

# Altered heart rate dynamics associated with antipsychotic-induced subjective restlessness in patients with schizophrenia

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**Background:** Antipsychotic-induced subjective inner restlessness is one of the common and distressing adverse effects associated with antipsychotics; however, its underlying neurobiological basis is not well understood. We examined the relationship between antipsychotic-induced subjective inner restlessness and autonomic neurocardiac function.

**Methods:** Twenty-two schizophrenia patients with antipsychotic-induced subjective restlessness, 28 schizophrenia patients without antipsychotic-induced subjective restlessness, and 28 matched healthy control subjects were evaluated. Assessments of the linear and nonlinear complexity measures of heart rate dynamics were performed. Multivariate analysis of variance and correlation analysis were conducted.

**Results:** The mean interbeat (RR) interval value was significantly higher in control subjects than in patients with and without antipsychotic-induced subjective restlessness ( $P < 0.05$ ). The low frequency/high frequency ratio was significantly higher in patients with antipsychotic-induced subjective restlessness than in control subjects and in patients without antipsychotic-induced subjective restlessness ( $P < 0.05$ ), while the approximate entropy value was significantly lower in patients with antipsychotic-induced subjective restlessness than in control subjects and in patients without antipsychotic-induced subjective restlessness ( $P < 0.05$ ). Correlation analyses controlling for psychotic symptom severity showed that the degree of antipsychotic-induced restlessness had a significant negative correlation with the value of approximate entropy ( $P < 0.05$ ).

**Conclusion:** The results indicate that antipsychotic-induced subjective restlessness is associated with altered heart rate dynamics parameters, particularly the nonlinear complexity measure, suggesting that it might adversely affect autonomic neurocardiac integrity. Further prospective research is necessary to elucidate the precise interrelationships and causality.

**Keywords:** antipsychotics, subjective restlessness, heart rate dynamics

## Introduction

Several psychotropic drugs produce subjective inner restlessness in therapeutic or nontoxic doses.<sup>1</sup> The most important clinical syndrome in this context is that caused by dopamine antagonists.<sup>1,2</sup> Antipsychotic-induced subjective restlessness has been receiving increased attention because of its significant impact on drug compliance.<sup>3</sup> In addition, it causes considerable distress in an already vulnerable group of patients and may also represent a risk factor for suicidal behavior.<sup>3</sup>

The neurobiological basis for antipsychotic-induced subjective restlessness is not well understood, although the associated strong affective component suggests that it is of central origin. One of the crucial elements may be dysfunction of cortical-subcortical circuits involving dopamine and other neurotransmitter systems.<sup>1,3</sup> The basal ganglia,

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the common site of action for antipsychotics, also interact strongly with the limbic system, which controls the affective domain.<sup>1,3</sup> Considering that the limbic system is substantially involved in the pathophysiology of autonomic nervous system (ANS) reactivity,<sup>4</sup> it is possible that the parameters measuring autonomic neurocardiac regulation may reflect the functional state of the cortical and mesolimbic system, which could be linked to the pathogenesis of antipsychotic-induced restlessness. Nevertheless, few studies have examined its relationship with autonomic neurocardiac dysregulation. The investigation of autonomic correlates of antipsychotic-induced subjective restlessness may provide valuable insight and understanding into its pathophysiology.

In the present study, we examined the relationship between antipsychotic-induced subjective inner restlessness and autonomic neurocardiac function using analysis of heart rate variability (HRV) in patients with schizophrenia treated with risperidone.

## Materials and methods

### Subjects

The study protocol was approved by the local ethical committee, and all procedures used in the study were conducted in accordance with international ethical standards, Declaration of Helsinki. The criteria for patient recruitment were (1) a diagnosis of schizophrenia by *Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)*,<sup>5</sup> which was established using the Structured Clinical Interview for *DSM-IV*<sup>6</sup>; (2) age 20–50 years; (3) inpatients on monotherapy with risperidone without adjunctive medications; and (4) no treatment with psychotropic drugs known to cause subjective inner restlessness other than antipsychotics within the 2-week period prior to the beginning of the study. The drugs included lithium carbonate, tricyclic antidepressants, selective serotonin reuptake inhibitors, and calcium channel blockers. None of the patients were taking drugs known to treat akathisia, such as beta blockers, mianserin, or mirtazapine, at the time of enrollment.

Patients were excluded if they (1) met diagnostic criteria for a psychiatric diagnosis other than schizophrenia; (2) had a concurrent diagnosis of substance abuse or dependence (including nicotine dependence); or (3) had concurrent cardiovascular, neurological, or endocrinological diseases. Healthy control subjects were also recruited and screened by a complete medical and psychiatric examination, and none had a history of any disease or medication that might affect the ANS. Informed consent was obtained after a full explanation of the study procedure.

## Assessments

Antipsychotic-induced subjective inner restlessness was assessed using the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS).<sup>7</sup> Antipsychotic-induced subjective restlessness was distinguished from psychotic agitation by a sense of being driven and the awareness of inner tension, as proposed previously.<sup>2,3,7</sup> The diagnosis of antipsychotic-induced subjective restlessness was made if the score on the item of LUNSERS was more than 2.<sup>7</sup> The severity of schizophrenic symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS).<sup>8</sup>

HRV measurements were performed after assessing subjective inner restlessness and schizophrenic symptoms on the same day. Smoking was strictly prohibited by hospital policy. In addition, vigorous exercise and caffeinated beverages including coffee and tea were not allowed on the day prior to HRV measurement. After each subject had been allowed to adapt to the experimental conditions for approximately 10 minutes, a 10-minute single channel (three-lead) electrocardiogram (ECG) recording was performed in the seated position at complete rest. The ECG signal was amplified and digitized at a sampling rate of 400 Hz (width path, 0.05–35 Hz). The interbeat (RR) interval time series was generated using the automatic scheme in order to detect the R peak in the ECG, using methods proposed previously.<sup>9</sup>

In the conventional time domain analysis of HRV, the mean length of all RR intervals was computed according to standardized procedures.<sup>10</sup> For the frequency domain analysis, a spectral analysis was carried out using fast Fourier transformation and the low frequency ([LF]: 0.04–0.15 Hz)/high frequency ([HF]: 0.15–0.4 Hz) ratio was calculated to assess the sympathovagal balance, as proposed previously.<sup>10</sup> For the nonlinear complexity measure, the approximate entropy (ApEn), which is a parameter developed to quantify the degree of regularity versus the unpredictability in a higher dimensional attractor reconstructed from a time series, such as the instantaneous heart rate time series, was calculated using the method proposed by Pincus.<sup>11</sup> The ApEn measures the difference between the logarithmic frequencies of similar runs of length  $m$  and runs with the length  $m + 1$ , calculating the logarithmic likelihood that runs of patterns that are close to each other will remain close in the next incremental comparisons.<sup>12–16</sup> The ApEn is strongly correlated with HF power, which mainly reflects respiratory sinus arrhythmia.<sup>14–16</sup> A lower value of ApEn reflects a higher degree of regularity, and the higher the entropy value, the more unpredictable the time series.

## Statistical analysis

Demographic and clinical variables were compared between the groups using one-way analysis of variance, *t*-test, and Chi-square test, as appropriate. The values of the HRV measures of the groups were compared using multivariate analysis of variance with post hoc Scheffé tests. The relationship between antipsychotic-induced subjective restlessness and HRV measures was also evaluated using Pearson's partial correlation analyses controlling for PANSS total score. The level of statistical significance was defined as  $P < 0.05$  (two-tailed).

## Results

Fifty inpatients (35 men, 15 women) with schizophrenia and 28 healthy control subjects were enrolled. The patients had a mean age of 32.0 years  $\pm$  9.2 years and a mean duration of illness of 7.3 years  $\pm$  5.0 years. All patients were receiving risperidone monotherapy with a mean dosage of 2.9 mg/day  $\pm$  1.5 mg/day at the time of enrollment. The mean total PANSS score of the patients was 93.7  $\pm$  15.8 at enrollment.

A diagnosis of antipsychotic-induced subjective restlessness based on the LUNBERS was made in 22 (44%) of the 50 patients. Table 1 presents the demographic characteristics of the groups. There were no significant differences in age, sex, or smoking status among the groups ( $P > 0.1$ ). No significant differences in illness duration (8.5 years  $\pm$  5.2 years versus 6.4 years  $\pm$  4.7 years,  $P = 0.15$ ) or antipsychotic dosage (risperidone: 3.1 mg/day  $\pm$  1.3 mg/day versus 2.6 mg/day  $\pm$  1.6 mg/day,  $P = 0.24$ ) were observed between patients with and without antipsychotic-induced subjective restlessness (Table 1).

A comparison of the HRV parameters among groups is shown in Table 2. The analysis using multivariate analysis of variance (Wilks'  $\lambda = 0.53$ ,  $F = 9.20$ ,  $P < 0.001$ ) and follow-up *F* tests showed significant group differences in all parameters ( $P < 0.01$ ). Post hoc analyses with Scheffé tests indicated that the mean RR interval value was significantly higher in the healthy control group than in patients with

and without antipsychotic-induced subjective restlessness ( $P < 0.01$ ) (Table 2). The LF/HF ratio was significantly higher in patients with antipsychotic-induced subjective restlessness than in control subjects and in patients without antipsychotic-induced subjective restlessness ( $P < 0.05$ ) (Table 2). Regarding the nonlinear complexity measure, the ApEn value was significantly lower in patients with antipsychotic-induced subjective restlessness than in control subjects and in patients without antipsychotic-induced subjective restlessness ( $P < 0.01$ ) (Table 2).

In the patient group, partial correlation analyses controlling for PANSS total score showed that the severity of antipsychotic-induced subjective restlessness had a significant negative correlation with the ApEn value ( $r = -0.29$ ,  $P = 0.04$ ) (Figure 1). No significant correlations were observed between the other HRV measures and the antipsychotic-induced subjective restlessness score (mean RR interval:  $r = -0.04$ ,  $P = 0.81$ ; LF/HF:  $r = 0.14$ ,  $P = 0.33$ ).

## Discussion

In the present study, we examined the relationship between antipsychotic-induced subjective restlessness and autonomic neurocardiac function using analysis of HRV in patients with schizophrenia. We observed that the ApEn value was significantly lower in patients with antipsychotic-induced subjective restlessness than in those without it as well as in healthy control subjects, while the LF/HF ratio was significantly higher in patients with antipsychotic-induced subjective restlessness than in control subjects and in patients without antipsychotic-induced subjective restlessness, suggesting a shift in sympathetic–parasympathetic balance in favor of sympathetic tone. Notably, a significant negative correlation between antipsychotic-induced subjective restlessness and the nonlinear complexity measure; ie, ApEn, was observed while controlling for the influence of psychotic symptom severity, suggesting its association with reduced neurocardiac dynamics.

**Table 1** Comparison of demographic variables among groups

Variables	Group 1 <sup>a</sup>	Group 2 <sup>b</sup>	Group 3 <sup>c</sup>	F value	P value
Age <sup>d</sup>	32.3 $\pm$ 7.9	31.7 $\pm$ 10.3	29.6 $\pm$ 8.0	0.69	0.51
Sex (male/female)	17/5	18/10	19/9	1.01 <sup>e</sup>	0.60
Smokers/nonsmokers	12/10	11/17	10/18	1.95 <sup>e</sup>	0.38
Duration of illness (years) <sup>d</sup>	8.5 $\pm$ 5.2	6.4 $\pm$ 4.7	NA	1.48 <sup>f</sup>	0.15
Antipsychotic dosage (mg/day) <sup>d</sup>	3.1 $\pm$ 1.3	2.6 $\pm$ 1.6	NA	1.19 <sup>f</sup>	0.24

**Notes:** <sup>a</sup>Patients with antipsychotic-induced subjective restlessness; <sup>b</sup>patients without antipsychotic-induced subjective restlessness; <sup>c</sup>healthy control subjects; <sup>d</sup>values are presented as mean  $\pm$  standard deviation; <sup>e</sup>Chi-square value; <sup>f</sup>*t* value.

**Abbreviations:** NA, not applicable.

**Table 2** Comparison of heart rate variability parameters among groups

Variables	Group 1 <sup>a</sup>	Group 2 <sup>b</sup>	Group 3 <sup>c</sup>	F value	P value
Mean RR interval <sup>d</sup>	637.28 ± 106.96	681.91 ± 97.75	799.83 ± 80.50	20.28	<0.01 <sup>e</sup>
LF/HF <sup>d</sup>	9.67 ± 7.53	6.13 ± 4.34	3.35 ± 2.19	10.08	<0.01 <sup>f</sup>
ApEn <sup>d</sup>	1.13 ± 0.26	1.34 ± 0.19	1.47 ± 0.17	17.02	<0.01 <sup>g</sup>

**Notes:** <sup>a</sup>Patients with antipsychotic-induced subjective restlessness; <sup>b</sup>patients without antipsychotic-induced subjective restlessness; <sup>c</sup>healthy control subjects; <sup>d</sup>values are presented as mean ± standard deviation; <sup>e</sup>differences between groups 1 and 3 ( $P < 0.01$ ) as well as between groups 2 and 3 ( $P < 0.01$ ) on Scheffé tests; <sup>f</sup>differences between groups 1 and 2 ( $P < 0.05$ ) as well as between groups 1 and 3 ( $P < 0.01$ ) on Scheffé tests; <sup>g</sup>differences between groups 1 and 2 ( $P < 0.01$ ) as well as between groups 1 and 3 ( $P < 0.01$ ) on Scheffé tests.

**Abbreviations:** ApEn, approximate entropy; HF, high frequency; LF, low frequency; RR, interbeat.

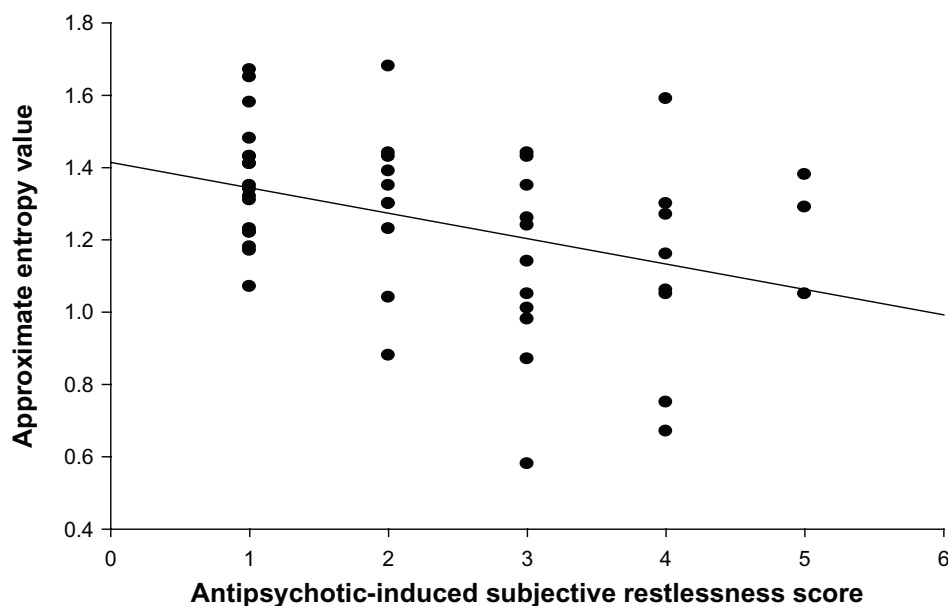
The results are partly in line with previous reports showing that patients with Parkinson's disease exhibit lower HRV measures than those of healthy controls and that the severity of extrapyramidal features is negatively associated with HRV measures;<sup>9</sup> however, previous studies did not include symptoms of restlessness nor apply the nonlinear complexity measures of HRV.

Although the pathogenesis of antipsychotic-induced subjective restlessness is unclear, the neuronal circuits involved in its pathophysiology are thought to have complex afferent and efferent connections with large parts of the cortical and subcortical areas.<sup>1,17</sup> Considering the primary role of the limbic system in both central ANS reactivity and emotional behavior, it may be that certain HRV parameters reflect the functional state of mesolimbic activity, which could be associated with the pathophysiology of antipsychotic-induced subjective restlessness. The altered neurocardiac dynamics associated with antipsychotic-induced restlessness may also be attributed, in part, to dysphoric affective

symptoms closely related to it such as depressive and anxiety symptoms.<sup>1</sup>

Considering the accumulating evidence demonstrating that autonomic dysfunction seen in patients with schizophrenia may indicate underlying disease-inherent vulnerability,<sup>4,18</sup> which was supported by the low HRV findings in the patient groups in our study, the reduced dynamics of HRV associated with the adverse effects of antipsychotics might exacerbate compromised autonomic cardiac modulation and increase cardiovascular morbidity in vulnerable patients.<sup>4,18–23</sup>

It is interesting to note that the nonlinear complexity measure was significantly correlated with the severity of antipsychotic-induced subjective restlessness and that a significant difference between the patient groups was also found in this parameter. Central autonomic regulation causes nonlinear phenomena in sinus rhythm generation. An analysis of HRV by methods based on the nonlinear theory has been shown to better depict the multiple regulatory systems influencing the heart rate time series modulation



**Figure 1** Scatter plots showing the relationship between the severity of antipsychotic-induced subjective restlessness as measured by the Liverpool University Neuroleptic Side Effect Rating Scale and the approximate entropy value.

in complex biological systems.<sup>12</sup> The decrease in entropy value means a decrease in the number of the variables and their levels of interactions involved in neuroautonomic regulation.<sup>15</sup> Therefore, decreased entropy measures in patients with antipsychotic-induced subjective restlessness suggest that the degree of distribution of stochastic process gets lower<sup>11</sup> and that the neuroautonomic control system governing the heart rate loses complexity in those patients. These changes may be substantially associated with the diminished adaptability of the biosystem.<sup>15</sup> However, the effect size of the correlation between the antipsychotic-induced subjective restlessness and the ApEn was 0.29, indicating a less than moderate effect size. Therefore, the mechanisms causing antipsychotic-induced subjective restlessness may differ from those leading to impairment of neuroautonomic regulation and other mechanisms may also be involved.

The HRV values of the patients included in our study were higher than those observed in patients receiving clozapine<sup>22–24</sup> and similar to or slightly lower than those observed in patients receiving haloperidol.<sup>23</sup> These findings indicate a relatively favorable profile of risperidone in terms of the effects on HRV,<sup>20,25–27</sup> which reflects the fact that risperidone shows no anticholinergic activity in the in vitro receptor binding profile. However, the effects of antipsychotics on HRV in patients with schizophrenia cannot be attributed simply to their receptor binding profile, as multiple other factors, such as disease processes, symptom severity, and adverse effects, also play a significant role in the complex regulation of HRV.<sup>28</sup> Therefore, further prospective investigations of the neurocardiac effects of various antipsychotics in patients with different clinical characteristics are required to better understand the complex interaction between antipsychotics and HRV.<sup>19</sup>

In the present study, we did not perform actometry recordings to evaluate objective restlessness, since we focused on the subjective aspect of restlessness. However, since psychomotor activity and autonomic cardiac functioning are closely interrelated,<sup>29</sup> it would have been helpful to measure objective restlessness using an accelerometer, which has been reported as a valuable objective tool for assessing restlessness.<sup>30–33</sup> Further studies using actometry are required to better understand the physiological basis of multiple aspects of restlessness and to investigate whether subjective restlessness and objective motor manifestations are differentially associated with HRV parameters.

The interpretation of the results should be considered in light of some limitations. A cross-sectional design limits the

firm interpretation of the results observed. We evaluated the relationships in patients receiving risperidone monotherapy without adjunctive medications. Therefore, the results may not be generalized to other groups receiving different antipsychotics. We did not measure body mass index, which was reported to be one of the factors influencing baroreflex sensitivity.<sup>34</sup> In our study, the consumption of coffee or tea was not allowed on the day prior to HRV measurement. However, we did not measure the daily average amount of coffee or tea intake, which might have affected autonomic regulation.<sup>35</sup>

In conclusion, the present study indicates that antipsychotic-induced subjective restlessness is associated with altered HRV parameters, particularly the nonlinear complexity measure, suggesting that it might adversely affect autonomic neurocardiac integrity. Further prospective studies are necessary to elucidate the precise interrelationships and causality. The nonlinear complexity measures of HRV may be useful in evaluating the subtle subjective forms of adverse effects of antipsychotics, serving as a practical noninvasive method.

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## Disclosure

The authors report no conflicts of interest in this work.

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