Heart rate variability response to mental arithmetic stress in patients with schizophrenia
Autonomic response to stress in schizophrenia

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Abstract

Background: The vulnerability-stress hypothesis is an established model of schizophrenia symptom formation. We sought to characterise the pattern of the cardiac autonomic response to mental arithmetic stress in patients with stable schizophrenia.

Methods: We performed heart rate variability (HRV) analysis on recordings obtained before, during, and after a standard test of autonomic function involving mental stress in 25 patients with DSM-IV schizophrenia (S) and 25 healthy individuals (C).

Results: Patients with schizophrenia had a normal response to the mental arithmetic stress test. Relative contributions of low-frequency (LF) HRV and high-frequency (HF) HRV influences on heart rate in patients were similar to controls both at rest (LF 64±19% (S) vs. 56±16% (C); HF 36±19% (S) vs. 44±16% (C), t=1.52, p=0.136) and during mental stress, with increased LF (S: 76±12%, C: 74±11%) and decreased HF (S: 24±12%, C: 26±11%) in the latter study condition. Whilst healthy persons recovered the resting pattern of HRV immediately after stress termination (LF 60±15%, HF 40±15%, F=18.5, p<0.001), in patients HRV remained unchanged throughout the observed recovery period, with larger LF (71±17%) and lower HF (29±17%) compared with baseline (F=7.3, p=0.013).

Conclusions: Patients with schizophrenia exhibit a normal response to the mental arithmetic stress test as a standard test of autonomic function but in contrast with healthy individuals, they maintain stress-related changes of cardiac autonomic function beyond stimulus cessation.

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Keywords: Schizophrenia; Stress; Autonomic nervous system; Heart rate variability

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1. Introduction

Schizophrenia is characterised by macroscopic and histopathological abnormalities of cortical structures concerned with autonomic control, including the hippocampi, and temporal, cingulate, and prefrontal areas. (McDonald et al., 2004). Although it is well established that schizophrenia is highly heritable (Kendler et al., 1994; Cardno et al., 1999), the syndrome probably requires the concerted effect of several susceptibility genes, in addition to exposure to environmental noxious stimuli (e.g. perinatal damage and psychosocial stressors) in order to be expressed (McDonald and Murray, 2000). Environmental stress influences the time of emergence of symptoms of psychosis (Doering et al., 1998), and according to this “vulnerability-stress model” (Nuechterlein and Dawson, 1984), psychotic symptoms appear whenever stressors exceed the afflicted person’s vulnerability level, which is considered a stable, or “trait,” characteristic (Nuechterlein and Dawson, 1984).

The autonomic nervous system is a major bodily mediator of stressful emotions, hence theories of symptom development in schizophrenia have long incorporated the notion of autonomic dysfunction as central to the manifestation of psychosis. Kraepelin (1899) identified extensive autonomic alterations in schizophrenic patients, including pupillary, vasomotor, sweating, heart rate, salivation, and temperature changes, most of them suggesting increased sympathetic output, decreased parasympathetic activity, or both. Later studies on the subject have confirmed and extended those early observations (Lindstrom, 1996). Most available data about autonomic responses to environmental stress in schizophrenia refer to alterations of electrodermal responses (Venables, 1992; Grossberg, 2000). Although skin conductance orienting “hyporesponsiveness” in schizophrenia was suggested to be related to attentional and arousal deficits characteristic of the disorder (Dawson et al., 1994), skin lacks significant parasympathetic innervation.

In the last two decades heart rate variability (HRV) analysis has been developed as a tool to probe the peripheral autonomic output in the cardiovascular territory (Boettger et al., 2006). Most available data obtained with this tool in schizophrenia refer to acute states and show vagal withdrawal or decreased baroreflex sensitivity (Boettger et al., 2006), which support a status of baseline autonomic “hyperarousal” (Williams et al., 2004) in acute schizophrenia. We sought to probe the autonomic reaction to stress in patients with schizophrenia using this tool.

In light of previous observations, we hypothesised that in the patient sample the cardiovascular autonomic status at rest would be characterised by an increased sympathetic/vagal balance and response to stress would be less intense than in controls, paralleling the “hyporesponsiveness” observed in electrodermal studies. Patients with schizophrenia have increased cardiovascular morbidity and cardiac autonomic alterations have been implicated in the increased cardiovascular mortality (Ewing, 1992; Hennekens et al., 2005). Alterations of the cardiac autonomic response to stress may therefore have a cardiovascular prognostic value as well.

2. Methods

2.1. Participants

2.1.1. Patients

Psychiatry outpatients reaching DSM-IV diagnostic criteria were invited to participate in the study if (a) diagnosis was confirmed with a Composite International Diagnostic Interview (Robins et al., 1988) administered by a psychiatrist participating in the study, (b) aged 18 to 75 years, and (c) on stable medication for at least two weeks. Exclusion criteria were (a) use of illegal substances in the previous 6 months or a history of substance abuse/dependence (b) active symptoms having recently (<2 weeks) warranted antipsychotic dose adjustment or admission to the hospital, (c) history of mental retardation, (d) cardiac arrhythmias, (e) presence of diseases associated with neuropathy or autonomic nervous system involvement (e. g. diabetes), (f) use of medication with anticholinergic activity in the preceding week. Patients were identified by a staff-grade psychiatrist and referred only after both patient and accompanying first-degree relative signed an informed consent, as approved by the local ethics committee. Severity of schizophrenia symptoms was measured by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) administered the day of the heart rate testing session by a psychiatrist who was blind to the results of heart rate variability analysis.

2.1.2. Controls

Healthy comparison individuals were recruited from staff at FLENI, and from local community attendees to free lectures related to health promotion as advertised in posters and the media. Individuals were selected to match patients’ gender and age. All participants signed an informed consent form as approved by the ethics committee. Exclusion criteria included (a) the lifetime presence of any DSM-IV Axis I anxiety, mood, or psychotic disorder diagnosis as detected by a psychiatric interview with a consultant psychiatrist and a medication
history of antidepressants, antipsychotics, anticonvulsants or lithium, (b) the current use of any psychopharmacologic agent, or any medication with anticholinergic activity in the previous week, (c) cardiac arrhythmia, or (d) medical conditions potentially associated with autonomic nervous system dysfunction (including diabetes mellitus and Parkinson’s disease).

2.2. Testing session

Participants were tested between 0900 h and 1300 h, 2–4 h post-prandial, and having abstained from smoking for 2 h, consuming caffeinated beverages for 6 h, and vigorous exercise for 24 h. Testing was carried out whilst seated in a quiet, dimly lit room after 10 min of rest. A baseline heart rate variability recording with at least 550 beats was obtained prior to the test. We used a standard test of autonomic function, the mental arithmetic task to induce mental stress (Ewing, 1992), which consisted in subtracting serial 7’s starting from 700. Patients were requested to keep their eyes closed and pronounce aloud each response. The test was chosen because it consistently induces sustained psychological stress resulting in an autonomic profile of sympathetic activation and parasympathetic inhibition, manifested by sustained increases in heart rate and blood pressure (Ewing, 1992) during the time necessary to collect at least 550 beats, which was estimated to be 7 min in a pilot study. Heart rate signal data was collected for an additional 7 min after participants were instructed to stop the task to assess the autonomic recovery from mental stress. Respiratory rate was visually monitored simultaneously.

2.3. Heart rate data acquisition and analysis

We analysed HRV on recordings of successive RR intervals of sinus node origin as described previously (Task Force, 1996; Guinjoan et al., 2004). Patients were connected to an interphase which detected R-waves in a surface electrocardiographic signal (as obtained from a V4 or a V5 lead) and fed into a computer which stored RR intervals sampled at 1250 Hz (VariaDat® HRV package, University of Entre Ríos School of Bioengineering). Premature and lost beats were individually identified and manually tagged in the file of RR intervals. These abnormal beats were replaced for RR intervals resulting from linear interpolation. Time-(non-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sample characteristics</th>
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<tbody>
<tr>
<td>Patients (n=25)</td>
<td>Controls (n=25)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34±11</td>
</tr>
<tr>
<td>Female</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>26±6</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11±4</td>
</tr>
<tr>
<td>Smokers</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>23±6</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>10±8</td>
</tr>
<tr>
<td>Total PANSS</td>
<td>86±24</td>
</tr>
<tr>
<td>Positive subscale</td>
<td>16±7</td>
</tr>
<tr>
<td>Negative subscale</td>
<td>27±11</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>5 (20)</td>
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<tr>
<td>Novel antipsychotic</td>
<td></td>
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<tr>
<td>Risperidone</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Selective Serotonin Reuptake Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>12 (48)</td>
</tr>
</tbody>
</table>

PANSS: Positive and Negative Symptom Scale. Shown are mean±standard deviation or number (percentage).
2.3.1. Non-spectral HRV analysis

Time domain measures of HRV included mean RR interval (RR), standard deviation of all normal RR intervals (SDNN), and rMSSD (square root of the mean squared differences of successive normal RR intervals). SDNN estimates global HRV, mediated by sympathetic and parasympathetic nervous systems. rMSSD reflects short-term, beat-to-beat variations in heart rate.

2.3.2. Spectral HRV analysis

Frequency domain measures of HRV were quantified through fast Fourier transform (Task Force, 1996) and included low-frequency power (LF, 0.03–0.15 Hz),
high-frequency power (HF, 0.15–0.40 Hz), and the LF/HF ratio (L/H). The purpose of the Fourier analysis is to decompose a complex time series \( f(t) \) with cyclical components into the underlying sinusoidal functions of particular wavelengths. Mathematically, the process of Fourier analysis is represented by the Fast Fourier Transform, which is the sum over all time of the signal \( f(t) \) multiplied by a complex exponential. The results of the transform are the Fourier coefficients; the squared coefficients for each frequency are the power spectral density of the signal \( f(t) \). The goal of spectral estimation is to describe the distribution (over frequency) of the power contained in a signal. The average power of a signal over a particular frequency band can be found by integrating the power spectral density over that band. The power spectral density of the original heart rate signal thus provides information of how variance distributes as a function of frequency (Task Force, 1996), and was calculated with Matlab V6 software. The high-frequency (HF) component of HRV is related to respiratory sinus arrhythmia (mediated by parasympathetic activity), and the low-frequency (LF) component is related to Mayer waves of blood pressure, which influence heart rate via the baroreceptor reflex. Thus LF depends on both sympathetic and parasympathetic influences, although in most instances (with the notable exceptions of strenuous physical exercise and heart failure) it is thought to reflect mainly sympathetic activation (Malliani et al., 1991; Montano et al., 1994; Task Force, 1996). We report absolute (natural logarithm of HRV amplitude, ms\(^2\)) values and normalised units of each component. Normalised units are calculated in relative terms as follows: LF: LF/(Total power − very low-frequency power)×100, and HF: HF/(Total power − very low-frequency power)×100. This form of expression permits the comparison of groups of individuals with different absolute values of HRV, because when the spectral components are expressed in absolute units, the changes in total power influence LF and HF in the same direction and prevent the accurate appreciation of the fractional distribution of the energy (Task Force, 1996).

2.4. Statistical analysis

Discrete variables in patients and controls were compared using the chi-square test (\( \chi^2 \)), and continuous variables were compared with an independent-samples \( t \) test. This method was also used to compare HRV measurements in patients on risperidone with those who were not taking it, as this antipsychotic was the most commonly used in the present sample and may affect heart rate. Within-subject comparisons of HRV data obtained during baseline, mental stress, and recovery phases were performed with a repeated-measures ANOVA followed by post hoc Bonferroni analysis. PANSS scores were correlated with HRV measures with a Pearson’s \( r \) test. Significance was assumed at \( \alpha=0.05 \), after a Bonferroni correction was applied to multiple measurements. All results are two-tailed.

3. Results

Table 1 shows the demographic and clinical characteristics of patients and controls. Two women and one man
declined to participate in the study. Patients showed a trend towards greater body mass index (BMI), and were less educated than controls. All patients had been on stable doses of antipsychotics for at least two weeks; three were receiving two different antipsychotics simultaneously. Respiratory rate ranged between 13 and 21 cpm (0.22–0.35 Hz) in all participants throughout testing.

3.1. Baseline heart rate variability (HRV)

Baseline non-spectral data for the entire sample of patients and controls are shown in Fig. 1. Patients had a higher heart rate (Fig. 1 top panel) and a globally decreased HRV (reflected by smaller SDNN and rMSNN, Fig. 1 bottom panel). Fig. 2A shows the tachograms (i.e., the series of sinus RR intervals, top panels) and their corresponding power spectra (bottom panels) obtained at baseline in a 34-year-old male with schizophrenia (left), and a 27-year-old male in the healthy comparison group (right). The patient displays a higher heart rate (i.e., shorter RR intervals) and decreased HRV at baseline compared to the healthy person. Spectral measures of HRV suggest that these changes in heart rate and non-spectral HRV are mostly due to high-frequency (HF) oscillations (4.03±1.28 ln ms² vs. 5.02±1.37 ln ms² in healthy persons, \( t = -2.64, p = 0.011 \)), as HRV in the low-frequency (LF) spectrum exhibited a tendency to be lower in patients (4.68±1 ln ms² vs. 5.34±1.3 ln ms² in healthy persons, \( t = -2, p = 0.051 \)). Relative HF and LF contributions to total HRV, as expressed by normalised units, were on the other hand similar in patients and controls (Fig. 2 B). Accordingly, L/H was similar in both groups as well (2.7±2.3 in patients vs. 2±2.3 in controls).

3.2. Mental stress-related changes in HRV

Patients and controls had a normal response to the mental arithmetic test, as indicated by the significant tachycardia associated with it (i.e., shortening of average RR interval), which was immediately followed by a recovery of the baseline heart rate (Fig. 3, top panel). Fig. 3 (bottom panel) depicts mental stress-related changes in non-spectral HRV, which reveals smaller variability in patients. Fig. 4A displays oscillations of heart rate during, and immediately after, a 7-minute period of mental stress in the same individuals as in Fig. 2A. Shown are the tachograms (top), the power spectra corresponding to the task itself (middle) and post-task recovery phase (bottom) in the same patient (left) and healthy person (right) as in Fig. 2A. Mental stress brought about a shortening of RR intervals, followed by a noticeable interval lengthening after the task (Fig. 4A, top graphics). On the other hand, the recovery of frequency components of HRV after the period of stress is most noticeable in the normal individual (Fig. 4A, right middle and bottom graphics), whereas the patient with schizophrenia maintains a similar pattern of HRV during mental stress (Fig. 4A, left middle graphic) and during recovery (Fig. 4A, left bottom graphic). In the sample as a whole, the response of each autonomic component was different in healthy individuals and persons with schizophrenia. In normal individuals, mental stress evoked an increase in absolute LF power, which abated immediately after the task (5.34±1.3 ln ms² baseline vs. 6.09±1.03 ln ms² mental stress vs. 5.44±1.25 ln ms² post-task, \( F = 8.3, p = 0.012 \)), and these changes were paralleled by equal changes in LF HRV relative to total HRV as expressed by normalised units (Fig. 4, panel B). Whereas absolute HF power did not change significantly during the task, the relative contribution of HF in terms of normalised units showed a significant withdrawal during the mental stress-inducing task followed by restoration to baseline levels immediately after mental stress cessation (Fig. 4, panel B). HRV response to the mental stress-inducing task in patients was similar to that attained by healthy persons, namely, an increase in absolute power in the LF range (4.68±1 ln ms² baseline vs. 5.36±0.95 ln ms² mental stress), and both an increase in the relative LF contribution to total variability, and a significant decrease in relative HF HRV as measured by normalised units, so that both relative HRV components were indistinguishable from controls during stress (Fig. 4, panel B). This is also reflected in a similar sympathovagal balance in both groups as measured by the L/H quotient (4.5±3.2 in patients vs. 3.7±2.5 in controls). However, in contrast to healthy participants, patients with schizophrenia displayed a prolonged autonomic activation as indicated by sustained increase in absolute LF power (5.25±1.01 ln ms², \( F = 11.6, p < 0.001 \) vs. baseline LF), and decreased normalised HF variability throughout the observed recovery period (Fig. 4, panel B). Normalised LF in patients was also significantly higher than that observed in controls as far as the post-task period (Fig. 4, panel B). Consistent with these observations, sympathovagal balance reflected by L/H quotient was higher in patients with schizophrenia after stress cessation (4.1±3.9 vs. 2.2±2.2 in controls, \( t = 2.13, p = 0.039 \)).

3.3. Relationship between psychotic symptoms or antipsychotic use and HRV

No positive or negative correlations were found between the negative and positive subscales or total PANSS scores, and measures of HRV during baseline,
4. Discussion

This study shows that patients with schizophrenia exhibit (a) a decreased baseline HRV and an increased baseline heart rate probably related to impaired parasympathetic input to the heart (as measured by HF-HRV), (b) a normal heart rate response to the standard mental arithmetic stress test of autonomic function, (c) a normal pattern and intensity of the cardiac autonomic response to mental stress in terms of increased sympathetic input (as inferred from increases in LF-HRV) and decreased vagal input to the heart (as indicated by decreases in HF-HRV), and (d) an abnormal prolongation of this pattern once stress is terminated, as compared to healthy individuals who exhibit an immediate recovery of the cardiac autonomic balance characteristic of baseline resting conditions.

In humans, stimulation of the insula, medial prefrontal cortex and anterior cingulate, and medial temporal lobe elicit changes in blood pressure and heart rate that are occasionally accompanied by subjective mood changes (Critchley et al., 2000). Critchley et al. (2000) additionally characterised activation of brain areas in association to stressful mental arithmetic, confirming significant involvement of cingulate cortex (particularly on the right anterior region), cerebellar vermis, and pons. Most of these areas have been implicated by structural and functional brain studies of schizophrenia (Lawrie and Abukmeil, 1998; Harrison, 1999; Wright et al., 2000) and the autonomic alterations described may ultimately reflect the alteration of those central structures, expressed as an inability to “switch off” the cardiovascular autonomic profile characteristic of mental stress. Williams et al. (2004) proposed that schizophrenia might be characterised by a disjunction of autonomic arousal and amygdala–prefrontal circuits that impede appropriate processing of stressful signals. Excessive arousal together with decreased amygdala activation in schizophrenia might reflect a dysregulation of the normal positive feedback between amygdala function and autonomic activity due to failure of regulation by prefrontal structures, thus leading to a perseveration and exacerbation of arousal responses (Williams et al., 2004). This phenomenon would then lead to an internally generated cycle of hypervigilance and misattribution that feeds into paranoid cognition (Williams et al., 2004; Phillips et al., 2000). Regarding negative symptom generation, some of the central structures potentially involved in autonomic control additionally mediate social and emotional behaviour; hence both these areas of functioning are compromised when disrupted (Damasio et al., 1991). It has been recently documented that right ventromedial prefrontal lesions result in excessive sympathetic responses to stressful stimuli (Hilz et al., 2006). Orbitofrontal damage reduces anticipatory arousal to emotive stimuli, whilst lesions of the amygdala block autonomic responses that accompany conditioning (Damasio et al., 1991). Lesions of these areas are associated with changes in social behaviour and emotional responses, suggesting that feedback of altered autonomic arousal (represented in cortical regions such as the orbitofrontal/ventromedial prefrontal cortex) may directly influence social behaviour and decision making (Damasio et al., 1991).

An additional potential clinical implication refers to mounting evidence on the role of cardiac autonomic dysfunction as a culprit for increased cardiovascular mortality observed in individuals with schizophrenia. Increased sympathetic and/or decreased parasympathetic input to the heart have been repeatedly shown to increase the proclivity to malignant ventricular arrhythmias and myocardial ischaemia (Schwartz and Priori, 1990; Smith et al., 2005), ultimately resulting in increased incidence of cardiovascular deaths (Gerritsen et al., 2001). Patients with schizophrenia indeed have an excessive cardiac mortality when compared with healthy cohorts (Brown et al., 2000; Hennekens et al., 2005). The emerging evidence in the field indicates that schizophrenia patients consistently display a decreased vagal input to the heart compared to normal individuals, both in acute phases of the disease in which patients have not yet received antipsychotics and in stable phases whilst taking the latter (Toichi et al., 1999;
Bar et al., 2005; Boettger et al., 2006). Along with accumulating evidence of reduced vagal tone, our results indicative of protracted stress-related cardiac sympathetic responses suggest that this factor should also be taken into account in future studies as a potential mechanism for the association. In general, typical high-potency antipsychotics like haloperidol and most novel agents have limited effects on HRV recordings (Rechlin et al., 1994; Bar et al., 2005; Boettger et al., 2006), whereas clozapine is consistently associated with a significant reduction in total HRV (Rechlin et al., 1994; Cohen et al., 2001; Mueck-Weymann et al., 2002). In our study, with the main finding being the presence of a protracted stress-related HRV profile, it therefore seems unlikely that the latter was caused by clozapine, used in three patients.

Anxiety (including obsessive–compulsive) disorders are sometimes comorbid with schizophrenia and in most cases have been shown to exhibit diagnosis-specific abnormalities of heart rate variability or heart rate responses to stress (Buhlmann et al., 2007; Friedman, 2007). Whilst our patients did not exhibit comorbid anxiety disorders, further studies that investigate the contribution of anxiety to the described findings are probably warranted.

In summary, in a standard test of autonomic function involving mental stress, patients with schizophrenia exhibit an autonomic response that is abnormally maintained beyond the cessation of the stress source, as compared to healthy individuals. It remains to be further elucidated to what extent this pattern is related to increased cardiovascular mortality and precipitation of psychotic episodes in schizophrenia.

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Contributors

SMG and MNC designed the study and wrote the protocol. SMG, MNC, HW, and EC managed the literature searches and analyses. SMG, MNC, HW, RDF, MN, DA, and RCL collected experimental data. DEV, SMG, MNC, DPC, and HW undertook the statistical analysis, and MNC wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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