphi 3):

(i) Time series of heart rate consisting of successive beat-to-beat intervals (BBI) and

(ii) Time series of respiratory frequency (RESP). All time series were visually inspected and if appropriate re-edited. To obtain synchronized time series both BBI and RESP were resampled using a linear interpolation method (2Hz). Afterwards, to remove and interpolate ventricular premature beats and artefacts (e.g. movement, electrode noise and extraordinary peaks) both time series were filtered with an adaptive variance estimation algorithm.

2.3. High Resolution Joint Symbolic Dynamics - HRJSD

HRJSD [8] was developed to analyse nonlinear cardiovascular couplings in acute schizophrenia treated

with antipsychotics and based on the analysis of dynamic processes by means of symbols [9]. In this study we adopted HRJSD for the quantification of cardiorespiratory couplings. Therefore, both time series (BBI and RESP) were transformed into symbol sequences. X as a bivariate sample vector, x_{BBI} and x_{RESP} were n beat-to-beat values of BBI and RESP, respectively.

$$X = \left\{ \left[x_n^{BBI}, x_n^{RESP} \right]^T \right\}_{n=0,1,\dots} \quad x \in R \quad (1)$$

Afterwards, X is transformed into a bivariate symbol vector S defined as

$$S = \left\{ \left[s_n^{BBI}, s_n^{RESP} \right]^T \right\}_{n=0,1,\dots} \quad s \in 0,1,2 \quad (2)$$

with the following definitions:

$$s_n^{BBI} = \begin{cases} 0: (x_{n+1}^{BBI} - x_n^{BBI}) < -l^{BBI} \\ 1: -l^{BBI} \leq (x_{n+1}^{BBI} - x_n^{BBI}) \leq l^{BBI} \\ 2: (x_{n+1}^{BBI} - x_n^{BBI}) > l^{BBI} \end{cases} \quad (3)$$

$$s_n^{RESP} = \begin{cases} 0: (x_{n+1}^{RESP} - x_n^{RESP}) < -l^{RESP} \\ 1: -l^{RESP} \leq (x_{n+1}^{RESP} - x_n^{RESP}) \leq l^{RESP} \\ 2: (x_{n+1}^{RESP} - x_n^{RESP}) > l^{RESP} \end{cases} \quad (4)$$

and the threshold levels l^{BBI} and l^{RESP} equal to 25% of the standard deviation ($1/4sd_{TH}$) of the BBI- and RESP time series as an adapted threshold to the individual physiological dynamic variability. Symbol sequences with increasing values were coded as ‘2’, decreasing values were coded as ‘0’ and unchanging (no variability) values were coded as ‘1’. The symbol vector S was subdivided into short words (bins) w_k of length $k=3$. Thus, using three symbols led to 27 different word types for BBI (w_{BBI}) and RESP (w_{RESP}) were formed (total number of all word type combinations: $729=27 \times 27$) (Figure 1). Afterwards, all single word types $w_{BBI,RESP}$ were grouped into 8 pattern families’ wf whereby the probabilities of all single word family’s occurrences $p(wf)$ was normalised to 1. These 8 pattern families ($E0, E1, E2, LUI, LDI, LAI, P, V$) represent different aspects of autonomic modulation and were sorted into an 8×8 pattern family density matrix Wf resulting in 64 cardiorespiratory coupling patterns (Figure 1). Pattern definition:

$E0, E1$ and $E2$: no variation within the word consisting of three symbols of type ‘0’, ‘1’ and ‘2’, respectively.

LUI and LDI : one variation within the word consisting of two different symbols with low increasing behaviour (LUI) and low decreasing behaviour (LDI).

LAI : one variation within the word consisting of two different alternating symbols of type ‘0’ and ‘2’ with an

increasing-decreasing behaviour.

P and V : three variations within the word consisting of three different symbols with peak-like behaviour (P) and with valley-like behaviour (V).

In addition, from the matrix Wf the sum of each ($n=8$) column cf_{RESP} , the sum of each ($n=8$) row rf_{BBI} and the Shannon entropy ($HRJSD_{shannon}$) of Wf as a measure of the overall complexity of cardiorespiratory coupling were computed (Figure 1).

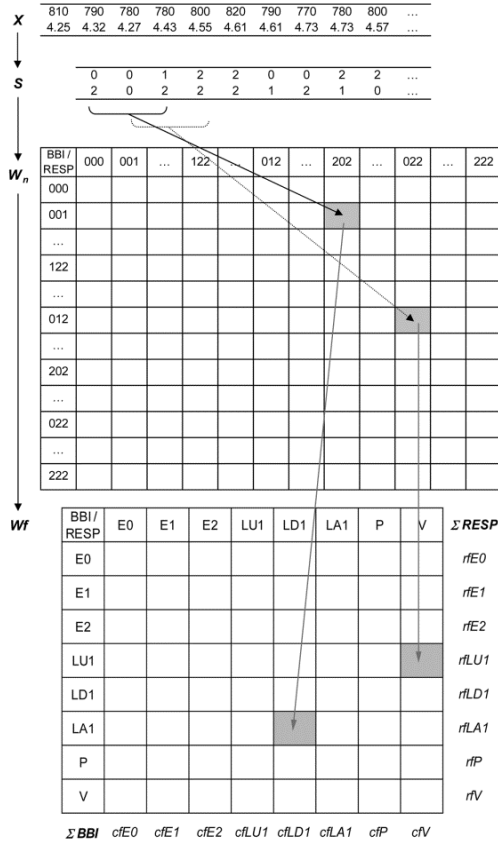


Figure 1. (top): Transformation of the bivariate sample vector X (BBI = beat-to-beat intervals [ms]; RESP = respiratory frequency [s]) into the bivariate symbol vector S (0: decreasing values, 1: equal values 2: increasing values); (middle): Word distribution density matrix W_n (27x27); (bottom): Word pattern family distribution density matrix Wf (8x8) with 8 pattern families wf , rf_{BBI} row sum of specific word family and cf_{RESP} column sum of specific word family.

2.4. Statistics

The nonparametric Mann-Whitney U-test was performed to evaluate differences between SZO and CON. Significances were considered for values of $p^* < 0.00061$ (Bonferroni-Holm adjustment). All results were presented as mean \pm std.

3. Results

HRJSD revealed 24 significant ($p < 0.01$) different cardiorespiratory coupling patterns between SZO and CON. 12 of these 24 cardiorespiratory coupling patterns fulfilled the Bonferroni-Holm adjustment ($p^* < 0.00061$). Seven significant ($p < 0.01$; $n=4$, $p^* < 0.00061$) respiratory and three significant ($p < 0.01$, $n=2$, $p^* < 0.00061$) heart rate families pattern showed also univariate changes in SZO in comparison to CON (Table 1). Thereby, the respiratory patterns were dominated by the families $LU1$, $LD1$, $LA1$, P , V , $E1$ and $E2$; heart rate patterns were dominated by $LD1$, $LU1$ and $E1$, respectively. Furthermore, it was found that nearly 92% of the cardiorespiratory coupling patterns and 50% of heart rate patterns were significantly increased in SZO in comparison to CON.

Table 1. Significant HRJSD indices from cardiorespiratory coupling analysis ($p^* < 0.00061$) between unmedicated patients suffering from schizophrenia (SZO) and healthy controls (CON).

index	P	CON	SZO	
		mean \pm std	mean \pm std	
RESP-BBI	$RESP-E1/BBI-E1$	0.00006	2.9 \pm 3.6	8.9 \pm 8.9
	$RESP-E2/BBI-LU1$	0.00000	9.7 \pm 4.5	4.8 \pm 3.7
	$RESP-LU1/BBI-E1$	0.00001	0.3 \pm 0.4	2.1 \pm 3.3
	$RESP-LU1/BBI-LD1$	0.00002	1.5 \pm 0.8	3.5 \pm 1.8
	$RESP-LD1/BBI-E1$	0.00001	0.4 \pm 0.5	2.3 \pm 3.3
	$RESP-LD1/BBI-LD1$	0.00008	2.5 \pm 1.5	3.9 \pm 1.7
	$RESP-LA1/BBI-LU1$	0.00002	0.01 \pm 0.02	0.1 \pm 0.2
	$RESP-LA1/BBI-LD1$	0.00001	0.01 \pm 0.02	0.2 \pm 0.4
	$RESP-P/BBI-E1$	0.00000	0.01 \pm 0.03	0.3 \pm 0.4
	$RESP-P/BBI-LD1$	0.00005	0.1 \pm 0.1	0.4 \pm 0.4
RESP	$RESP-V/BBI-E1$	0.00012	0.03 \pm 0.06	0.5 \pm 1.1
	$RESP-V/BBI-LD1$	0.00000	0.07 \pm 0.06	0.7 \pm 1.1
	$RESP-E2$	0.00015	14.5 \pm 6.2	9.2 \pm 4.7
	$RESP-LA1$	0.00000	0.02 \pm 0.06	0.6 \pm 0.9
BBI	$RESP-P$	0.00007	0.5 \pm 0.4	1.5 \pm 1.2
	$RESP-V$	0.00006	0.4 \pm 0.2	2.4 \pm 3.1
	$BBI-E1$	0.00005	3.9 \pm 4.6	15.4 \pm 17.2
$BBI-LU1$	0.00000	40.0 \pm 8.2	31.0 \pm 7.5	

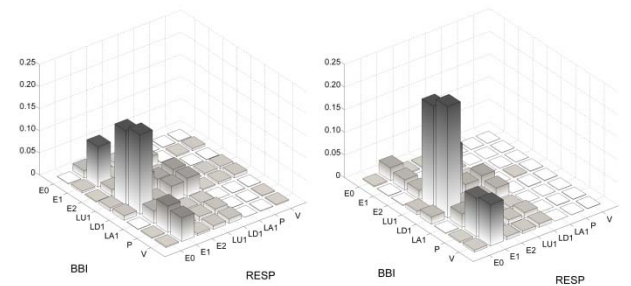


Figure 2. Three-dimensional plots of the HRJSD distribution density matrix Wf (l^{BBI} and $l^{RESP} = 1/4sd_{TH}$) for SZO (left) and CON (right) (average group values). (BBI = beat-to-beat intervals, RESP = respiratory frequency).

4. Discussion

We could demonstrate a significantly altered and widely distributed cardiorespiratory coupling in patients with acute schizophrenia applying HRJSD. SZO revealed a higher number of CRC patterns that were less predominant and widely distributed in comparison to CON that can be defined as a decreased CRC in SZO.

The altered CRC in SZO was mainly characterized by a larger amount of increased short-term alternating and fluctuating patterns (*LUI*, *LDI*, *LAI*, *P*, *V*). Further on, the respiratory regulation seems to be more complex and does mainly affect the CRC in SZO. These changes could be disease inherent characteristics and might reflect arousal during the psychosis stage in acutely ill patients. Bär et al. [5] also demonstrated that SZO have an impaired cardiorespiratory coupling and reduced RSA inherent. They suggested that their findings based on the decreased vagal activity within the brainstem or its suppression from higher regulatory centres. It is known that respiration is primarily regulated for metabolic and homeostatic purposes in the brainstem but do also change in response to changes in emotions, such as sadness, happiness, anxiety or fear [10]. Thus, that these centres (e.g., limbic system, amygdala, and hypothalamus) are closely associated with regulation of mood and thought it seems not to be surprisingly that there are reciprocal and interconnected interactions between respiration and emotional states [11].

In addition, it could be shown that there is intriguing evidence suggesting pathophysiologic relationships among dyspnoea, hyperventilation, and panic anxiety. Thereby, symptoms of panic attacks and pulmonary disease can overlap as a consequence panic anxiety can reflect underlying cardiopulmonary disease and dyspnoea can reflect an underlying anxiety disorder [12]. Due to, that schizophrenia is related to panic attacks, this fact could be further support the assumption that the changes of cardiorespiratory couplings in SZO might be a results of panic related changes in the brainstem in the acute psychotic state. In addition, due to the link between the central nervous system and respiration a small change in respiratory functioning may lead to background symptoms of panic and anxiety in any disorder [11].

In conclusion, applying HRJSD we were able to provide detailed information about short-term cardiorespiratory physiological regulatory mechanisms of the autonomic nerve system in acute schizophrenia. Our results might be indicating to an impairment of short-term respiratory regulation probably due to an altered or suppressed interaction of the brainstem and higher regulatory centres in the patients.

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