Unexpected cardiovascular coupling in schizophrenia

Ioana EDU[1], Felix ADOCHIEI[2], Narcis ADOCHIEI, Nicolae JULA[1]
[1]*Military Technical Academy, Bucharest, Romania*
[2]*POLITEHNICA University of Bucharest*
edu_ioana_raluca@yahoo.com

Abstract — **This article aims to attract the attention of specialists from medical and health sciences on cardiovascular disorders that are occurring before schizophrenia in people with highly genetic risk to develop schizophrenia. We are interested in the schizophrenia changes that affect the nervous system proper functioning, more specific about the cardiovascular system symptoms that are triggered before the onset of schizophrenia. The autonomous nervous system behavior, represented by the cardiovascular system signal correlations was investigated using a recently developed method, the *NSTPDC* method. Our main goal was to gather data not only on the existence of some specific changes that occur before schizophrenia but also on the extent and future effects of the cardiovascular signal correlations. At present, we do not have access to studies that investigate the onset of schizophrenia symptoms and we hope to bring valuable contributions in this area of interest.**

Index Terms — schizophrenia prediction, autonomous nervous system.

I. INTRODUCTION

Schizophrenia has certainly an important genetic component, as can be seen from the graph in Figure 1. People who have a third degree relative with schizophrenia are twice as likely to develop schizophrenia compared with the general population. Those with a second degree relative have a more pronounced relative incidence of developing schizophrenia and first-degree relatives with schizophrenia have an incident with an order of magnitude higher than the general population.

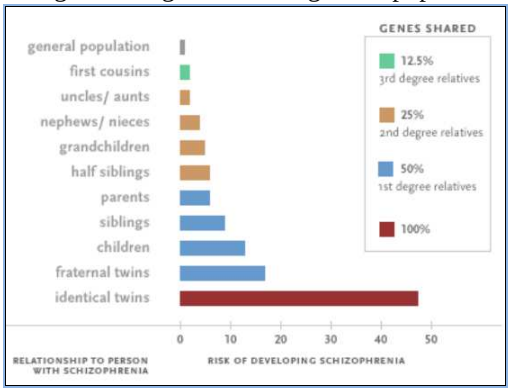

Figure 1 - Schizophrenia and genetic risks

In this paper schizophrenia specific cardiovascular correlations will be investigated because most of the people with schizophrenia die of natural causes but most deaths are caused by cardiovascular diseases [1], briefly investigated to date.

We are especially interested in the schizophrenia early diagnosis possibility for first-degree relatives of individuals with schizophrenia.

II. PATIENTS

In this work we investigated a group of first degree relatives of patients with schizophrenia (*1stDRS*) beat-to-beat (*BBI*), systolic and diastolic blood pressure (*SBP* and *DBP*) specific signal correlations because we aimed to observe whether there is a predictable risk of developing heart disease, knowing that genetic factors play a decisive role in the emergence of schizophrenia and the detection of cardiac risk before the onset of schizophrenia would be an important breakthrough and of extra importance to human health at risk to develop schizophrenia. For results interpretation two control groups were considered, one of healthy patients (*CG1*) and one of patients diagnosed with schizophrenia (*SZO*).

Table 1 - Patients study

Clinical data	*1stDRS*	*SZO*	*CG1*
Number of patients	15	15	15

III. METHOD

According to recently developed studies [2, 3], multivariate autoregressive models (*MVAR*) are able to represent interactions between physiological signals as linear difference equations. The Partial Directed Coherence (*PDC*) method [4] is among the most applied linear approaches in the linear frequency time series analysis approaches and investigations of the complex physiological systems coupling dynamics. Recently we introduced the *Normalized Short Time PDC* (*NSTPDC*), a new time frequency approach, and demonstrated that this method is applicable for non-stationary time series and it has the capacity to detect dynamical changes of coupling in complex dynamic systems. *NSTPDC* method main advantages are: the ability to detect direct and indirect causal information transfer and the capacity to provide significant information about physiological signal coupling levels and directions (within multivariate

dynamic systems).

The *PDC* coupling estimation between two time series (*Xi* and *Xj*) was defined by Baccala et al. [4] as:

$$\pi_{ij}(n) \overset{\Delta}{=} \frac{A_{ij}(n,f)}{\sqrt{a_j^H(n,f)a_j(n,f)}} \quad (1)$$

where $\pi_{ij}(n)$ is the correlation parameter, $(.)^H$ the Hermitian transpose, $A_{ij}(n,f)$ the $A_r(n)$, the Fourier transform of the matrix in the frequency domain, $a_j(n,f)$ the *j'th* column number of the matrix $A(n,f)$, *n* the number of windows and *f*, the frequency.

The π_{ij} parameter normalization conditions in the frequency domain ($\pi_{ij}(f)$) were defined as:

$$0 \le \left|\pi_{ij}(f)\right| \le 1, \quad \sum_{i=1}^{m} \left|\pi_{ij}(f)\right| = 1 \quad (2)$$

for all $1 \le j \le m$ values.

These measures were considered to provide information on the presence and level of causal correlation between two time series (*Xi* and *Xj*) as follows:

a) high values reflecting a directionally linear influence from *Xj* to *Xi*, meaning that, for values equal to 1, all the causal influences originating from *Xj* are directed towards *Xi*,

b) low values (≈0) suggesting the absence of any causal correlation from *Xj* to *Xi*, meaning that *Xj* does not influence *Xi*.

In order to estimate the direction and the strength of these couplings, an extended version of the *PDC* method, the *NSTPDC* method, based on the calculation of an extra number of parameters is proposed. A normalisation factor *NF={-2,-1,0,1,2}* (Eq. 3) is calculated as the mean value of X_j coupled with X_i divided by the mean value of X_i coupled with X_j, where *-2* and *2* values suggests a strong unidirectional coupling (increased absolute values meaning increased coupling strength), *-1* and *1* values indicates a bidirectional coupling and the master signal, while *0* value denotes an equal influence (for both directions) or no coupling at all. The *NSTPDC* was achieved by means of a short time implementation with a Hamming window of 300 samples length and 50 samples overlap.

In this study, *NF* parameters were calculated in order to investigate the dynamic couplings of *EKG* time series in schizophrenia.

$$a = mean \quad PDC(X_i - X_j)$$
$$b = mean \quad PDC(X_j - X_i)$$
$$Max(a,b)$$
$$NF = \begin{cases} 2, & if\ (Max = a \quad and \quad a/b > 5) \\ 1, & if\ (Max = a \quad and \quad 2 < a/b \le 5) \\ 0 & if\ (Max = a \quad and \quad 0 \le a/b \le 2) \end{cases} \quad (3)$$
$$NF = \begin{cases} -2, & if\ (Max = b \quad and \quad b/a > 5) \\ -1, & if\ (Max = b \quad and \quad 2 < b/a \le 5) \\ 0 & if\ (Max = b \quad and \quad 0 \le b/a \le 2) \end{cases}$$

Supplementary, a *PDC* areas estimation was proposed: by assigning *a* letter to the influence of the second signal on the first signal and *b* letter to the influence of the first signal on the second signal $A_{REA}a$ and $A_{REA}b$ parameters were calculated to observe the couplings strength between the pairwise signals according to (4):

$$A_{REA}a = \sum_{i=0}^{lenght(x)} \frac{(t_i x_i + t_{i+1} x_{i+1}) t_i t_{i+1}}{2} \quad (4)$$

The determination of the cardiovascular signals interactions and couplings (by calculating the *NF* parameters) and the determination of the couplings strength (by calculating $A_{RIA}a$ and $A_{RIA}b$ parameters) led us to significant conclusions that might predict cardiovascular diseases and eventually schizophrenia in people susceptible to develop schizophrenia (I^{st} degree relatives of patients diagnosed with schizophrenia).

IV. STATISTICS

For discrimination, the nonparametric Mann-Whitney U-test was used to statistically measure the differences between the *NSTPDC* indices, calculated for the three groups. For comparing, three levels of significance were considered: significant p □ (0.01, 0.05], very significant p □ (0.001, 0.01] and highly significant p □ (0, 0.001] indices.

V. RESULTS

NSTPDC method was applied to analyse the *BBI*, *SBP* and *DBP* signal couplings of the I^{st} degree relatives of patients diagnosed with schizophrenia ($I^{st}DRS$), schizophrenia patients (*SZO*) and healthy control group (*CON*). The normalisation factor (*NF*) and area ($A_{RIA}a$ and $A_{RIA}b$) parameters were computed for each pair of channels (*BBI-SBP*, *BBI-DBP* and *SBP-DBP*) for each group under investigation. Data was collected in Tables II, III and IV.

TABLE II
NSTPDC INDICES FOR BBI AND SBP SIGNALS.
U TEST SIGNIFICANT INDICES (ARE MARKED IN GREEN FOR P □ (0.01, 0.05], THE COLOR YELLOW FOR P □ (0.001, 0.01] AND RED FOR P □ (0,001])

***PDC* indices**	***1ST DRS* vs. *CG1***	***1ST DRS* vs. *SZO***	***GC1* vs. *SZO***
NF	0.019	0.821	0.056
$A_{REA}A$	0.942	0.175	0.077
$A_{REA}B$	0.004	0.041	0.570

By comparing *BBI* and *SBP* signals we found two significant indices between $1^{ST}DRS$ and *CG1* and *SZO* groups and a very significant index between $1^{ST}DRS$ vs. *SZO*. After visual inspection, according to area parameters, was observed that the correlation between *SBP* and *BBI* signals is higher in *CON*, lower in $1^{ST}DRS$ and very low in *SZO*. *BBI* and *SBP* correlation level between is increased for SZO and highly increased for $1^{ST}DRS$.

TABLE III
NSTPDC INDICES FOR BBI AND DBP SIGNALS.
U TEST SIGNIFICANT INDICES

***PDC* indices**	***1ST DRS* vs. *GC1***	***1ST DRS* vs. *SZO***	***GC1* vs. *SZO***
NF	0.000	0.342	0.000
$A_{REA}A$	0.097	0.002	0.000
$A_{REA}B$	0.005	0.231	0.348

By comparing *BBI* and *DBP* signals we found a very significant index and a highly significant index between

1ST DRS and *CG1* groups, a very significant index between *1ST DRS* vs. *SZO* and two highly significant indices between *GC1* vs. *SZO*. After a visual inspection, according to area parameters, was observed that the correlation between *DBP* and *BBI* signals is higher in *CON*, lower in *1ST DRS* and very low in *SZO*. *BBI* and *SBP* correlation level between is increased for *SZO* and highly increased for *1ST DRS*.

TABLE IV
NSTPDC INDICES FOR SBP AND DBP SIGNALS
U TEST SIGNIFICANT INDICES

PDC indices	*1ST DRS* vs. *GC1*	*1ST DRS* vs. *SZO*	*GC1* vs. *SZO*
NF	0.013	0.359	0.004
$A_{REA}A$	0.001	0.179	0.000
$A_{REA}B$	0.470	0.421	0.179

By comparing *SBP* and *DBP* signals we found a highly significant index and a significant index between *1ST DRS* and *CG1* groups and a highly significant index and a significant index between *GC1* vs. *SZO*. After a visual inspection, according to area parameters, was observed that the correlation between *DBP* and *SBP* signals is lower in *CON*, and higher in *1ST DRS* and in *SZO*. *DBP* and *SBP* correlation level between is decreased for *SZO*.

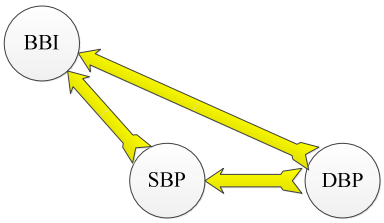

Figure 2 - Directions and levels of correlation for *BBI*, *SBP* and *DBP* signals for *1ST DRS*

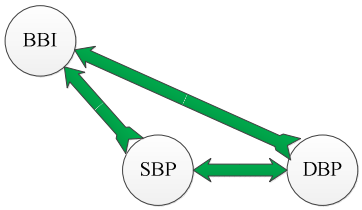

Figure 3 - Directions and levels of correlation for *BBI*, *SBP* and *DBP* signals for *GC1*

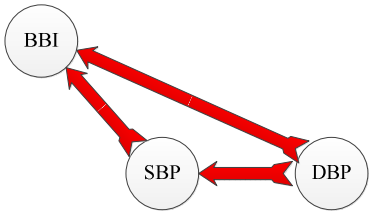

Figure 4 - Directions and levels of correlation for *BBI*, *SBP* and *DBP* signals for *SZO*

VI. DISCUSIONS

Using the *NSTPDC* approach we have found the existence of significantly reduced cardiovascular correlations in patients with schizophrenia and in their first degree relatives, indicating a low blood pressure and an insufficient autonomous regulation in these groups in comparison with the control group.

Healthy first-degree relatives of patients with schizophrenia showed reduced *BBI-SBP* and *BBI-DBP* signal correlations and increased *SBP-DBP* signal correlations, similar to patients with schizophrenia, as compared to healthy control group of patients, evidence that proves that the genetic factor affects the body functioning early, long before the diagnosis of schizophrenia.

CONCLUSION

It is important to mention that up to the present time no previous studies were developed to investigate the risk of developing schizophrenia in terms of cardiovascular correlations in healthy first-degree relatives of people diagnosed with schizophrenia.

Unexpectedly, healthy relatives of patients with schizophrenia showed similar cardiovascular correlations comparing with patients with schizophrenia, evidence that suggests that the genetic factor is affecting the normal body functioning, long before the diagnosis of schizophrenia, indicating both the possibility of developing cardiovascular diseases and schizophrenia.

These results suggest the necessity of early investigations for the anticipation and prevention of cardiovascular deficiencies in individuals with a high genetic risk of schizophrenia.

In conclusion it was shown the existence of significant altered cardiovascular correlations (in terms of direction and level of correlation) in patients with schizophrenia and their first-degree relatives.

Results of both studies could lead to a deeper understanding of the relationship between schizophrenia and increased cardiac risk and the risks of increased morbidity demonstrated in individuals affected by this severe mental disorder.

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