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Non-linear complexity measures of heart rate variability in acute schizophrenia

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Abstract

Objective: Cardiovascular mortality is significantly increased in patients suffering from schizophrenia. The mechanisms currently discussed contain unhealthy lifestyle with obesity and smoking, increased incidence of diabetes, adverse pro-arrhythmic effects of antipsychotic medication and altered autonomic function. It is therefore likely that the adaptation of the heart rate to different requirements is faulty in schizophrenia. One way to detect adaptive capabilities and thus stability of regulation is to measure complexity of heart rate fluctuations, with more complex heart rate fluctuations indicating better adaptability of the underlying system.
Methods: We calculated novel non-linear measures for beat-to-beat interval complexity from short-term ECG recordings in 20 unmedicated patients suffering from acute schizophrenia and compared them to those obtained from matched controls.
Results: Data from all mathematical models applied, i.e. joint symbolic dynamics, compression entropy, fractal dimension and approximate entropy, revealed significantly reduced complexity of heart rate time series in acute schizophrenia. When using heart rate as a covariate, only fractal dimension remained significantly altered, thus appearing to be a relatively more important heart rate independent parameter.
Conclusions: Complexity of heart rate modulation is significantly reduced in acute, untreated schizophrenia, thus indicating an increased risk for cardiovascular events in these patients.
Significance: These data might eventually add to the currently discussed monitoring of physical health in patients with schizophrenia, possibly providing a promising tool for cardio-arrhythmic risk stratification.

Keywords: Autonomic function; Cardiac mortality; Psychosis; Non-linear parameters; Complexity; Beat-to-beat interval

1. Introduction

Mortality in patients with schizophrenia is at least two times higher than in reference populations (Black and Fisher, 1992; Brown et al., 2000). Apart from suicide (Meltzer, 1998) cardiovascular causes account for the majority of these events (Brown et al., 2000; Enger et al., 2004). The latter have been associated with unhealthy lifestyle, adverse effects caused by antipsychotics and higher incidence of diabetes as well as metabolic syndrome (Ruschena et al., 1998; Glassman and Bigger, 2001; Grundy et al., 2004), which resulted in the recommendation to routinely monitor physical health in these patients (Marder et al., 2004). The impact of antipsychotic medication has been studied in the greatest extent due to these substances' ability to significantly prolong QTc intervals (Titier et al., 2005). However,

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even unmedicated patients with schizophrenia face an increased incidence of sudden cardiac death (Ray et al., 2001; Jindal et al., 2005). As we and others already assumed previously, one possible underlying cause might be autonomic dysfunction during acute psychosis as reflected by altered heart rate variability and autonomic function parameters. These include reduced time and frequency measures of heart rate variability (HRV) (Valkonen-Korhonen et al., 2003; Bar et al., 2005; Mujica-Parodi et al., 2005), reduced baroreflex sensitivity (Bar et al., 2007a) and reduced QT variability (Bar et al., 2007c) in short-term recordings. Besides linear HRV parameters describing the variance of beat-to-beat intervals, non-linear complexity parameters have been developed to describe the regularity of heart rate time series. The application of these novel analyses has led to a higher sensitivity for detecting autonomic dysfunction (Baumert et al., 2004b; Hoyer et al., 2006) and patients at risk for sudden death (Voss et al., 1996) in different diseases. To date, there is limited information about complexity measures of HRV in schizophrenia. Reduced complexity was found in 24 h recordings in unmedicated patients (Boettger et al., 2006) and in clozapine-treated patients when applying the sample entropy parameter, which negatively correlated with the degree of positive psychotic symptoms (Kim et al., 2004).

Even less data exist on complexity measures obtained from short-term recordings, owing to the fact that the calculation of such parameters requires a significant amount of raw data. Here, we aimed to fill this gap employing novel non-linear complexity measures that have been shown to reveal reliable results even in short recording times in patients suffering from different cardiovascular diseases. These are compression entropy Hc (Baumert et al., 2004b), probability of high or low variability sequences (phvar and plvar, respectively) (Voss et al., 1996), fractal dimension (Katz, 1988) and approximate entropy (Pincus, 1991). These were applied to electrocardiographic data obtained from 20 unmedicated patients with acute schizophrenia and 20 matched controls.

2. Methods

2.1. Participants

Twenty patients suffering from paranoid schizophrenia and 20 healthy controls matched with respect to age, sex, weight, smoking habits and education (see Table 1) were included in this study. Patients were examined unmedicated in the acute stage on the day of admission to the hospital and were only included in the study, when they had not taken antipsychotic medication for at least 8 weeks prior to the study. Control subjects were recruited from hospital staff and medical students. Neither patients nor controls suffered from any medical or additional psychiatric disease and none of them was in receipt of any medication that would affect the results of the study (e.g. cardiac medications or tranquilizer). Participants were asked to refrain from smoking, heavy eating or exercising 2 h prior to the investigation. Diagnosis of paranoid schizophrenia was established by a staff psychiatrist when symptoms of patients who were admitted to our inpatient wards fulfilled DSM-IV criteria (Diagnostic and statistical manual of mental disorders, 4th edition, published by the American Psychiatric Association) as assessed by the Structured Clinical Interview for DSM-IV (SCID; First, 2005). Psychotic symptoms were quantified by means of the scale for the assessment of positive symptoms (SAPS) and negative symptoms (SANS; Andreasen et al., 1995). 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 Friedrich-Schiller-University, Jena. Furthermore, patients were advised that the refusal of participating in the study would not affect future treatment. Every effort was made to ensure that patients were able to give informed consent and did not have to suffer additional distress from the examination setting.

Table 1
Clinical and demographic data of participants

	Controls	Patients
Participants	20	20
Male/female	11/9	11/9
Age (years)	33.8 ± 2.8	31.6 ± 3.0
Body mass index	24.12 ± 1.02	24.75 ± 1.08
Smoker/non-smoker	$n = 9/11$	$n = 8/12$
First episode of psychosis	–	$n = 5$
Duration of illness (years)	–	8.66 (0–33)
Age of onset in male/female	–	$23 \pm 1.3/30 \pm 4.1$
SAPS	–	42.1 ± 3.9
SANS	–	37.4 ± 4.8

SAPS, scale for the assessment of positive symptoms.
SANS, scale for the assessment of negative symptoms.
There were no significant differences between patients and controls.

2.2. Data acquisition and preprocessing

Examinations were performed in a quiet room which was kept comfortably warm (22–24 °C) between 1 and 6 p.m. Subjects were asked to relax, breath regularly and move as little as possible. Respiratory rate was obtained for all patients.

The electrocardiogram (high resolution, 1000 Hz) was recorded for 30 min from two separate adhesive monitoring electrodes (CNSystems®, Medizintechnik GmbH, Austria), which were placed on the chest wall to assure maximal R-wave amplitude. From this, the device automatically extracted the RR-intervals (beat-to-beat interval). RR-interval time series were afterwards filtered and interpolated for ectopic beat and artifact rejection using linear interpolation (see Lippman et al., 1994).