Prolonged Reaction to Mental Arithmetic Stress in First-Degree Relatives of Schizophrenia Patients

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Abstract

Objective: Several studies have reported abnormal heart rate variability (HRV) in schizophrenia patients, suggesting a pathophysiological link between central autonomic dysfunction and symptoms of schizophrenia and that these could be heritable. This study aimed at evaluating cardiac autonomic response to mental arithmetic stress in first-degree relatives of schizophrenia patients (FDRS) employing HRV analysis. **Methods**: HRV measures were computed for 25 healthy FDRS and 25 age- and gender-matched controls during rest, mental arithmetic stress task and recovery period. Subtracting serial sevens from 700 for five minutes formed the stress task. Recovery period lasted five minutes starting from the termination of the stress task. **Results:** Both groups showed similar alterations during the stress task. After stress termination, recovery to the basal values was observed in controls but not in patients' relatives, maintaining a pattern similar to that during the stress task. **Conclusions:** Poor recovery from cardiac autonomic functions (CAF) alterations induced by arithmetic stress may be a heritable trait marker of schizophrenia. Our report supports endophenotypic potential of HRV in schizophrenia research.

Key Words: Heart Rate Variability, Schizophrenia, First-Degree Relatives, Arithmetic Stress Test, Endophenotype

Introduction

Impaired central autonomic regulation has been described in schizophrenia. In particular, cardiac (1-3), gastro intestinal (4), pupillary (5), and cardio-respiratory coupling (6) autonomic parameters have been demonstrated in detail. Similar abnormalities were reported in unaffected first-degree relatives of schizophrenia patients (FDRS) as well (7-10).

Heart rate variability (HRV) is a non-invasive method by which cardiac autonomic function can be assessed (11). Studies have shown that HRV pattern is heritable and that it is more evident during stress tasks (12). HRV abnormality demonstrated in schizophrenia patients has a potential to be an endophenotypic marker if demonstrated in healthy, unaffected first-degree relatives of schizophrenia patients. An earlier study from Argentina reported longer autonomic response in first-degree relatives of schizophrenia patients (FDRS) than controls during stress task (9). In the current study, we used a similar methodology to evaluate cardiac autonomic functions (CAF) during mental arithmetic stress task among in Asian FDRS who were free of any psychiatric illness and medications.

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Clinical Implications

The most important finding of this study is that first-degree relatives of schizophrenia (FDRS) patients showed poorer recovery from cardiac autonomic functions (CAF) changes induced by arithmetic stress. This is consistent with earlier studies—which used heart rate variability (9) and galvanic skin response—in which FDRS patients displayed impaired habituation of autonomic nervous system activity (21-23). Schizophrenia patients also show similar pattern of CAF changes (24). Cases showed significantly poorer recovery in low frequency power indicating sympathetic system abnormality. This is similar to the findings of the Castro et al. (2009) study. In the Castro study, the abnormality among cases was predominantly vagal. Consistent with this, high frequency power of cases in our study also showed poorer recovery suggesting vagal abnormality, but this was at a trend level significance (p=0.076; see Table 2). The reason for not obtaining a statistically significant result could be due to greater variability of data, leading to possible type-II error. In addition, participants in the Castro et al. (2009) study (mean age about 45 years) were substantially older than our study participants (mean age about 28 years). It is possible that normally expected decline in high frequency power with age (25) could be exaggerated among the cases. In summary, this study showed that relatives of schizophrenia patients show prolonged autonomic response to stress. The heuristic and clinical implications of this finding need further investigation.

Methods and Materials

Participants

Siblings or offspring of schizophrenia inpatients (n=25) from the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India, formed the "cases." We did not include parents of schizophrenia patients, as their "at-risk" status for schizophrenia is doubtful vis-à-vis siblings and offspring, in whom the genetic risk is more likely to be higher. Age- and gender-matched individuals (n=25) were recruited from hospital staffs and investigators' friends as "controls." Subjects with schizophrenia and major medical illnesses (diabetes, hypertension, thyroid disorders, and cardiac disorders, all diseases potentially related to autonomic neuropathy and psychiatric disorders) were excluded by means of history and detailed physical and systemic examination. Alcohol and tobacco use were assessed using the Alcohol Use Disorders Identification Test (AUDIT) (13) and the Fagerström Nicotine Dependence Scale (14), respectively. Physical activity questionnaire was administered to assess the amount of physical activity per day (15). The Family Interview for Genetic Studies (FIGS) (16) was used in both cases and controls. Controls did not have any family history of psychiatric disorders. Cardiac autonomic functions were assessed in an Autonomic function tests laboratory under standard conditions. The study protocol was approved by an institutional ethics committee. Written informed consent was obtained from all participants.

Data Acquisition

Autonomic function tests were carried out in the Autonomic lab, Department of Neurophysiology, NIMHANS, under standardized conditions. Error-free, lead II electrocardiogram (ECG) was recorded in all subjects at rest in supine position and signals were conveyed through analog digital converter (Power Lab, 16 channels data acquisition system, AD Instruments, Australia) with a sampling rate of 1024 Hz. The raw ECG was converted into consecutive RR intervals for analysis. The data were analyzed offline using an automatic program that allows visual checking of the raw ECG and breathing signals. It was ensured that subjects breathed with a respiratory rate of 12–15 breaths/min (17, 18).

Fifteen minutes of basal recording was done. After that, subjects were subjected to a mental arithmetic stress by asking them to subtract serial sevens from 700 for five minutes. This has been proposed as a standard mental arithmetic stress test (19). ECG was continuously recorded. HRV data were collected for an additional five minutes starting from the completion of the stress task to test the recovery.

HRV Analysis

In accordance with the Task Force of European Society of Cardiology guidelines (20), we computed measures of HRV in time and frequency domains. Analysis was performed using HRV Analysis Software (AD Instruments, chart 5). The following parameters were computed:

1. Time domain parameters:
   a. heart rate (HR) calculated in beats per minute (beats/min)
   b. mean RR interval in milliseconds (ms)
   c. standard deviation of RR intervals (SDNN) in ms
   d. square root of the mean squared differences of successive intervals (RMSSD) in ms.
2. Spectral analysis for frequency domain parameters was done using parametric spectrum (Auto regressive Modeling). The following parameters were measured:
   a. total power (TOT) in milliseconds squared (ms^2)
   b. low frequency power (LF) in ms^2
   c. high frequency power (HF) in ms^2
   d. low frequency absolute power in normalized units (LF_nu)

Table 1 Sociodemographic Details

Parameter		Cases (n=25)	Controls (n=25)	P-Values
Mean age in years (SD)		28.8 (10.7)	28.8 (10)	1.00
Males: females		20 (16 sibling, 4 offspring): 5 (4 sibling, 1 offspring)	20:5	
Mean years of education		12 (3.9)	16.2 (3.5)	<0.001
Mean BMI (kg/m^2)		23.5 (3.9)	23.2 (3.5)	0.8
Mean basal SBP (mm Hg)		121.2 (12.2)	118.3 (8.3)	0.3
Mean basal DBP (mm Hg)		78.7 (7.6)	79.5 (7.3)	0.7
Physical activity (hours per day)	Sleeping	7.8 (1.3)	7.5 (1.1)	0.4
	Sitting	8.3 (2.8)	9.3 (2.4)	0.2
	Standing	4.6 (1.8)	4.2 (1.5)	0.4
	Walking	2.6 (1.2)	2.1 (1.1)	0.3
	Exercise	0.8 (0.9)	0.6 (0.8)	0.3

e. high frequency absolute power in normalized units (HF_nu)
f. ratio of low frequency to high frequency powers (LF/HF) ratio.

Statistical Analysis

Groups were compared using t-test for continuous variables and chi-squared test for discrete variables. HRV components obtained were not normally distributed and, hence, had to be square root transformed to produce normal distributions. Within-subject comparisons of HRV data were obtained by applying repeated measures ANOVA separately for cases and controls. Where within-subject differences were significant, post hoc comparisons were conducted by comparing baseline with stress, stress with recovery and recovery with baseline using Bonferroni correction. Alpha was set at $p<0.05$.

Results

Sociodemographic Details

Both groups were comparable on age, gender, and body mass index (BMI) and physical activity (see Table 1). Though FDRS had fewer years of education, on correlation analysis, none of the HRV parameters showed correlation with educational status (data not shown). None of the subjects had hazardous alcohol use or nicotine use. Further, none were using any psychotropic or other medications in the past one month.

HRV Analysis

Baseline HRV measures were similar across both groups. Table 2 shows that during stress, both groups showed similar alterations. However, FDRS recovered more slowly than controls. This was statistically significant in SDNN, LF power and LF/HF ratio (see Table 2). Typical tachograms of RR intervals of 1case and 1control are shown in Figure 1.

Discussion

The most important finding of this study is that first-degree relatives of schizophrenia (FDRS) patients showed poorer recovery from CAF changes induced by arithmetic stress. This is consistent with earlier studies—which used HRV (9) and galvanic skin response—in which FDRS patients displayed impaired habituation of autonomic nervous system activity (21-23). Schizophrenia patients also show similar pattern of CAF changes (24). Cases showed significantly poorer recovery in LF power indicating sympathetic system abnormality. This is similar to the findings of the Castro et al. (2009) study. In the Castro study, the abnormality among cases was predominantly vagal. Consistent with this, HF power of cases in our study also showed poorer recovery suggesting vagal abnormality, but this was at a trend level significance ($p=0.076$; see Table 2). The reason for not obtaining a statistically significant result could be due to greater variability of data, leading to possible type-II error. In addition, participants in the Castro et al. (2009) study (mean age about 45 years) were substantially older than our study participants (mean age about 28 years). It is possible that normally expected decline in HF power with age (25) could be exaggerated among the cases.

It has been hypothesized that this protracted response to stress in schizophrenia patients reflects dysregulation of autonomic nervous system by areas of brain—which have been found to be abnormal in schizophrenia patients—like prefrontal cortex, medial temporal structures and amygdala-hippocampal complex (26-28). Our findings add

Table 2 Heart Rate Variability (HRV) Measures During Baseline, Stress and Recovery

HRV Measures		Basal	Mental Arithmetic Stress	Recovery	P-Values		
		Mean (SEM)*	Mean (SEM)	Mean (SEM)	Basal vs. Stress	Stress vs. Recovery	Basal vs. Recovery
Mean NN (ms)	Cases	853.8 (21.1)	792.4 (23.6)	870.6 (22.6)	<.001	<.001	0.076
	Controls	914.2 (31.1)	847.6 (27.2)	924.5 (30.9)	<.001	<.001	0.475
HR (BPM)	Cases	71.4 (1.8)	77.4 (2.5)	70.1 (1.9)	<.001	<.001	0.120
	Controls	67.4 (2.2)	72.4 (2.2)	66.6 (2.2)	<.001	<.001	0.463
SDNN (ms)	Cases	46.2 (3.7)	59.1 (4.1)	55.0 (4.3)	**0.006**	**0.966**	**0.001**
	Controls	53.8 (4.7)	66.3 (6.3)	56.2 (4.4)	**0.004**	**0.018**	**0.587**
RMSSD (ms)	Cases	45.5 (4.7)	47.56 (5.3)	48.9 (4.7)	1.00	1.00	0.199
	Controls	54.6 (7.7)	58.69 (9.6)	54.2 (7.0)	1.00	1.00	1.00
Total power (ms^2)	Cases	2381.2 (421)	3679.1 (516.1)	3432.7 (646.4)	0.018	1.00	0.016
	Controls	3401.4 (635.8)	4844.2 (1056.4)	3276.3 (550.8)	0.035	1.00	0.037
LF (ms^2)	Cases	628.7 (151.5)	1273.6 (201.2)	967.3 (192.5)	**<.001**	**0.258**	**0.012**
	Controls	878.5 (200.3)	1352.3 (247.2)	723.5 (110.3)	**0.029**	**0.003**	**1.00**
LF.Nu	Cases	37.3 (2.6)	51.0 (2.2)	43.3 (3.0)	<.001	0.013	0.041
	Controls	40.5 (3.1)	45.8 (3.1)	41.5 (3.4)	0.196	0.216	1.00
HF (ms^2)	Cases	889.4 (184.7)	1188.6 (230)	1137.9 (265.2)	0.336	1.00	0.076
	Controls	1421.6 (375.9)	2071.5 (713.4)	1339.8 (347.1)	0.176	0.107	1.00
HF.Nu	Cases	51.9 (2.9)	41.0 (1.9)	48.0 (3.0)	0.002	0.092	0.164
	Controls	53.0 (2.9)	46.1 (2.7)	52.9 (3.2)	0.059	0.022	1.00
LF/HF	Cases	0.84 (0.1)	1.4 (0.1)	1.08 (0.2)	**<.001**	**0.046**	**0.045**
	Controls	0.89 (0.1)	1.2 (0.2)	1.00 (0.2)	**0.101**	**0.201**	**1.00**

*SEM: standard error of mean; Mean NN=mean of normal RR intervals; HR=heart rate; SDNN=standard deviation of RR intervals; RMSSD=square root of the mean squared differences of successive intervals; LF=low frequency power; LF.Nu=low frequency absolute power in normalized units; HF=high frequency power; HF.Nu=high frequency absolute power in normalized units.

to the existing literature, suggesting similar abnormalities are present even in unaffected FDRS patients. It is well known that relatives of schizophrenia have higher risk of developing the disorder. Some researchers believe that CAF abnormalities found with schizophrenia may be responsible for the generation of certain symptoms of the disorder, indicating their higher vulnerability to stress (29). Williams et al. suggested that dysfunction of autonomic neural circuit—particularly in amygdala and medial prefrontal cortex for processing threat-related signals—might produce hypervigilance state. Further, paranoid cognition may be due to dysregulation of processing of fear signals.

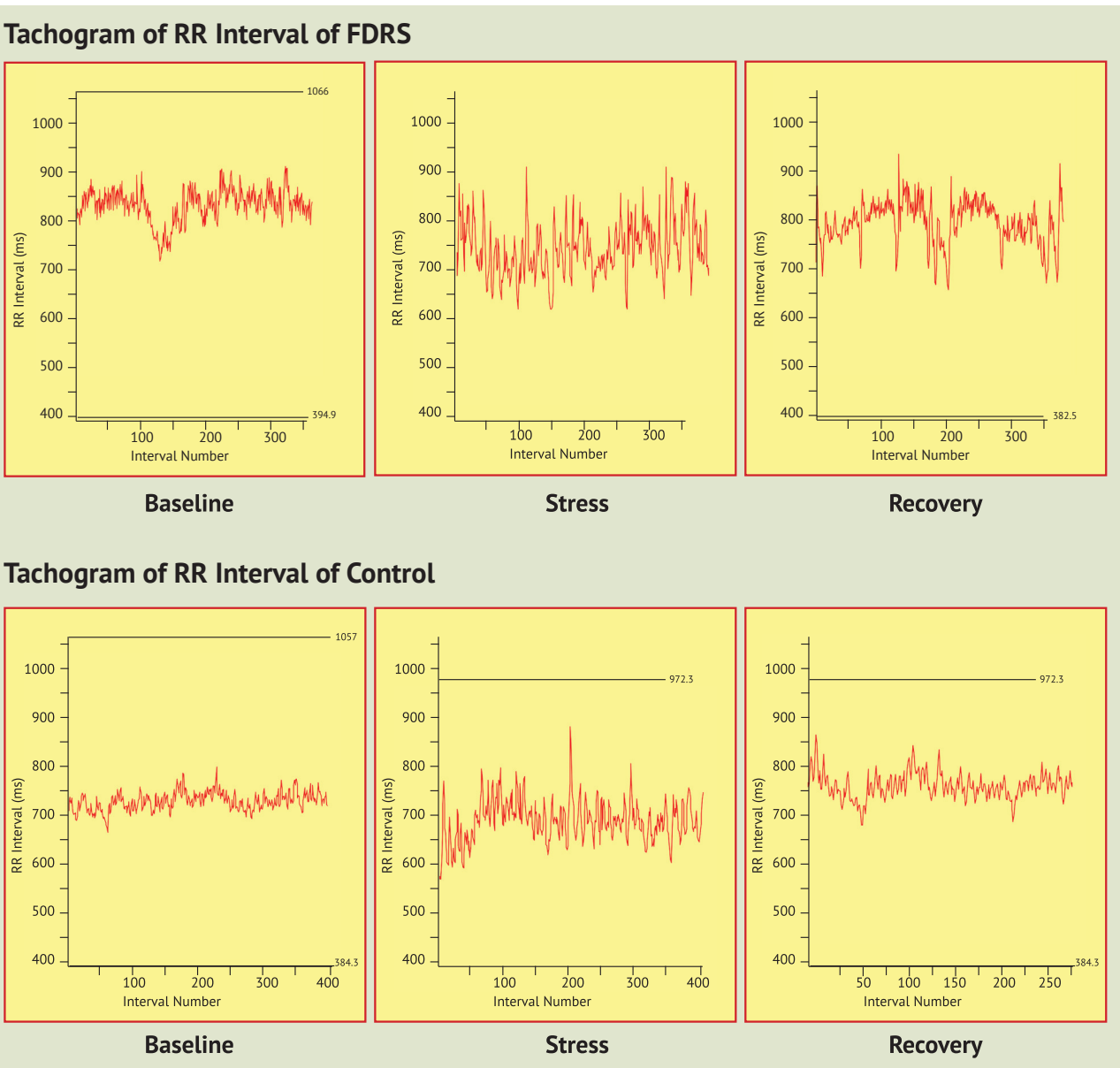
Consistent finding of abnormalities in CAF in unaffected FDRS suggests that these individuals also share this abnormal physiology, possibly due to a shared genetic risk. In other words, relatives of schizophrenia may be genetically vulnerable to the effect of stress. Certain measures, which possibly represent the pathway from genetic risk to symptoms, are called endophenotypes (30). An important quality of an endophenotype is that it should be shared by relatives of affected individuals (31). CAF abnormalities seem to fulfill this criterion.

Abnormal CAF response to stress might: 1) put individuals at greater risk of cardiac morbidity and/or 2) lead to greater perception of stress, leading to other psychiatric problems including depression, anxiety and substance use. Such influence of CAF abnormalities in first-degree relatives of schizophrenia patients needs to be evaluated by prospective studies.

Strengths of the study include:

1) to the best of our knowledge, this is first study in an Asian culture investigating cardiac autonomic functions in FDRS. Replication of finding in different ethnicity gives strong evidence for its biological basis;
2) in our study, cases and controls were comparable on several factors that could influence HRV, including age, gender, physical activity, smoking and alcohol consumption;
3) further, none of the cases or controls had any psychiatric disorders; nor were they on any medications. This is in contrast to the Castro et al. (2009) study in which the effect of depression, smoking and psychiatric medications could have influenced the results; and,
4) we did not recruit parents of patients since they would have crossed the risk period for schizophrenia, which can limit the interpretation on the results.

Figure 1



X axis denotes RR interval number and Y axis indicates duration of RR interval in milliseconds. It can be observed that controls showed similar response in baseline and recovery, whereas first-degree relatives showed similar response in stress and recovery.

Certain caveats need to be considered while interpreting these results. In conventional HRV measures following arithmetic stress, more variables would have been significant if we used a larger sample. However, it should be noted that the direction of difference between cases and controls in all these parameters was consistent; in none of the parameters did the controls show more abnormality than the cases. Second, controls were more educated than cases in our study. As the stress task is arithmetic, the contrasting finding could be argued as being confounded by this difference. However, as mentioned in the results section, we did not find correlation between years of education and any of the HRV measures. Hence, we believe that difference in education may not have contributed to the differential results. Third, specificity of these abnormalities to schizophrenia is questionable; comparative studies across different psychiatric disorders may clarify its specificity. A recent study by Berger et al. (2011) could not demonstrate abnormalities of HRV in healthy relatives of patients with major depressive disorder (32).

In summary, this study showed that relatives of schizophrenia patients show prolonged autonomic response to stress. The heuristic and clinical implications of this finding need further investigation.

Acknowledgments/Declarations of Interest

None.

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