
Diminished Cardiac Vagal Tone in Schizophrenia: Associations to Brain Laterality and Age of Onset

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We measured high-frequency (rapid) heart rate variability (HRV) from 24-hour Holter electrocardiograms to index cardiovagal tone in 23 patients with DSM-III-R schizophrenia or schizoaffective disorder. High-frequency HRV, quantitated by measuring the percent of successive normal interbeat intervals greater than 50 msec (PNN50), demonstrated a bimodal distribution: 11 of 23 patients had a PNN50 of ≥ 8.0 (mean value = 17.7 ± 11.0), and 12 had a PNN50 of ≤ 4.0 (mean value = 1.8 ± 1.0); no subject had a PNN50 value between 4.0 and 8.0. All 12 low cardiovagal tone patients (versus only 6/11 of the other patients) had a schizophrenia (not schizoaffective) diagnosis ($p = .013$). PNN50 was not associated with present age, gender, smoking, IQ scores, or symptomatology, but patients with lower cardiovagal tone did have a significantly later age of onset (20.5 ± 5.3 vs. 14.8 ± 2.8 years: $p = .005$). PNN50 subgroups also differed on dichotic listening measures of brain laterality. The low group failed to show left ear (right hemisphere) advantage for complex tones seen in the other patients and normal adults. They also showed larger right ear (left hemisphere) advantage for dichotic words than the other patients. This evidence of relative right hemisphere disadvantage in patients with low cardiovagal tone is consistent with findings linking autonomic nervous system and right hemisphere function. These findings also support the existence of subgroups of schizophrenia patients differing in autonomic activity, brain laterality, and clinical features. © 1997 Society of Biological Psychiatry

Key Words: Schizophrenia, cardiac, HRV, laterality, ANS, age of onset

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Introduction

A significant proportion of patients with schizophrenia have abnormalities in autonomic nervous system (ANS) function. These measures reflect the balance and interplay

of the sympathetic and parasympathetic nervous systems. Abnormalities in electrodermal activity, heart rate, pupil reactivity, vascular activity, and orienting responses to novel stimuli have been identified in up to 50% of schizophrenia patient samples. Research efforts in the field have focused on the power of these ANS measurements to identify subgroups among schizophrenic patients (Zahn et al 1991; Zahn 1988; Straube 1979; Gruzeliier 1976; Bernstein et al 1981, 1982).

Recently described techniques that assess heart rate variability (HRV) appear to be good candidates to assess

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autonomic function in schizophrenia. Cardiologists became interested in these measures when a strong relationship between HRV and increased mortality after myocardial infarction was demonstrated (Kleiger et al 1987). A statistic can be derived that gives a relatively pure measure of tonic parasympathetic cardiac activity from 24-hour Holter electrocardiogram data (Katona and Jih 1975; Ewing et al 1981). The difference between successive normal to normal (NN) sinus heart beats can be quantitated, and the percent of differences between successive NN sinus beats that deviate by more than 50 msec from the previous interbeat interval, the PNN50, provides an estimate of the cardiovagal (parasympathetic) contribution to HRV. This measure is relatively independent of patient motivation and cooperation, overcoming some of the obstacles to psychophysiological study presented by many other paradigms. It has been shown to be both stable and reliable in both normal subjects and in patients with previous myocardial infarction and ventricular arrhythmias (Bigger et al 1991; Kleiger et al 1991). To test the reliability of the PNN50 measure in schizophrenia patients we have examined PNN50 values in a test-retest study of 7 schizophrenia patients (unpublished data), finding the measures to be highly stable (8.3 ± 10.4 versus 8.37 ± 9.7 ; correlation = .98, $p < .001$).

ANS indices have also been used to examine the lateralization of brain dysfunction in schizophrenia (Bernstein et al 1981; Gruzulier 1994). Although abnormal response asymmetries have been found in schizophrenia for ANS measures and other indicators of cerebral laterality, there is yet no consensus on the direction and clinical significance of these findings. Flor Henry (1969, 1976) first postulated left hemispheric dysfunction in schizophrenia, but other findings were consistent with left hemisphere overactivation (Nachshon 1980). Indeed, left hemispheric overactivation and dysfunction have both been included in some postulations about schizophrenia (Gur 1978; Walker and McGuire 1982). It has also been suggested that different subtypes of schizophrenia have different hemispheric imbalance. For instance, paranoid patients were found to have left-sided overactivation with the reverse true in nonparanoid patients (Gruzulier 1981). Gruzulier (1984) also proposed that patient heterogeneity could be explained by differences in hemispheric imbalance. Active patients, who were delusional and excited, exhibited left hemisphere dominance, whereas withdrawn patients had predominantly negative symptoms and had right hemispheric dominance. Electrodermal responsivity has been frequently used as a probe of the sympathetic and parasympathetic nervous systems. Gruzulier (1981) reported more left hemispheric activation for subjects who had stable responses (rapid habituators with few nonspecific responses) and more right activation in those who

were electrodermally labile, with high frequencies of nonspecific responses. Tranel and Damasio (1994) experimentally tested the general consensus that right-sided lesions reduce or abolish electrodermal responses. In patients with central nervous system (CNS) lesions, they found that the right inferior parietal lobe was consistently associated with defective electrodermal responding, as well as bilateral ventromedial frontal and anterior cingulate regions.

Brain asymmetries have also been associated with patterns of heart rate changes. Yokoyama et al (1987) reported an absence of vagally mediated heart rate changes in patients having right hemispheric strokes, with exaggerated responses with left hemispheric strokes. Consistent with this report, Zamrini et al (1990) showed differential heart rate responses in human subjects undergoing the Wada test, with heart rate decreasing with right-sided carotid injection of amobarbital, and the converse with left-sided injection of amobarbital, consistent with left-sided disinhibition of right-sided autonomic function.

The present study was designed to determine whether subgroups of schizophrenia patients that were formed on the basis of an autonomic nervous system measure, i.e., the PNN50 measure of HRV, would differ in their cerebral laterality and clinical picture. Laterality was measured using both a verbal and a nonverbal dichotic listening task. Schizophrenia patients have generally been found to show the expected left ear (right hemisphere) advantage for nonverbal dichotic tasks (Colburn and Lishman 1979; Yozowitz et al 1979; Overby et al 1989; Raine et al 1989). Although the findings for verbal dichotic tests have been less consistent, studies using dichotic fused words or syllable tasks have agreed in finding reduced right ear (left hemisphere) advantage in schizophrenia (Colburn and Lishman 1979; Wexler et al 1991; Bruder et al 1995). The distribution of asymmetry scores for schizophrenia patients on these dichotic tasks did, however, reveal very wide individual differences (Wexler et al 1991), which might be related to the clinical and biological heterogeneity of the patient samples.

We have adopted the direction suggested by several authors (including Gruzulier 1994 and Andreasen et al 1989) to use physiological, rather than symptom, measures to examine the heterogeneity of schizophrenia. In this pilot study, we have examined the associations of tonic cardiovagal (parasympathetic) tone with dichotic listening measures of hemispheric laterality advantage and with clinical measures.

Methods

Subjects for this study were 23 consecutive patients with a diagnosis of DSM-III-R schizophrenia or schizoaffective

depression recruited from the New York State Psychiatric Institute Schizophrenia Research Unit. All participants gave informed consent for the study, which was approved by the Institutional Review Board. The sample was comprised of 8 women and 15 men with ages from 21 to 55 (mean age = 32.5; SD = 7.8). All patients were physically healthy as indicated by recent physical examinations, laboratory evaluation of Sequential Multiple Analyzer plus Computer (SMAC), complete blood count (CBC), erythrocyte sedimentation rate (ESR), and thyroid function tests and normal 12 lead clinical electrocardiograms (ECGs). No patient had cardiovascular, respiratory, or endocrine illness, current substance abuse other than nicotine, or a history of substance abuse that obscured diagnosis. Diagnosis was based on structured clinical interviews with the Diagnostic Interview for Genetic Studies (Nurnberger et al 1994). Clinical data included age of onset of positive symptoms, DSM-III-R diagnosis, education, and brief psychiatric rating scale (BPRS) symptom ratings, which were obtained for 18 of the patients the week of the 24-hour Holter monitor. A subsample of 11 of the 23 patients also received Wechsler Adult Intelligence Scale IQ testing.

Patients were studied on neuroleptic medication of haloperidol 0.3 mg/kg and benztropine 1.0 mg b.i.d. (or equivalent for 3 patients). High-frequency heart rate measurements (rapid changes in heart rate from beat to beat) were made from 24-hour Holter ECG recordings at 128 samples per second and stored on standard Marquette recorders. These 24-hour monitoring sessions were well tolerated by all patients. The duration of time between successive R to R waves in all normal heartbeats was computed from the Holter ECG tapes as the absolute value of each individual difference between the adjacent normal RR intervals. The percent of differences between adjacent normal heartbeats exceeding 50 msec (PNN50) was calculated on the normal RR intervals over the entire 24 hours.

Dichotic listening tasks were performed by 15 of the patients while they were receiving antipsychotic medication. We have not found a difference in dichotic listening laterality for patients tested when on and off of antipsychotic medications (Bruder et al 1995). Patients were excluded if they had a hearing loss greater than 30 dB in either ear or an ear difference greater than 10 dB at 500, 1000, and 2000 Hz. The Fused-Rhymed Words Test was used to provide an index of hemispheric dominance for language (Wexler and Hawles 1983). It yields a mean right ear (left hemisphere) advantage in normal adults. Single syllable word pairs differing only in the initial consonant were presented simultaneously to the right and left ear (e.g., coat, goat), via a matched pair of TDH-49 headphones at a comfortable level of 75 dB SPL. The words

fuse into a single percept and the subjects use a multiple-choice answer sheet to indicate the word they heard. Four 30-item blocks yield a total of 120 trials. The Complex Tone Test was used to measure cerebral dominance for pitch discrimination; it yields a mean left ear (right hemisphere) advantage in normal adults (Sidtis 1981). Different complex tones were presented to the two ears, followed by a binaurally presented probe tone that was the same as one member of the dichotic pair or different than both. Subjects pointed to a response card labeled yes or no to indicate whether or not the probe tone matched either member of the dichotic pair. The tones consist of square waves with different fundamental responses. Subjects were tested for four blocks of 28 trials. Dichotic listening laterality scores were computed from the number of right or left ear words/sounds correctly reported, as $100(R - L)/(R + L)$. Positive scores are indicative of a right ear (left hemisphere) advantage, whereas negative scores are indicative of a left ear (right hemisphere) advantage. All clinical data and dichotic listening data were obtained and analyzed by separate examiners, blind to the HRV results.

Results

The percent of successive normal interbeat intervals greater than 50 msec (PNN50) had a mean of 9.27 (SD = 10.6) with a minimum of 0.3 and a maximum of 42. Post hoc inspection of the distribution of the PNN50s revealed a bimodal distribution: 11 of the 23 patients had a PNN50 greater than 8.0 (mean value = 17.7 ± 11.0), and 12 of the 23 patients had PNN50 less than 4.0 (mean value = 1.8 ± 1.0); no subject had a PNN50 value between 4.0 and 8.0. These values were used to divide the patients into lower and higher HRV subgroups. The PNN50 values for the 3 patients not on haloperidol were 16.6 for a patient on fluphenazine, 2.1 (pimozide), and 1.7 (chlorpromazine). Of note, even the group of schizophrenic patients with higher heart rate variability had low PNN50 values compared to normals; a published control group of 14 subjects (age 25–55 years) had a mean PNN50 of 30 ± 14 (Kleiger et al 1991).

The PNN50 grouping was significantly associated with DSM-III-R diagnosis; all 12 of the lower PNN50 patients had received diagnoses of DSM-III-R schizophrenia, but only 6 of the other 11 patients had DSM-III-R schizophrenia, with the other 5 being diagnosed with DSM-III-R schizoaffective depressed (Fisher's Exact $p = .013$). Later age of illness onset was also significantly correlated with the low cardiovascular tone ($r = -.57$, $df = 21$, $p = .005$). The patients with lower PNN50 had a mean age of onset of 20.5 ± 5.3 years, compared to 14.8 ± 2.8 years in the subjects with higher PNN50 ($t = 3.18$, $df = 21$, $p = .005$).

Table 1. Differences in Patients Grouped by High-Frequency Heart Rate Variability

	PNN50 > 8 (n = 11)	PNN50 < 4 (n = 12)	
PNN50 ^a	17.7 ± 11.0	1.8 ± 1.0	
Present age (years)	30.5 ± 6.7	35.2 ± 9.6	
Gender	33% female	36% female	
Age of onset	14.8 ± 2.8	20.5 ± 5.3	<i>p</i> = .005
Education	12.5 ± 0.5	12.7 ± 1.3	
Right-handed	82%	92%	
Cigarette smokers	45%	58%	
BPRS sum	39.9 ± 12.2	36.2 ± 9.7	
Dichotic tone task ^a	-6.1 ± 16.6 (n = 8)	14.7 ± 20.8 (n = 7)	<i>p</i> = .05
Dichotic word task ^b	2.5 ± 7.3 (n = 7)	13.2 ± 8.2 (n = 6)	<i>p</i> = .03
DSM-III-R Diagnosis			
Schizophrenia	54.5%	100%	
Schizoaffective	45.5%	0	<i>p</i> = .013

^a Mean in 20 normal adults = -7.2 (Tenke et al 1993).

^b Mean in 85 normal adults = 16.0 (Wexler and Goodman 1991).

Post hoc inspection showed that the two HRV groups had similar rates of left-handedness and male gender.

The mean BPRS score was 33.1 ± 10.3, with no BPRS item or subscale (positive, negative, or depression) showing a significant Spearman correlation to the PNN50 when a Bonferroni corrected *p* value of < .002 was used as the criteria for significance. Only baseline "excitement" was associated with the PNN50 at the conventional significance of *p* < .05 (*r* = .49, *df* = 17, *p* = .048). Correlations to other BPRS symptoms ranged from *r* = -.37, *df* = 16, *p* = .14 (for blunted affect), to *r* = .30, *df* = 16, *p* = .24 (for unusual thought content). The PNN50 was also not associated with present age, gender, or educational level, or IQ (Table 1). The mean PNN50 value of the 12 smokers (12.1 ± 13.4) and 11 nonsmokers (6.0 ± 5.0) was not significantly different (*t* value = 1.44, *df* = 21, *p* = .16), nor were the odds of smoking significantly associated with PNN50 grouping (odds ratio of smoking in the lower versus higher PNN50 group = 1.68, 95% confidence interval: 0.3, 8.8; *p* = .54). Intelligence test scores did not appear to differentiate the groups, although conclusions regarding IQ results are precluded by the small sample size. Eight of the 11 tested patients were in the higher PNN50 grouping and 3 patients were in the lower group. Mean scores were full scale 84.1 ± 24.0, verbal 88.5 ± 25.6, and performance 76.8 ± 17.9 in the former group; and full scale 85.6 ± 22.8, verbal 91 ± 27.8, and performance score 79 ± 10.8 in the latter group (all *p*'s > .8 on *t* tests).

As can be seen in Figure 1, patients with low PNN50 had larger right ear (left hemisphere) advantage for dichotic words when compared to the patients with higher

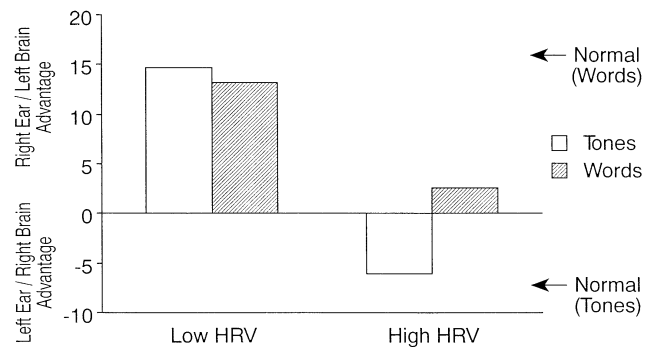


Figure 1. Dichotic tone and word laterality scores in schizophrenia patients with low and high PNN50, and in published normal controls. The arrows indicate the laterality quotients of the normal controls.

HRV (*t* = 2.50, *df* = 11, *p* = .03). Moreover, the groups showed a significant laterality difference in the same direction on the complex tone task (*t* = 2.17, *df* = 13, *p* = .05). Low PNN50 patients showed a right ear (left hemisphere) advantage for dichotic complex tones, whereas the high HRV group had the expected left ear (right hemisphere) advantage. A mean laterality quotient for the dichotic tone task of -7.2 was recently reported for 20 normal adults (Tenke et al 1993). Thus, our patients with low HRV failed to show the normal right hemisphere dominance for complex tones, whereas our other patients had evidence for a reduced left hemisphere dominance for words; a mean laterality score of 16.0 was recently reported for 85 normal adults (Wexler and Goodman 1991). Thus, brain lateralization measured by both tone and word dichotic tasks was disassociated by the PNN50 subgrouping. As seen in Figure 1, the lower PNN50 patients did not evidence a right brain advantage for either task; and patients with higher PNN50 showed the expected direction of hemispheric lateralizations, but did not show the degree of left brain advantage reported in normals for the words task.

Discussion

A subgroup of schizophrenic patients with low PNN50 heart rate variability failed to show a right hemisphere advantage for dichotic pitch discrimination seen for other patients and for normal adults in prior studies (Sidtis 1981; Tenke et al 1993). In contrast, patients with higher heart rate variability had a normal right hemisphere advantage for tones but failed to show a left hemisphere advantage for dichotic fused words. Evidence for left hemisphere disadvantage in schizophrenia has previously been reported using this same fused-words test (Wexler and Goodman 1991). Also, reduced left hemisphere advantage for dichotic words or syllables was found to be particularly

evident in schizophrenic patients with positive symptoms, such as hallucinations (Bruder et al 1995; Green et al 1994).

Vagal activity is higher during recumbency, but the patients in this report were all on a ward schedule that required similar daily activities. Thus activity and recumbency would be unlikely to account for the differences among patients. Parasympathetic activity also declines with age, at about 10% per decade (Piha 1991), but PNN50 was unassociated with patient age in these schizophrenia subjects. The absence of normative age-matched PNN50 data from our own laboratory is a limitation of this study.

Several clinical variables, in addition to brain lateralization, were dissociated by the PNN50 groupings. Patients with low cardiovagal tone had a significantly later age of onset, and they uniformly received a schizophrenia diagnosis, whereas the patients with higher values were more diagnostically heterogeneous, with half of them having schizoaffective depression. These findings lend support for the hypothesized existence of subtypes of schizophrenia with different pathophysiology, which is reflected in distinctive patterns of brain lateralization and autonomic activity (Gruzelier 1984). This heterogeneity could account for conflicting reports concerning the direction of the abnormal laterality in schizophrenia. It is also interesting that a lack of a right hemisphere advantage for dichotic tones, which characterized these schizophrenic patients with low heart rate variability, has been found in patients having melancholic depression (Bruder et al 1989). In this regard, melancholic depression has also been associated with low heart rate variability (Rechlin 1994). This suggests that the pattern of low heart rate variability and relative right hemisphere disadvantage may extend across traditional diagnostic lines. Nonetheless, although melancholic depression patients also demonstrate a right hemisphere underactivation, there is no reason to expect that the same lesion underlies the right hemisphere disadvantage in these schizophrenia patients and in melancholic depression. Thus, the absence of affective syndromes in the schizophrenia patients with right hemisphere underactivation and low HRV does not conflict with findings in depression.

The lack of a right hemisphere advantage in schizo-

phrenic patients with low heart rate variability could stem from right hemisphere dysfunction or left hemisphere overactivation. The data for the dichotic words task lend no support for left hemisphere overactivation because the right ear (left hemisphere) advantage for words in patients with low heart rate variability was *not* larger than that seen for normal adults (Wexler and Goodman 1991). Neither the literature nor the present study can resolve if the hypothesized right hemisphere dysfunction in the patients with low cardiovagal tone stems from either hypoactivation of the right hemisphere or hyperfunction of the left hemisphere. A hypothesis of right hemisphere disadvantage in patients with low heart rate variability would be consistent with the consensus favoring right hemisphere dominance for afferent and efferent visceral innervation, and for control of autonomic function (Mesulam 1981; Lane and Jennings 1995). Right hemisphere disadvantage and diminished parasympathetic tone could also be associated with a general reduction in CNS arousal and with diminished orienting responses. Schizophrenic patients have, for instance, been reported to have diminished cardiac decelerations to novel stimuli (Zahn et al 1991). The absence, or reduction, of cardiac decelerations when orienting to external or internal stimuli might account for the decreased variability in beat to beat intervals observed over a 24-hour period. Future studies of heart rate variability in schizophrenia would do well to include other psychophysiologic measures to examine its relation to ongoing CNS activity, by measuring the electroencephalogram and orienting responses to stimuli, such as by recording electrodermal measures to tones.

Converging evidence from these electrophysiologic measures, as well as behavioral laterality measures, could be of particular value in further characterizing subtypes of schizophrenia that differ in cardiovagal tone.

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