Autonomic Dysfunction in Unaffected First-Degree Relatives of Patients Suffering From Schizophrenia

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Recent studies revealed cardiac autonomic dysfunction in patients with acute schizophrenia, which appears to be mainly related to reduced vagal and increased sympathetic modulation. To understand the significance of cardiac autonomic function in patients with schizophrenia, we extended these studies to relatives of patients. In this study, we assessed cardiac autonomic modulation in healthy first-degree relatives of patients with schizophrenia (n = 36) to investigate a putative genetic influence. Data were compared with control subjects matched for age, gender, and physical activity as well as to patients suffering from schizophrenia. First-degree relatives showed an attenuated, yet identical pattern in autonomic dysfunction as patients with decreased vagal modulation of heart rate, decreased baroreflex sensitivity, but no difference in blood pressure variability could be detected. The patients’ relatives also showed a similar pattern in regards to QT variability. In addition, the subgroup comparison of offspring vs. siblings showed a significant difference in heart rate variability suggesting a higher degree of heritability in offspring. In conclusion, the pattern of autonomic dysfunction seen in patients and relatives might indicate underlying disease-inherent genetic vulnerability, especially because autonomic parameters are heritable. In addition, these findings may be of value to identify the high-risk group of patients’ relatives in regards to serious cardiovascular events so that early preventive measures can be taken.

Key words: autonomic nervous system/schizophrenia/vagal/offspring/heart rate variability/baroreflex sensitivity/genetic

Introduction

A growing number of studies describe cardiac autonomic dysregulation in patients with acute schizophrenia which is possibly associated with an increased risk for cardiac arrhythmias and sudden cardiac death.1–9 In particular, a disease-associated decrease in vagal modulation causes reduced heart rate variability (HRV) and diminished baro-reflex sensitivity (BRS).2 HRV describes the continuous interplay between sympathetic and parasympathetic modulation of heart rate that reflects information on autonomic flexibility and responsiveness. In general, high variability is regarded as an index of cardiac health. Many measures of HRV have been proposed, which can be subdivided according to their underlying calculation into time domain, frequency domain, and nonlinear measures (table 1). Furthermore, the baroreceptor reflex is one of the body’s homeostatic mechanisms for maintaining blood pressure. It provides a negative feedback loop in which an elevated blood pressure reflexively causes heart rate deceleration and similarly decreased blood pressure induces heart rate acceleration. High sensitivity of baroreflex regulation mirrors healthy cardiovascular function.

Both HRV and BRS mainly reflect vagal modulation. In contrast, parameters indicating sympathetic activity such as the QT variability index (QTvi) or dilation of the pupil have been shown to be significantly increased in untreated patients suffering from acute schizophrenia.10,11 QTvi describes the variance of the QT interval duration and thus indicates the likelihood for life-threatening arrhythmias.

The underlying mechanisms for these disease-inherent autonomic changes have not been investigated to date. However, the lack of activation in the medial prefrontal cortex that has been shown in patients with schizophrenia might affect the inhibitory control over autonomic function of...
The latter can lead to an exacerbation of arousal responses, which may result in low efferent vagal modulation and increased sympathetic activity. Unlike HRV and BRS, previous research indicated no changes in the variability of blood pressure in the disease. Hence, a distinct pattern of autonomic dysregulation might be assumed. An important question remains, however, whether cardiac autonomic changes emerge due to arousal and tension in the acute episode and might become even more prominent under neuroleptic medication or whether autonomic dysfunction indicates a disease-associated biological abnormality. Various parameters have been identified that belong to the latter group, mainly because they could be detected in patients and their relatives. Some of these markers are not specific to schizophrenia such as the rate of nonspecific fluctuations of the electrodermal activity (EDA). Others are regarded to be more specific, for instance smooth pursuit eye movement dysfunction, which is known to reflect a genetic vulnerability to schizophrenia (eg, ocular motor abnormalities). Autonomic dysfunction associated with decreased vagal and increased sympathetic modulation occurs in various psychiatric conditions such as major depression, anxiety disorders or alcohol dependency, and withdrawal. Thus, one could assume that autonomic dysfunction is rather less likely to be specific for one disease. However, the previously described pattern of autonomic dysfunction in schizophrenia with decreased HRV and BRS, but unaltered blood pressure variability, has not been investigated in the context of disease specificity to date. In addition, there is good evidence from recent twin and family studies in healthy individuals pointing toward a significant genetic determination of HRV. Heritability of HRV ranges from 13% to 39% at rest, but can increase up to 51% when recorded during exposure to various stress tasks. Furthermore, BRS which plays a pivotal role in short-term blood pressure regulation and which is decreased in acute schizophrenia shows strong genetic determination.

In order to clarify the relation of autonomic dysfunction to the biology of the disease, we comprehensively investigated cardiac autonomic function in healthy first-degree relatives of patients with schizophrenia. In particular, we hypothesized that similar to patients suffering

<table>
<thead>
<tr>
<th>Parameter Abbreviation</th>
<th>Parameter</th>
<th>Mathematical Background</th>
<th>Autonomic Significance</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate variability</td>
<td>HR</td>
<td>Heart beats per minute</td>
<td>Standard deviation</td>
<td>Vagal modulation</td>
</tr>
<tr>
<td></td>
<td>RMSSDHRV</td>
<td>Root mean square of differences of beats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time domain</td>
<td>LF/HF ratioHRV</td>
<td>Ratio of low frequency and high-frequency components</td>
<td>Fourier transformation</td>
<td>Sympathovagal balance</td>
</tr>
<tr>
<td>Frequency domain</td>
<td>HCHR</td>
<td>Compression entropy</td>
<td>Nonlinear data compression</td>
<td>Vagal modulation</td>
</tr>
<tr>
<td>Complexity measure</td>
<td>sBP</td>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure variability</td>
<td>dBP</td>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RMSSDBPV</td>
<td>Root mean square of differences of successive blood pressure values</td>
<td>Standard deviation</td>
<td>Sympathetic modulation</td>
</tr>
<tr>
<td>Time domain</td>
<td>LF/HF ratioBPV</td>
<td>Ratio of low frequency and high-frequency components</td>
<td>Fourier transformation</td>
<td>Sympathetic modulation</td>
</tr>
<tr>
<td>Frequency domain</td>
<td>HCBPV</td>
<td>Compression entropy</td>
<td>Nonlinear data compression</td>
<td></td>
</tr>
<tr>
<td>Complexity measure</td>
<td>b-slope</td>
<td>Bradycardic slope</td>
<td>Regression analysis between blood pressure and heart rate</td>
<td>Vagal modulation</td>
</tr>
<tr>
<td>Baroreflex sensitivity</td>
<td>QTvi</td>
<td>QT variability index</td>
<td>Log transformed relation of QT and RR variance</td>
<td>Sympathetic modulation</td>
</tr>
</tbody>
</table>
from schizophrenia, measures of HRV, BRS, and QT variability differ from healthy controls, whereas parameters of blood pressure variability remain unaffected. For this purpose, we investigated 36 siblings and offspring of patients suffering from schizophrenia. All measures were compared with those of 36 age- and sex-matched healthy controls. In addition, all parameters were obtained from related patients to delineate previously observed changes in the disease.

### Methods

#### Study Population

Thirty-six patients suffering from paranoid schizophrenia, their healthy first-degree relatives (18 siblings, 18 offspring), and controls matched to relatives for age, sex, weight, smoking habits, and education were included in this study (see table 2). Sixteen patients had not received any psychotropic medication for at least 4 weeks, 16 patients were treated with olanzapine (10–15 mg/day for 14.2 ± 7.6 days), and 4 patients with risperidone (2–3 mg/day for 11.1 ± 3.4 days). Seven patients were in receipt of 2 mg/day of lorazepam. Control subjects were recruited from hospital staff (n = 14), medical students (n = 7), and the local community (n = 15). None of the participants suffered from any medical or additional psychiatric disease. No one took any other interfering medication (eg, cardiac medications or central nervous system active medications) with confounding effects as assessed using a questionnaire. Participants were asked to refrain from smoking, drinking coffee, heavy eating, or exercising 2 h prior to the investigation. Subjects suffering from nicotine withdrawal were not included in the study.

Patients suffering from schizophrenia were diagnosed by a staff psychiatrist. They fulfilled DSM-IV criteria (Diagnostic and statistical manual of mental disorders, 4th edition, published by the American Psychiatric Association) for paranoid schizophrenia, assessed by the Structured Clinical Interview for DSM-IV (SCID).

Psychotic symptoms were quantified using the scale for the assessment of positive symptoms and negative symptoms. Similarly, healthy relatives and controls were examined by a psychiatrist. The Structured Clinical Interview SCID II and a personality inventory (Freiburger Persönlichkeitsinventar) were additionally applied to detect personality traits or disorders which might influence autonomic function.

This study was carried out in accordance with the Declaration of Helsinki. After having been thoroughly informed about the nature of the procedures, all participants gave written informed consent to a protocol approved by the ethics committee of the University Hospital, Jena. Furthermore, relatives were advised that the refusal of participating in this study would not affect future treatment of their family members.

#### Measures

Examinations were performed in a quiet room which was kept comfortably warm (22–24°C) between 3 and 6 pm.

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### Table 2. Clinical and Demographic Data of Participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Relatives</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of kinship</td>
<td>n.a.</td>
<td>Offspring</td>
<td>Siblings</td>
</tr>
<tr>
<td>Number of participants, n</td>
<td>36</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Male/female</td>
<td>14/22</td>
<td>4/14</td>
<td>10/8</td>
</tr>
<tr>
<td>Age (years), mean ± SD (min–max)</td>
<td>27.7 ± 7.8 (18–50)</td>
<td>26.6 ± 9.9 (18–51)</td>
<td>29.8 ± 9.7 (18–49)</td>
</tr>
<tr>
<td>Body mass index, mean ± SD</td>
<td>22.5 ± 2.9</td>
<td>23.2 ± 3.6</td>
<td>23.2 ± 3.2</td>
</tr>
<tr>
<td>Education, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–10 Years at school</td>
<td>11</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>12 Years at school (A-level)</td>
<td>25</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Attended university</td>
<td>25</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Smoker/nonsmoker, n</td>
<td>12/24</td>
<td>4/14</td>
<td>8/10</td>
</tr>
<tr>
<td>&lt;5 Cigarettes/day</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5–10 Cigarettes/day</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 Cigarettes/day</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Sport, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No sport</td>
<td>16</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>&lt;2 h/week</td>
<td>7</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>2–5 h/week</td>
<td>10</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>&gt;5 h/week</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Sport not reported</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SANS, mean (min–max)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>SAPS, mean (min–max)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

SANS, scale for the assessment of negative symptoms; SAPS, scale for the assessment of positive symptoms; n.a., not applicable.
Subjects were asked to relax, breathe regularly, and move as little as possible. Respiratory rate was obtained for all participants.

The electrocardiogram (high resolution, 1000 Hz; Task Force Monitor, CNSystems, Medizintechnik GmbH, Austria) was recorded for 30 min from adhesive monitoring electrodes located on the chest wall to assure maximal R-wave amplitude. From this, the device automatically extracted the RR intervals (beat to beat interval). RR intervals were filtered afterwards and interpolated for ectopic beats and artifacts. Continuous blood pressure was simultaneously recorded noninvasively from the third and fourth finger using the vascular unloading technique and was corrected to absolute values with oscillometric blood pressure measurement to obtain blood pressure values for every consecutive beat.35

Heart Rate Variability. In accordance with the suggestions of the recommendations for autonomic testing as suggested by the Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology,36 we computed measures of HRV in the time and frequency domains which had been applied in studies on patients with schizophrenia previously. In particular, we obtained the square root of the meansquared differences of successive NN intervals (normal to normal beat interval, RMSSD) which is a reliable marker of parasympathetic function of the time domain of HRV analysis (for explanation see table 1 and Supplementary figure 1A). Furthermore, ratios of low frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.4 Hz) components (LF/HF ratio) were calculated as described for HRV (table 1).

Blood Pressure Variability. From the continuously recorded blood pressure values, similar parameters were calculated for blood pressure variability (RMSSD_BPV, LF/HF ratio_BPV, Hc_BPV) as described for HRV (table 1).

Baroreflex Sensitivity. The BRS was assessed using the sequence method as described previously.2,21,39 In brief, spontaneous sequences of at least 3 consecutive beats were analyzed when an increased systolic blood pressure of at least 1 mmHg caused an increased RR interval of at least 5 ms (bradycardic sequence). For each sequence, the regression between the 3 systolic blood pressure values and 3 RR intervals was calculated and the slope (brady-cardiac slope [b-slope]) of the regression line was used as an index of BRS (table 1 and Supplementary figure 2).

QT Variability. The QT variability algorithm has been described by Berger et al in detail and has been used by his and our group in previous studies.10,22,40 This algorithm detects the QT and RR intervals for every single beat. The RR and QT interval data were then detrended using the best fit line prior to the computation of the spectral analyses. The mean RR (RR mean), detrended RR variance (RRv), mean QT interval (QTm), and detrended QT interval variance (QTv) were calculated from the instantaneous RR and QT time series of 1024 points (256 s). Then the normalized QTvi was calculated as follows (table 1 and Supplementary figure 3)40:

\[ QTvi = \log_{10}\left(\frac{QTv}{QTmean^2}/(RRv/RRmean^2)\right). \]

This index represents the log ratio between QT interval and the RR variabilities, each normalized for the corresponding mean.

Statistical Analyses

We performed the following statistical analyses for all log-transformed parameters, which beforehand had been tested for normal distribution applying the Kolmogorov-Smirnov test. A multivariate analysis of covariance (MANCOVA) was applied with the factor GROUP for the parameters of HRV (heart rate, RMSSD_HRV, LF/HF ratio_HRV, Hc_HRV), BRS (b-slope), blood pressure variability (systolic blood pressure, diastolic blood pressure, RMSSD_BPV, LF/HF ratio_BPV, Hc_BPV), and QT variability (QTvi) to uncover differences between relatives, control subjects, and patients suffering from schizophrenia. Age and gender were used as covariates to minimize their effect on the study variables. Similarly, analyses of covariance (ANCOVAs) for each parameter were calculated to demonstrate difference between relatives, controls, and patients. To reveal the differences between relatives and patients and also between relatives and control subjects for single parameters, a Bonferroni-Holm corrected pair-wise comparison was performed as a post hoc analysis. Results are indicated in figure 1 and table 3.

A second MANCOVA was performed to test for differences within the relatives applying the factor RELATIONSHIP (sibling vs. offspring) for parameters (heart rate, RMSSD_HRV, Hc_HRV, QTvi, b-slope) to
examine possible differences with age as covariate. This was followed up by an ANCOVA for single parameters.

Scores of personality traits assessed in the Freiburg Persönlichkeitsinventar were compared between relatives and controls by means of a 2-tailed t-test applying Bonferroni-Holm correction. Furthermore, these values were correlated with autonomic parameters for the relatives and controls separately.

Results

Multivariate Analysis of Data of Relatives, Control Subjects, and Patients Suffering From Schizophrenia

The MANCOVA comparing first-degree relatives, controls, and patients in respect to HRV, BRS, QT variability, and blood pressure variability parameters revealed a significant overall difference between groups \( F(186,22) = 4.1, P < .001 \).

ANCOVAs for Relatives, Control Subjects, and Patients for Single Parameters

ANCOVAs for single parameters revealed a highly significant group difference for heart rate \( F = 16.1; P < .001 \) (figure 1A) and the parasympathetic parameter \( \text{RMSSD}_{\text{BPV}} F = 9.3; P < .001 \) (figure 1B). The nonlinear parameter compression entropy \( \text{Hc}_{\text{HRV}} \) (figure 1C) revealed a significant difference of heart rate complexity between groups \( F = 9.5; P < .001 \). Similarly, BRS was also significantly different between groups as assessed by the parameter b-slope \( F = 18.2; P < .001 \) (figure 1D). Furthermore, QTvi showed significant group differences \( F = 8.5; P < .001 \) (figure 1E). In contrast to significant difference between relatives, controls, and patients for LF/HF ratio \( F = 6.6, P < .002 \) (table 3), no difference was observed for \( \text{RMSSD}_{\text{BPV}} (P < .5) \), LF/HF ratio \( P < .2 \) as well as \( \text{Hc}_{\text{BPV}} (P < .2) \) of blood pressure variability (see table 3). Systolic blood pressure \( F = 3.5, P < .035 \) (figure 1F) and diastolic blood pressure \( F = 6.2, P < .003 \) (table 3) were also significantly different.
comparable to the changes seen in patients suffering from schizophrenia.\textsuperscript{1,2,10} Similar to patients,\textsuperscript{14} blood pressure variability was not significantly different in relatives included in this study. This might suggest that decreased HRV and complexity of heart rate represent the primary abnormality in patients and their relatives. The absence of changes of blood pressure variability might suggest the possibility that the fundamental inherited cardiovascular phenotype is more likely to be the vagal rather than the sympathetic component, although a larger number of patients would be required to prove this hypothesis. Therefore, further studies on this issue are needed to examine

**Fig. 1. Differences Between Relatives, Controls, and Patients Suffering From Schizophrenia Are Displayed.** Heart rate was significantly increased in relatives when compared with controls (A). No significant dissimilarities were found between relatives and patients in regard to heart rate (A). The RMSSD\textsubscript{HRV} of relatives indicating parasympathetic activity was significantly reduced when compared with control subjects, whereas no difference was observed when compared with patients (B). Similarly, the nonlinear parameter compression entropy H\textsubscript{CHRv} indicated reduced complexity in relatives of patients when compared with controls, whereas no difference was observed to patients (C). Baroreflex sensitivity was significantly decreased in relatives when compared with controls and values of patients were even more reduced when compared with their relatives (D). The QTv\textsubscript{i} was significantly increased in relatives when compared with controls, no difference was observed between patients and their relatives (E). No difference was observed for systolic blood pressure between control subjects and relatives as well as between relatives and patients (F). Boxes indicate data between the 25th and 75th percentile with the horizontal bar reflecting the median (filled squares = mean; open circles = first and 99th percentile; solid line = minimum and maximum of data; *P < .05; **P < .01; ***P < .001).
possible less robust and small effects in blood pressure variability, which might have been missed in our sample.

We investigated unaffected first-degree relatives of patients with schizophrenia to examine whether autonomic dysfunction might be solely related to arousal due to acute psychopathology of the disease or whether a genetic background predisposes for autonomic dysfunctions. Great efforts have been made to identify intermediate phenotypes that are detectable both in patients with schizophrenia and in a higher proportion in their unaffected relatives than in the general population. The observed finding in our study suggests the latter assumption and a genetic contribution might be assumed for the autonomic pattern observed in relatives in our study. This might correspond to the slightly increased lifetime disease expectancy of children of patients in comparison to their siblings. Results of our study suggest that a close monitoring of cardiovascular regulation in relatives might prove very valuable. Especially the increased QT variability in relatives needs to be followed up to assess whether relatives might be a population at risk for the development of arrhythmias and sudden cardiac death.

Similar to autonomic changes found in our study, there are important previous reports describing autonomic dysfunction in patients suffering from schizophrenia. Especially the EDA has been used in schizophrenia as a sensitive index of emotion-related sympathetic activity. Because at least 2 end organs under autonomic control, the cardiac autonomic system and the EDA, are altered in relatives of patients suffering from schizophrenia, altered activity in hierarchically higher centers of the central autonomic network might be assumed rather than peripheral autonomic dysfunction. In particular, it has been suggested that a lack of activation in the medial prefrontal cortex in schizophrenia possibly affects the inhibitory control over amygdala-driven autonomic function. It might therefore be relevant for the results reported here that voxel-based morphometry studies on high-risk subjects who are likely to develop schizophrenia indicated that some prefrontal reductions in brain volume are genetic trait markers. Furthermore, abnormal functional connectivities between the frontal and temporal cortices have been demonstrated in subjects at genetic risk for schizophrenia. It has also been suggested by some authors that the reduced volume of the amygdala-hippocampus complex in schizophrenia is genetically determined and thus might play a role in first-degree relatives. Similarly, reduced brain activity in the amygdala in both patients with schizophrenia and their nonaffected brothers has been observed after sad mood induction by functional magnetic resonance imaging. In addition, an enhanced sensitivity to metabolic stress was found in unaffected siblings. Thus, future studies need to evaluate a possible association between changes of autonomic function and disturbed stress response in first-degree relatives because it is highly likely that subcortical circuits regulating dopaminergic response to stress might also be involved in autonomic cardiac regulation.

Our results are limited by the uncertainty as to the possibility whether the investigated relatives might develop the disease in the future. Yet, no participant suffered from a personality disorder or a prevailing trait according to performed tests, although the indicated decreased scores of social orientation and openness in relatives might be associated with the higher frequency of schizotypical traits in this population. Still, the correlation analyses did not reveal any indication of an association between personality traits and autonomic function in our sample, thus decreasing the likelihood that personality traits might be associated with findings of our study. Furthermore, we tried to compare data of relatives to a suitable control group. In addition to education and smoking, we matched the amount of physical activity to minimize possible confounders. However, prospective studies might add valuable information on the stability and possible changes of autonomic dysfunction in first-degree relatives. Furthermore, nicotine abuse and dependency remain important confounders due to acute and long-term sequelae that warrant special efforts in future studies.

The patient group was included in this study to better understand the pattern of changes seen in their relatives and to corroborate previous findings. In contrast to previous studies, about half of the patients received antipsychotic medication, which possibly affects cardiac autonomic modulation, thus limiting the interpretation of data. However, we recently have demonstrated that olanzapine only exhibits minimal effects on the pattern of autonomic modulation, thus limiting the interpretation of data. However, we recently have demonstrated that olanzapine only exhibits minimal effects on the pattern of cardiovascular regulation in schizophrenia. Due to the inclusion of siblings and children of patients, the age and gender of participants were not entirely adjusted. We considered both as covariates to exclude any potential confounding effects of these variables.

In conclusion, we demonstrated substantial autonomic dysfunction in healthy first-degree relatives of patients suffering from schizophrenia. Thus, a genetic background for these alterations is highly likely and should be investigated. Further, the possible specificity of the described pattern for the risk of cardiac disease in relatives should be evaluated in future studies in detail.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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References


34. LeBlanc J, Ducharme MB, Thompson M. Study on the correlation of the autonomic nervous system responses to a stressor of high discomfort with personality traits. Physiol Behav. 2004;82:647–652.


