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Reduced cardio-respiratory coupling indicates suppression of vagal activity in healthy relatives of patients with schizophrenia

Sandy Berger [a], Michael Karl Boettger [b], Manuel Tancer [c], Salvador M. Guinjoan [d], Vikram K. Yeragani [c,e], Karl-Jürgen Bär [a,f,*]

[a] Department of Psychiatry and Psychotherapy, University Hospital, Jena, Germany
[b] Institute of Physiology, University Hospital, Jena, Germany
[c] Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, USA
[d] Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina
[e] Department of Psychiatry, University of Alberta, Edmonton, Canada
[f] Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, Ruhr-University, Bochum, Germany

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ABSTRACT

Previous studies have observed reduced vagal modulation in patients with acute schizophrenia and their first-degree relatives, thus suggesting a genetic predisposition.
To investigate vagal modulation, we analyzed the coupling between heart rate and breathing as a putative measure of central autonomic function in 19 patients, 19 of their relatives and 19 matched control subjects. The interaction of heart rate and breathing was investigated in all groups applying the non-linear parameter cross-ApEn, indicating the asynchrony between both time series. In addition, measures of the time and frequency domain of heart rate variability (HRV) were obtained.
The main finding of our study is a significantly increased cross-ApEn value, indicating reduced central vagal modulation both in relatives and patients suffering from schizophrenia. Non-linear measures of HRV proved to more sensitively differentiate relatives from control subjects. Furthermore, we observed a correlation between psychopathology and breathing, indicating that positive symptoms are associated with a higher degree of regularity in the breathing pattern.
Our results suggest that autonomic dysfunction previously described for patients suffering from schizophrenia is also present in first-degree relatives. This might relate to changes of brainstem activity in patients and relatives, and a common genetic background in patients and their family members can be assumed.

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1. Introduction

A genetic background predisposing for autonomic dysfunction in patients suffering from schizophrenia and their relatives has recently been suggested (Bär et al., 2010; Castro et al., 2009). This autonomic imbalance might be regarded as an intermediate phenotype (Pearlson and Folley, 2008). In particular, comparable autonomic responses to stress were shown in relatives and patients (Castro et al., 2009) and a decreased heart rate variability (HRV) and complexity seemed to represent the primary abnormality (Bär et al., 2009). Interestingly, other autonomic regulatory systems such as blood pressure variability were shown to be less affected by the disease and changes in patients and relatives were not found (Bär et al., 2006). Therefore, it was assumed that the fundamental inherited cardiovascular phenotype might be the vagal rather than the sympathetic component. Especially, acute psychotic episodes seemed to be associated with decreased parasympathetic modulation (Bär et al., 2007a,b, 2005; Okada et al., 2003). Interestingly, most studies show a positive correlation to positive symptoms reported during daytime, however, the autonomic dysbalance was likewise detectable at night time (Boettger et al., 2006). Furthermore, the autonomic imbalance was also observed at the pupil and stomach of patients (Bär et al., 2008a; Peupelmann et al., 2009).

To gain deeper insights into vagal regulation in patients and their relatives, we investigated the coupling between heart rate and breathing as a putative measure of the central nervous autonomic

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; ApEn, approximate entropy; CNS, central nervous system; ECG, electrocardiogram; EDA, electrodermal activity; FPI, Freiburger Persönlichkeitsinventar; HF, high frequency; HRV, heart rate variability; LF, low frequency; MANCOVA, multivariate analysis of covariance; MANOVA, multivariate analysis of variance; PANSS, Positive and Negative Syndrome Scale; RMSSD, root mean of squared successive difference; RTN, retro-trapezoid nucleus; SCID, Structured Clinical Interview for DSM Disorders; VRC, ventral respiratory columns.

* Corresponding author. Department of Psychiatry, Friedrich-Schiller-University Jena, Philosophenweg 3, 07743 Jena, Germany. Tel.: +49 3641 935282; fax: +49 3641 936217.
E-mail address: Karl-Juergen.Baer@med.uni-jena.de (K.-J. Bär).

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function (Pincus, 2006; Yeragani et al., 1996). In a recent study, Peupelmann et al. (2009) reported reduced coupling between heart rate and breathing in patients suffering from schizophrenia as indicated by the non-linear parameter cross-ApEn (cross-approximate entropy). It was assumed that decreased vagal activity within the brainstem or suppression of the latter due to higher regulatory centers might be responsible for this abnormality. Breathing movements are produced by a spatially distributed pontine–medullary respiratory network generating rhythmic patterns of alternating inspiratory and expiratory activities that drive and coordinate the activity of spinal and cranial motoneurons (Ramirez and Richter, 1996). The breathing pattern originates within the interconnected bilateral columns of medullary neurons, the ventral respiratory columns (VRCs) and is controlled by inputs from other medullary structures including the retrotrapezoid nucleus (RTN), raphe nuclei and more rostral pontine circuits. It is known that neurons in the amygdala complex are connected reciprocally with respiratory regions in the medulla and pons (Fulwiler and Saper, 1984; Yasui et al., 2004). The autonomic nervous system is known to play a major role in the interaction of respiration and circulation. The definite mechanisms responsible for the respiratory modulation of autonomic activity remain incompletely understood (Yasuma and Hayano, 2004). Two major mechanisms have been recognized for the close association of respiration and heart rate: direct modulation of the cardiac vagal preganglionic neurons by central respiratory drive; and inhibition of cardiac vagal efferent activity by lung inflation. Thus, the close interrelation also known as respiratory sinus arrhythmia is a measure of vagal modulation.

To investigate vagal modulation we assessed 19 first-degree relatives of patients suffering from paranoid schizophrenia, the respective patients and 19 matched controls. We hypothesized that cardio-respiratory coupling is reduced in relatives and patients in comparison to controls reflecting a predisposing genetic background. Furthermore, we intended to analyze the influence of psychopathology on the breathing pattern to verify earlier reports (Peupelmann et al., 2009).

2. Methods and materials

2.1. Participants

We included 19 patients suffering from paranoid schizophrenia and their healthy first-degree relatives (6 siblings, 13 offspring) and 19 healthy controls matched to relatives regarding age, sex, weight, smoking habits and education (see Table 1). Patients were included only when they had not taken any medication for at least 8 weeks. Eight patients were investigated during the first episode and followed-up for 6 months. Serum drug levels were controlled for legal (e.g., antipsychotics, antidepressants, benzodiazepines) and illegal drugs (e.g. cannabis). A clinical ECG was recorded prior to the investigation and evaluated by a cardiologist. Diagnosis of paranoid schizophrenia was established when patients fulfilled the DSM-IV criteria (Diagnostic and statistical manual of mental disorders, 4th edition, (First, 1997)). Psychotic symptoms were quantified using the Positive and Negative Syndrome Scale (PANSS, (Kay et al., 1987)).

Control subjects were recruited from hospital staff ($n=4$), medical students ($n=5$) and the local community ($n=10$). A careful interview and clinical investigation was performed for all relatives and controls to exclude any potential psychiatric or other disease as well as interfering medication. The Structured Clinical Interview SCID II and a personality inventory (Freiburger Persönlichkeitsinventar, FPI) were additionally applied for relatives and controls to detect personality traits or disorders which might influence autonomic function (LeBlanc et al., 2004). This study complied with the Declaration of Helsinki. All participants gave written informed consent to a protocol approved by the local Ethics Committee of the University Hospital, Jena. Patients and relatives were advised that the refusal of participating in this study would not affect future treatment.

Table 1
Clinical and demographic data of participants.

Parameter	Controls	Relatives	Patients
Number of participants	$n=19$	$n=19$	$n=19$
Male/female	5/14	5/14	9/10
Age, mean (SD; min–max), years	28.32 ± 9.54 (20–55)	26.68 ± 8.03 (18–51)	39.5 ± 9.33 (18–51)
Body mass index, mean (SD)	21.98 ± 2.65	22.99 ± 2.96	23.12 ± 3.97
Education			
8–10 years at school, no.	$n=5$	$n=6$	$n=11$
12 years at school (A-level), no.	$n=14$	$n=13$	$n=8$
Attended university, no.	$n=13$	$n=7$	$n=8$
Smoker/non-smoker	7/12	6/13	11/8
<5 cigarettes/day, no.	$n=3$	$n=1$	$n=1$
5–10 cigarettes/day, no.	$n=2$	$n=3$	$n=3$
>10 cigarettes/day, no.	$n=2$	$n=2$	$n=7$
Coffee consumption			
No coffee consumption, no.	$n=4$	$n=3$	$n=6$
1 cup/day, no.	$n=5$	$n=6$	$n=5$
2 cups/day, no.	$n=7$	$n=7$	$n=4$
≥3 cups/day, no.	$n=3$	$n=3$	$n=4$
Sport			
No sport, no.	$n=4$	$n=8$	$n=8$
<2 h/week, no.	$n=7$	$n=3$	$n=4$
2–5 h/week, no.	$n=5$	$n=4$	$n=2$
>5 h/week, no.	$n=3$	$n=4$	$n=2$
Sport not reported, no.	$n=0$	$n=0$	$n=3$
First episode of psychosis, no.	n.a.	n.a.	$n=8$
Duration of illness, years (min–max)	n.a.	n.a.	6.05 (0–15)
Age of onset in male/female (SD)	n.a.	n.a.	21.90 ± 4.78/ 32.67 ± 7.90
PANNS, mean (min–max)	n.a	n.a.	69.47 (42–95)

PANSS — Positive and Negative Syndrome Scale.
n.a. — not applicable.

2.2. Data acquisition and pre-processing

Investigations were performed between 3 and 6 p.m. in a quiet room which was kept comfortably warm (22–24 °C) and began after subjects had rested in supine position for 10 min. Subjects were asked to relax and to breathe normally to avoid hyperventilation. No further instruction for breathing was given.

The electrocardiogram (high resolution at 1000 Hz) was recorded for 20 min (Fan study® system, Schwarzer, Germany). From this, the device automatically extracted the RR intervals. In addition, respiratory signal was simultaneously obtained using the Fan study® device. A thoracic belt was applied and the breathing cycle was measured with a similar sampling rate (1000 Hz) allowing a direct tracking of both signals. Furthermore, the sensitivity of the thoracic belt was adjusted according to a visual screen prior to the investigation for optimal signal detection. The system allows an on- and off-line visual control of the breathing cycle and an artifact management of the breathing signal.

2.3. Data analysis

2.3.1. Heart rate variability (HRV)

We obtained the RMSSD (root mean of squared successive difference) as a time domain parameter of heart rate variability as well as low frequency (LF, 0.04–0.15 Hz) and high frequency parameters (HF, 0.15–0.40 Hz) of the frequency domain (Task Force of the European Society of Cardiology, 1996).

2.3.2. Non-linear approximate entropy of heart rate ($ApEn_{RR}$) and respiration ($ApEn_{Resp}$)

In contrast to measures from moment statistics and the frequency domain, non-linear parameters have been shown to better depict the multiple regulatory systems influencing heart rate time series modulation. ApEn is such a non-linear parameter that was calculated

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for heart rate and breathing rate as well as the interaction between both. In the model of approximate entropy, runs of patterns in time series are compared. If these runs remain similar in successive observations, overall regularity is high and thus complexity (or irregularity) of the series is low, resulting in smaller ApEn values. We applied the technique previously described by Pincus (2001), which we have also employed in previous studies (Bär et al., 2007a; Yeragani et al., 1993; Peupelmann et al., 2009; Quick et al., 2009).

Given 'N' data points $u(1)$, $u(2)$,..., $u(N)$, two input parameters should be set prior to the computation of ApEn. These are the run length 'm' and the filter level 'r'. From previous reports, a value of 2 for 'm' and 0.2 times the standard deviation of the time series for the value of 'r' have been shown to reveal reliable results. First, we obtained vector sequences from the consecutive data points, which represent 'm' consecutive 'u' values, beginning with the 'ith' point. Consecutively, the distance between vectors, $x(i)$ and $x(j)$ is defined as the maximum difference in their respective scalar components. Then the sequence $x(1)$, $x(2)$,..., $x(N-m+1)$ is used to construct $\ln C_i^m(r) = \{\text{number of } x(j) \text{ such that } d[x(i),x(j)] \le r\}/(N-m+1)$ for each 'i' $\le N-m+1$.

The $C_i^m(r)$ values measure, within a tolerance 'r', the regularity or frequency of patterns similar to a given pattern of window length, 'm'.

Here, ApEn is defined as

$$ApEn(m,r,N) = \Phi^m(r) - \Phi^{m+1}(r).$$

In this equation, $\Phi^m(r)$ is the average value of $\ln C_i^m(r)$, ln being the natural logarithm.

The value of 'N' is fixed, typically between 100 and 5000 points but it has been shown that one can get a reliable estimate of ApEn even with a data length of <50 points, especially in studies related to endocrinology (Pincus, 2000, 2001). In this study, we used 3000 points at 5 Hz for the analyses and this translates to 600 s of maximal stationarity. From these, ApEn was calculated for the obtained RR interval time series ($ApEn_{RR}$) and for the respiration time series ($ApEn_{Resp}$).

2.3.3. Cross-approximate entropy (cross-ApEn) between RR interval and respiration time series

Cross-ApEn resembles a non-linear measure of coupling between two signal time series (Pincus et al., 1996a,b). Two distinct variables in a network (here: heart rate and respiration) are compared by quantifying their asynchrony. When the association between the systems is strong, this would thus result in small values of cross-ApEn, since asynchrony is relatively low. In contrast, when there is only a weak association between two signal time series, larger cross-ApEn values would indicate a higher degree of asynchrony (Bär et al., 2008b; Pincus, 2000).

2.4. Statistical analyses

We performed the following statistical analysis for log-transformed parameters, which beforehand were tested for normal distribution using the Kolmogorov–Smirnov test. First, a multivariate analysis of covariance (MANCOVA) was applied to indicate overall differences between groups. This MANCOVA used age as a covariate and included the between-subject factor GROUP for the parameters heart rate, lnRMSSD, lnLF, lnHF, $lnApEn_{RR}$, breathing rate, $lnApEn_{Resp}$ and lncross-ApEn to uncover differences between relatives, controls and patients. Follow-up analyses of covariance (ANCOVAs) for single parameters using age as a covariate were calculated to demonstrate differences between relatives, controls and patients.

Furthermore, two MANCOVAs were performed to exclude possible interactions of age, smoking and activity level with obtained results in one model, as well as heart rate and breathing rate in a second model. Both MANCOVAs were completed by follow-up ANCOVAs for single parameters.

To reveal differences between relatives and patients and also between relatives and control subjects for single parameters, a Bonferroni–Holm corrected pair-wise t-test was performed as a post-hoc analysis. A comparison between patients and controls was not performed to reduce the number of performed tests.

Scores of personality traits assessed in the FPI and SCID II were compared between relatives and controls by means of two-tailed t-tests. Furthermore, these values were correlated with autonomic parameters for the relatives and the control group separately.

Spearman's rank-order correlation analyses were applied to test association between ratings of psychopathological scales (PANSS) and selected ECG and respiratory parameters. Significance was accepted for $p<0.05$.

3. Results

3.1. Multivariate analysis of covariance (MANCOVA) and follow-up analysis of covariance (ANCOVA) of single parameters for all groups controlled for age

The MANCOVA comparing first-degree relatives, controls and patients in respect to heart rate, lnRMSSD, lnLF, lnHF, $lnApEn_{RR}$, breathing rate, $lnApEn_{Resp}$ and lncross-ApEn revealed a significant overall difference between groups [$F(16,92)=2.6$; $p<0.002$].

Significant differences were observed in follow-up ANCOVAs for heart rate [$F=10.04$; $p<0.001$, Fig. 1A], breathing rate [$F=2.82$; $p<0.048$, Fig. 1B] and $lnApEn_{RR}$ [$F=7.2$; $p<0.002$, Fig. 1C]. Follow-up ANCOVAs did not reveal a group difference for lnRMSSD ($p=0.39$), lnLF ($p=0.28$) and lnHF ($p=0.3$; Table 2). While no difference was found for the complexity of breathing as indicated by $lnApEn_{Resp}$ [$p<0.36$], the coupling between heart rate and breathing as expressed by lncross-ApEn showed to be significantly different between groups [$F=4.8$; $p<0.012$, Fig. 1D].

3.2. MANCOVA and follow-up ANCOVAs for all groups controlled for age, smoking, and activity level

To control for a putative influence of age, smoking and daily activity we computed an additional MANCOVA for all parameters indicating a significant difference between groups [$F(12,84)=3.2$; $p<0.001$]. Significant differences remained in the follow-up ANCOVAs for heart rate [$F=8.5$; $p<0.001$], $lnApEn_{RR}$ [$F=6.7$; $p<0.003$] and lncross-ApEn [$F=3.8$; $p<0.03$].

3.3. Multivariate analysis of covariance controlled for heart rate and breathing rate

An overall difference remained after using heart rate and breathing rate as covariates to exclude possible influences [$F(8,98)=2.1$; $p<0.04$]. Similarly, $lnApEn_{RR}$ [$F=3.7$; $p<0.03$] and lncross-ApEn [$F=2.5$; $p<0.04$] remained significantly different.

3.4. Pair-wise t-tests of parameters between relatives and controls and between relatives and patients

Mean values of parameters of all groups are depicted in Fig. 1 and Table 2. As depicted in Fig. 1, relatives show a significantly increased heart rate ($p<0.01$; A) and respiratory rate ($p<0.05$; B) compared to controls. No differences were observed between relatives and patients (A, B). $LnApEn_{RR}$ was lower in relatives than in controls ($p<0.05$; C) and lower in patients as compared to relatives ($p<0.05$; C). Furthermore, non-linear coupling between both time series (lncross-ApEn) was significantly different between relatives and controls ($p<0.01$) with increased values in relatives indicating

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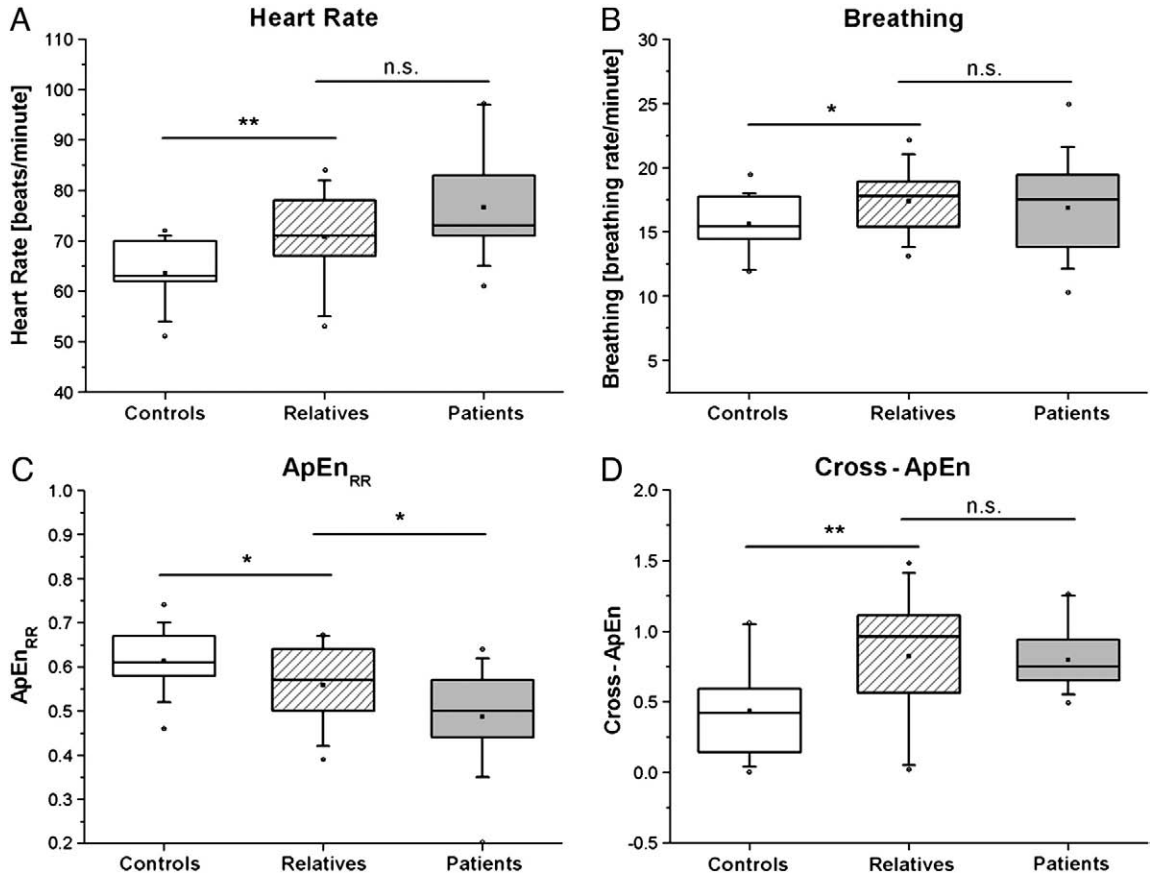

Fig. 1. Heart rate (A) and respiratory rate (B) of controls, relatives and patients. Approximate entropy of the heart rate time series ($ApEn_{RR}$) is presented in C. Non-linear coupling between both time series (cross-ApEn) is depicted in D. Medians are presented as horizontal lines; Θ = 1st and 99th percentiles; ■ = mean; $^{*}p<0.05$; $^{**}p<0.01$.

decreased vagal modulation (D). No difference was observed between relatives and patients.

No post-hoc comparisons were performed for lnRMSSD, lnLF, lnHF and $lnApEn_{Resp}$ (Table 2) since follow-up ANCOVAs did not reveal a significant difference between groups.

3.5. Influence of personality traits on autonomic function in relatives

A significant difference by means of a *t*-test between groups was found in the subscale "social orientation" ($p<0.032$) of the FPI indicating that relatives were less socially oriented than controls. Furthermore, a significant difference was observed for "achievement orientation" ($p<0.037$). The SCID II revealed no differences between relatives and controls.

Significant correlations between the subscales of the FPI and SCID II and autonomic parameters were neither observed in patients nor in controls and relatives.

3.6. Spearman's rank-order correlation analysis

There was a significant correlation between the ratings of global psychopathology of PANSS and $ApEn_{Resp}$ ($r=-0.621$; $p<0.005$; Fig. 2A), as well as general psychopathology of PANSS and $ApEn_{Resp}$ ($r=-0.641$; $p<0.003$; Fig. 2B). Furthermore, a significant relation of the G2 sub-item anxiety of PANSS was found with $ApEn_{Resp}$ ($r=-0.45$; $p<0.05$) and cross-ApEn ($r=0.48$; $p<0.03$). No further correlation was observed.

Table 2
Autonomic parameters of participants.

Parameter	Controls	Relatives	Patients
RMSSD	62.4 ± 11.5	47.0 ± 8.1	44.0 ± 6.4
$ApEn_{Resp}$	1.01 ± 0.04	0.91 ± 0.06	0.94 ± 0.05
LF	372 ± 97	303 ± 75	358 ± 66
HF	665 ± 222	352 ± 118	321 ± 96

RMSSD = root mean of squared successive difference; LF = low frequency; HF = high frequency; $ApEn_{Resp}$ = approximate entropy of respiration.

4. Discussion

Our study demonstrates decreased vagal modulation in healthy first-degree relatives of patients suffering from schizophrenia that was recently described for patients (Peupelmann et al., 2009). Thus, pointing to a possible common genetic background in patients and their family members. In contrast to previous investigations (Bär et al., 2009), we investigated unmedicated patients and kept the age range between groups fairly comparable, although patients were slightly older than their relatives. Here, we assessed the network interaction between heart and breathing which is known to be governed by vagal modulation. Low vagal modulation leads to increased asynchrony between heart rate and breathing, which is reflected in our study by increased cross-ApEn values in patients and their relatives.

Previous studies have shown low vagal function at the cardiac level (Bär et al., 2007c) in patients with schizophrenia, predominately shown by non-linear parameters. Linear parameters of the time and frequency domains were less sensitive in this respect (Bär et al., 2007c; Boettger et al., 2006). These results were corroborated in the current paper. To gain a better understanding, the analysis of more than one autonomically innervated organ seems to be promising (Bär et al., 2008a, 2009). The interaction of autonomic function assessed in the pupil and on the heart, for instance, was fundamentally different in patients and controls (Bär et al., 2008a). This is of great value since findings might be traced back to regulatory centers of the structures under investigation. Here, one might speculate, apart from findings related to the heart and

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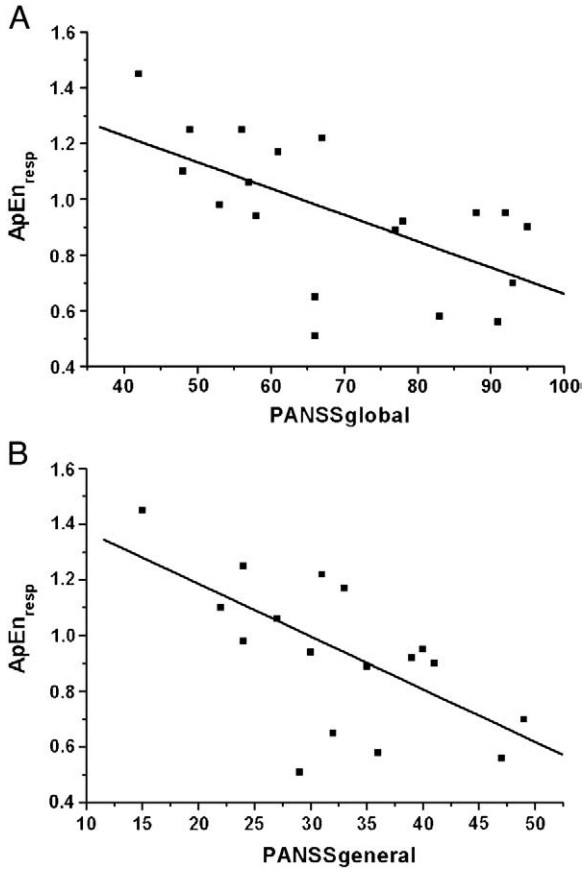

Fig. 2. The correlation between the ratings of global psychopathology of PANSS and $ApEn_{Resp}$ is shown in A, and the correlation between general psychopathology of PANSS and $ApEn_{Resp}$ is depicted in B.

respiration, that the network within the brainstem lacks regulatory control. It is likely that descending projections from the central nucleus of the amygdaloid complex are responsible (Hadziefendic and Haxhiu, 1999). On the other hand, neurotransmitters (e.g. dopamine (Lalley, 2008)) influence the primary locus for respiratory rhythm generation (pre-Bötzinger complex, (Rekling and Feldman, 1998)), thereby increasing the breathing frequency and influencing the breathing pattern (Chen et al., 2005).

It is remarkable, that the breathing rate is increased in relatives and patients, since relatives investigated in this study did not show any sign of a psychiatric disease. Thus, we conclude that the breathing pattern is not only influenced by psychotic symptoms in patients. Our findings presented here might relate to changes of brain activity in patients and relatives. Breathing is a dynamic behavior that is integrated with many other physiological functions controlled by the brainstem and higher CNS circuits including the limbic system and cortical structures. Stimulation of the amygdala, for instance, produces a rapid increase in respiratory rate followed by a feeling of fear and anxiety (Masaoka and Homma, 2004). Thus, one putative mechanism among others might be related to aberrant brain activity in the amygdala that has been demonstrated both in patients with schizophrenia and their non-affected siblings after sad mood induction (Steel et al., 2002; Habel et al., 2004). Similar to autonomic changes found in our study, non-specific fluctuations of electrodermal activity (EDA) are known to be more frequent among patients with schizophrenia and their relatives (Iacono et al., 1999). EDA is widely used as a sensitive index of emotion-related sympathetic activity (Dawson et al., 2000) and the close relationships between emotions and respiration (Boiten, 1998) might suggest similar underlying alterations of brain activity. Therefore, there is a need to simultaneously analyze EDA and HRV in patients suffering from schizophrenia to understand the specific relation of both signals due to aberrant central control.

In addition, we were able to demonstrate the strong influence of psychopathology on the complexity of the breathing pattern (Fig. 2). Increased scores in the PANSS scale are associated with higher regularity in patients. This corroborates results of an earlier study (Peupelmann et al., 2009). Previous studies have further suggested that an increased amount of positive symptoms are associated with a decrease in vagal activity (Bär et al., 2005, 2007b). It is a matter of speculation whether the increased amount of regularity observed in the breathing pattern is caused by vagal withdrawal or due to additional mechanisms.

The correlation between psychopathology and autonomic dysfunction indicates that the actual clinical state influences vagal and sympathetic function. The aberrant autonomic function in relatives additionally suggests a genetic trait of autonomic dysfunction present in patients and their relatives. Thus, future genetic studies assessing gene polymorphisms associated with altered autonomic function need to investigate the proportion of changes attributed to trait or state.

Furthermore, we have observed that the sub-item anxiety of PANSS correlated with reduced coupling between breathing and heart rate as assessed by cross-ApEn. It is interesting that the sub-item anxiety was negatively associated with the complexity of the breathing pattern. Therefore, the more anxious psychotic patients were in our study the more regular is their breathing pattern. This is in contrast to several previous studies on patients with panic disorder, which indicated that patients with anxiety exhibit irregular breathing patterns as measured by tidal volume and respiratory rate (Yeragani et al., 2004). Thus, two diseases with low vagal tone intriguingly display opposite breathing modalities, a fact that is not well understood to date. Therefore, functional fMRI studies are needed to elucidate the central origin of our finding.

Our results are limited by the relatively small sample size. Furthermore, we have investigated healthy relatives without any certainty whether relatives might develop a psychiatric disease in the future. A personality disorder or a prevailing trait according to performed tests was excluded, although the indicated decreased scores of social orientation in relatives might be associated with the higher frequency of schizotypical traits in this population. Our results are further limited by the age difference between patients and their relatives, since vagal function is age-dependent (Boettger et al., in press) and since the control group was matched for the age of relatives. However, results shown for patients corroborate findings of previous studies (Bär et al., 2005, 2007b,c; Peupelmann et al., 2009).

In conclusion, cardio-respiratory coupling in respective first-degree relatives is impaired in a similar fashion as seen in patients suffering from schizophrenia. Thus, a genetic background can be suggested. Since the breathing pattern is highly variable in patients and depends on psychopathology, future studies need to elucidate how alterations of breathing might affect cardiovascular regulation.

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