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# Cardiovascular and cardiorespiratory coupling in unmedicated schizophrenic patients in comparison to healthy subjects*

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***Abstract*—Schizophrenia is associated with a cardiac autonomic dysregulation which is characterized by a decreased vagal modulation. Nevertheless, there are less information about the interrelationships of the cardiovascular and respiratory systems in schizophrenia.**

**The aim of this study was to characterize short-term nonlinear cardiovascular and cardiorespiratory couplings in schizophrenia applying joint symbolic dynamics (JSD) analysis for an improved understanding of physiological processes of autonomic regulation in schizophrenia. We investigated 57 patients with schizophrenia (*SZO*) and 57 age-gender matched healthy controls (*CON*) for cardiovascular (N=37) and cardiorespiratory (N=20) coupling analysis. The results from cardiovascular coupling analysis demonstrated significantly decreased nonlinear bivariate word type combinations in *SZO* in comparison to *CON* (p<0.01) as a sign of an impaired baroreflex mediated cardiovascular regulation. Analysis of cardiorespiratory coupling revealed a significant restricted respiratory variability (respiratory sinus arrhythmia) and a decreased cardiorespiratory coupling in *SZO* in comparison to *CON* and might be interpreted as a suppression of higher respiratory brainstem centers.**

**In conclusion, we found an impaired and altered cardiovascular and cardiorespiratory coupling in unmedicated schizophrenic patients indicating a vagal withdrawal of autonomic modulation and an assumed suppression of higher regulatory centers of the brain stem in those patients.**

## I. Introduction

Schizophrenia is one of the most severe psychiatric disorder with a lifetime prevalence rate of approximately 1% (US: 2.2 million people) [1]. Patients suffering from schizophrenia 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]. Possible causes for this high mortality rates were controversially discussed as unhealthy lifestyle, cigarette smoking, obesity, insulin resistance, diabetes, hypertension, side effects of antipsychotic medication and an autonomic dysfunction reflected in altered heart rate variability (HRV). Studies which applied HRV analysis to schizophrenic patients commonly used linear time- and frequency domain as well nonlinear HRV indices [3-7]. For unmedicated schizophrenic patients usually a higher mean heart rate and reduced HRV indices were found in comparison to healthy controls. The findings from different studies suggest a higher risk for cardiovascular disease and even an increased risk for cardiac mortality [8]. However, there is limited information about short-term nonlinear cardiovascular and cardiorespiratory couplings in patients with schizophrenia [9, 10]. The bivariate coupling analysis of heart rate (HR) and systolic blood pressure (SBP) as well as of HR and respiration rate (RESP) time series, respectively, might provide further information about the complex system of autonomic regulation in schizophrenia than univariate approaches can do. Since cardiovascular and cardiorespiratory interactions are at least partly of nonlinear origin it seems to be necessary to apply methods that consider nonlinear interrelationships. For the characterization of the beat-to-beat changes between HR and SP time series the method of Joint Symbolic Dynamics (JSD) was introduced [11]. JSD allows a simplified quantification by coarse-gaining of the dynamics of HR and SBP or RESP, respectively, with a limited amount of symbols and was already successfully applied in several studies [12, 13].

We hypothesize that JSD indices derived from cardiovascular and cardiorespiratory time series can reveal more detailed information about bivariate alterations of autonomic regulation (couplings) and its complexity in patients with schizophrenia in comparison to healthy subjects than univariate approaches can do.

## II. Materials And Methods

### *A. Patient, Data Recording and Data Preprocessing*

In this study, thirty-seven unmedicated patients suffering from schizophrenia ($SZO_{CV}$, 14 female; 33.8±10.8 years) and age-gender matched healthy controls ($CON_{CV}$, 14 female; 33.9±7.6 years) were enrolled for the investigation of cardiovascular coupling ($_{CV}$) and twenty unmedicated patients suffering from schizophrenia ($SZO_{CR}$, 8 female; 33.7±12.6 years) and age-gender matched healthy controls ($CON_{CR}$, 8 female; 27.7±7.8 years) for cardiorespiratory coupling ($_{CR}$) analysis. Participants were asked to refrain from smoking, drinking coffee, heavy eating or exercising two hours prior to the investigation. Schizophrenia was diagnosed by psychiatrist 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 a personality inventory

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(Freiburger Persönlichkeitsinventar) were additionally applied to *CON* to detect personality traits or disorders which might influence autonomic function. 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.

### B. Data Recording and Data Preprocessing

For cardiovascular coupling analysis a high resolution short-term ECG (1000Hz sampling frequency) and synchronized continuously recorded noninvasive blood pressure from the third and fourth finger were recorded over 30 minutes with the Task Force monitor® (CNSystems, Graz, Austria). For cardiorespiratory coupling analysis a high resolution short-term ECG (1000Hz 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 the 30 minutes raw data records (cardiovascular, cardiorespiratory) we extracted: (i) time series of heart rate consisting of successive beat-to-beat intervals (tachogram, BBI), (ii) time series of systolic blood pressure (systogram, SBP) values over time and (iii) time series of successive breath durations (RESP). Thereafter, all time series were visually inspected and if necessary edited. For cardiorespiratory coupling analysis the time series (BBI, RESP) were resampled using a linear interpolation method with a sampling frequency of 2Hz to obtain synchronized time series. Finally, all time series were filtered by applying an adaptive variance estimation algorithm [14] to remove and interpolate ventricular premature beats and artifacts (e.g. movement, electrode noise and extraordinary peaks) to get normal-to-normal beat time series (NN).

### C. Joint Symbolic Dynamics - JSD

The JSD method as an enhanced version of the univariate [15] symbolic dynamics approach quantifies the bivariate nonlinear behavior of short-term cardiovascular and cardiorespiratory coupling by means of symbols. Thereby, JSD transforms, here e.g. cardiovascular coupling, the $n$ beat-to-beat values of BBI and SBP time series ($x^{BBI}$, $x^{SBP}$) from a bivariate sample vector $X$ into a bivariate symbol vector $S$ that consists of a sequence of symbols ($s^{BBI}$, $s^{SBP}$) using an alphabet $A=\{0,1\}$.

Symbol '1' represents increasing values and symbol '0' decreasing and unchanged values applying a threshold level $l=0$ (1, 2).

$$s_n^{BBI} = \begin{cases} 0: \left(x_n^{BBI} - x_{n+1}^{BBI}\right) \le l^{BBI} \\ 1: \left(x_n^{BBI} - x_{n+1}^{BBI}\right) > l^{BBI} \end{cases} \quad (1)$$

$$s_n^{SBP} = \begin{cases} 0: \left(x_n^{SBP} - x_{n+1}^{SBP}\right) \le l^{SBP} \\ 1: \left(x_n^{SBP} - x_{n+1}^{SBP}\right) > l^{SBP} \end{cases} \quad (2)$$

Afterwards, words ($w$) of symbol sequences with a length equal to three were formed. From all bivariate word type combinations the probability ($p(w_{i,j})$) of occurrence was estimated using an 8x8 word distribution density matrix $W$ (rows represent BBI, columns represent SBP or RESP) ranging from $(000, 000)^T$ to $(111, 111)^T$ whereby the sum of all word type probabilities was normalized to 1. From this matrix following indices were estimated:

- normalized probability occurrences of bivariate word type combinations (JSD1-JSD64) '*xxx'* of BBI time series and simultaneous '*yyy'* of SBP or RESP time series (e.g. *BBI-100/RESP-101*),
- sum of each row (combinations with equal BBI word: *BBIxxx*) and the sum of each column (combinations with equal SBP or RESP word: *SBPyyy*, *RESPyyy*),
- sums of diagonals within $W$: *SumSym* - symmetric word types and *SumDiam* - diametric word types,
- Shannon entropy (3) of the word distribution density matrix as a measure of the overall complexity of the cardiovascular ($JSDshannon_{CV}$) or cardiorespiratory ($JSDshannon_{CR}$) coupling.

$$\text{JSD}_{\text{shannon}} = -\sum_{i,j=1}^{8} \left[ p(w_{i.j}) \log_2 p(w_{i.j}) \right] \quad (3)$$

A more detailed visualization of the predominantly occurring word type combinations within $W$ was achieved applying an additional threshold level $TL$ (1.5%) to all probabilities of occurrence. Thus, we stepwise reduced (subtraction) the low variations within $W$.

### D. Statistics

The nonparametric Mann-Whitney U-test was applied for the statistical evaluation of all differences in JSD indices between $SZO_{CV}$ and $CON_{CV}$ as well as between $SZO_{CR}$ and $CON_{CR}$. Univariate significances were considered for values of $p<0.01$. Descriptive statistics was used to describe the basic features of the data as mean values and standard deviations.

## III. Results

### A. Cardiovascular couplings

Indices from JSD (11 bivariate word type combinations) revealed significant differences between $SZO_{CV}$ and $CON_{CV}$ ($p<0.01$). Theses word type combinations were mainly symmetric word types (diagonals within $W$, Fig. 1) quantifying baroreflex patterns [12] and were reduced in $SZO_{CV}$. In addition, the sums of diagonals within $W$ the symmetric (*SumSym*) and diametric word types (*SumDiam*) were significant different ($p<0.01$) whereas $JSDshannon_{CV}$

was highly significant (p<0.0006, Bonferroni correction) different between $SZO_{CV}$ and $CON_{CV}$ (Table 1). The sum of each row (*BBIxxx*) and each column (*SBPyyy*) did not reveal significant differences between the groups.

TABLE I. CARDIOVASCULAR (CV) AND CARDIORESPIRATORY (CR) JSD INDICES FOR THE DISCRIMINATION BETWEEN UNMEDICATED PATIENST SUFFERING FROM SCHIZOPHRENIA (*SZO*) AND HEALTHY CONTROLS (*CON*). (** P<0.01; *** P<0.0006 (BONFERRONI CORRECTION)).

| | JSD indices | SZO vs. CON | CON | SZO |
|---|---|---|---|---|
| CV | SumSym | ** | 0.36 ± 0.09 | 0.28 ± 0.11 |
| | SumDiam | ** | 0.03 ± 0.02 | 0.05 ± 0.04 |
| | JSDshannon | *** | 3.51 ± 0.23 | 3.71 ± 0.23 |
| CR | RESP001 | ** | 7.42 ± 1.74 | 9.16 ± 1.37 |
| | RESP010 | *** | 0.02 ± 0.05 | 1.01 ± 1.16 |
| | RESP011 | *** | 7.44 ± 1.76 | 10.56 ± 2.52 |
| | RESP100 | ** | 7.42 ± 1.73 | 9.15 ± 1.37 |
| | RESP101 | *** | 0.04 ± 0.08 | 2.41 ± 2.93 |
| | RESP110 | *** | 7.44 ± 1.74 | 10.55 ± 2.51 |
| | JSDshannon | *** | 3.32 ± 0.17 | 3.67 ± 0.22 |

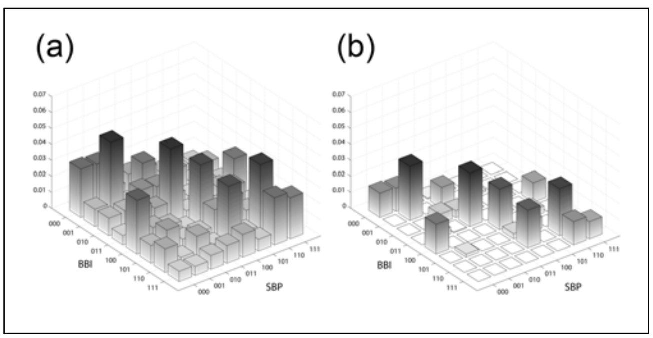

Figure 1. Probability distributions of word types within the 8x8 word distribution density matrix for cardiovascular coupling for unmedicated schizophrenic patients (BBI: beat-to-beat intervals, SBP: systolic blood pressure time series); (a): *TL*=0%, (b): after subtracting *TL*=1.5%.

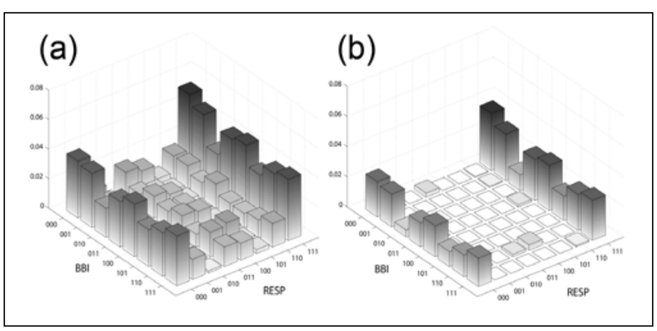

Figure 2. Probability distributions of word types within the 8x8 word distribution density matrix for cardiorespiratory coupling for unmedicated schizophrenic patients (BBI: beat-to-beat intervals, RESP: time series of successive breath durations); (a): *TL*=0%, (b) after subtracting *TL*=1.5%

### B. Cardiorespiratory couplings

42 of 64 bivariate word type combinations revealed significant differences between $SZO_{CR}$ and $CON_{CR}$ (14, p<0.01; 28, p<0.0006). The sum of 6 from 8 rows (*BBIxxx*) and the sums of all columns (*RESPyyy*) did reveal significant differences between $SZO_{CR}$ and $CON_{CR}$ (p<0.01) (Table 1). Furthermore, it could be shown that word type combinations with "000" or "111" for RESP, indicating lower variability, were the most dominant and declined in $SZO_{CR}$ (Fig. 2a). This behavior was even more obvious when *TL*=1.5% was applied (Fig. 2b). On the other side, the word type combinations with "000" and '111' for BBI were the most dominant word types for $SZO_{CR}$ (*BBI000*=16%, *BBI111*=13%) and revealed the lowest probability of occurrences for $CON_{CR}$ (*BBI000*=10%, *BBI111*=8%). After excluding the outer predominating columns *RESP000* and *RESP111* from the JSD word distribution density matrix all other *RESPyyy* word types occurred more frequently in combination with all other *BBIxxx* word types for $SZO_{CR}$ than for $CON_{CR}$ (Figure 3) and were significant (p<0.0006) different between both groups.

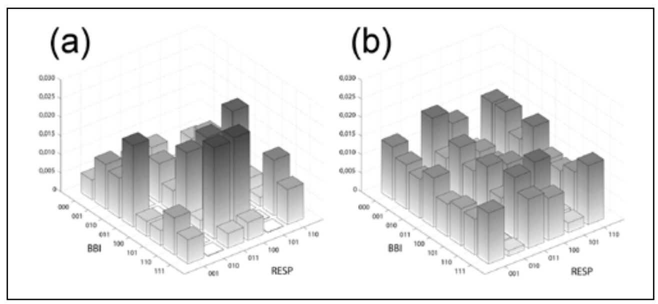

Figure 3. Probability distributions of word types within a zoomed 8x6 word distribution density matrix after excluding the outer columns *RESP000* and *RESP111* for cardiorespiratory coupling for (a) healthy controls and (b) unmedicated schizophrenic patients with *TL*=0% (BBI: beat-to-beat intervals, RESP: time series of successive breath durations).

## IV. DISCUSSION AND CONCLUSION

In this study we demonstrated reduced cardiovascular and cardiorespiratory couplings shown by significant altered JSD indices in patients with schizophrenia. These findings indicated an impaired autonomic modulation in comparison to healthy controls.

Cardiovascular coupling analysis revealed significant increased diametric (*SumDiam*) and significant decreased symmetric (*SumSym*) word types in *SZO* in comparison to *CON*. On the one side, symmetric word types are characterized by the fact that the patterns in SBP are equal to the patterns in BBI representing baroreflex-like response patterns. On the other side, diametric word types are characterized by the fact that the BBI response to SBP changes is asymmetric representing oppositional baroreflex patterns [12]. These findings might be interpreted as a loss of baroreflex mediated regulation pattern (nonlinear) in schizophrenic patients and is in accordance with recent findings [16]. The increased complexity of cardiovascular modulation was confirmed by $JSDshannon_{CV}$ (Table 1) and is most likely caused by impaired heart rate regulatory processes which is partly confirmed by Bär et al. [3] who could show a reduced complexity of heart rate time series in acute schizophrenia.

Analysis of cardiorespiratory coupling revealed various significant JSD indices differentiating between *SZO* and *CON*. The most occurring indices represented mainly monotonous word types "111" and "000", especially in RESP, indicating a consecutive increasing ("111") as well as an unchanging or decreasing ("000") of RESP and partly for HR (Fig. 2a-b). The two prominent RESP word types (111, 000) occurred mostly in combination with all other BBI word types in both $SZO_{CR}$ and $CON_{CR}$ (*RESP000*: $CON_{CR}$ = 33%, $SZO_{CR}$= 25%; *RESP111*: $CON_{CR}$=37%, $SZO_{CR}$=32%), but more frequently in $CON_{CR}$. These RESP patterns occur independently from the BBI patterns and reflect a sustained and from BBI decoupled behavior of cardiorespiratory regulation. In contrast to the monotonous RESP word types (000, 111) all other RESP word types which are characterized by more fluctuation patterns, especially the patterns "001, 011, 100, 110" (Figure 3) occurred more frequently in combination with all other BBI word types for *SZO* than for *CON*. These specific RESP patterns were much more pronounced, independent and detached from BBI patterns (HR regulation). This indicates a higher short-term variability accompanied with a reduced cardiorespiratory coupling (specific respiratory pattern over all RR intervals) in *SZO*. Moreover, the specific occurrences of predominant RESP patterns could be considered as a marker for a restricted respiratory sinus arrhythmia (RSA) as a measure of cardiac vagal activity, which is a basic cardiorespiratory principle, characterized by BBI fluctuations that are in phase with inhalation and exhalation. This is in accordance with Bär et al. [9] who found impaired cardiorespiratory coupling and reduced RSA in *SZO*. They speculated that decreased vagal activity within the brainstem or its suppression from higher regulatory centers might account for these findings. Peupelmann et al. [10] did also found decreased cardiorespiratory coupling (applying cross-approximate entropy) in *SZO* which was interpreted as an diminished vagal modulation at the brain stem level. Furthermore, they found that regularity of breathing correlated with disease severity and assumed a lack of inhibitory control over brainstem centers in schizophrenia. It has been shown that changed complexity indices, resulting from depressed organ function, a loss of interaction among subsystems, an overwhelming action of a subsystem over others and an impairment of regulatory processes, is a clear hallmark of a pathological situation [17] which seem to be present in *SZO*. It seems to be obviously that the cardiovascular and especially the cardiorespiratory regulatory processes are decoupled and interact in a more detached way in *SZO*. However, actually a clear physiological interpretation cannot be drawn about the impairments of the different underlying regulatory mechanisms in schizophrenia.

In conclusion, we demonstrated that cardiovascular and cardiorespiratory coupling is considerably impaired and altered in unmedicated schizophrenic patients in comparison to healthy controls. Thus, indicating to a vagal withdrawal of autonomic modulation and an assumed suppression of higher regulatory centers of the brain stem in those patients. The application of JSD, allows a simplified coarse-graining quantification of short-term dynamics of autonomic regulation processes (cardiovascular, cardiorespiratory). This might lead to an enhanced understanding of the relationship between schizophrenia as a mental disorder and an increased cardiac risk.

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