Autonomic Nervous System Activation During Social Cognition Tasks in Patients With Schizophrenia and Their Unaffected Relatives

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Objective: The objective of the study was to determine whether patients with schizophrenia and their unaffected first-degree relatives have abnormal autonomic nervous system (ANS) responses to social cognition tasks.

Background: Social cognition impairments are significant in schizophrenia. ANS activity has been shown to be abnormal in schizophrenia patients, and some of the abnormalities seem to be shared by patients' unaffected relatives.

Method: Heart rate variability (HRV) was measured at rest and during social cognition tasks, in patients with schizophrenia, their nonpsychotic first-degree relatives, and matched healthy controls (n = 19 in each group).

Results: Social cognition tasks induced a shortening of the RR interval in unaffected relatives, but not in patients. Social cognition tasks generated decreases in high-frequency (indicating cardiac vagal activity) and low-frequency (reflecting predominantly sympathetic activity) HRV in patients. In relatives, the decrease occurred in the high-frequency component only. Low-frequency HRV was higher in patients during a theory of mind task than a control task. These changes were not observed in the controls.

Conclusions: Social cognitive tasks induce a pattern of peripheral autonomic activity different from that seen in generic arousal responses, and this pattern is abnormal in schizophrenia patients. Autonomic abnormalities in unaffected first-degree relatives seem restricted to the parasympathetic division of the ANS.

Key Words: schizophrenia, social cognition, autonomic nervous system, endophenotype

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Schizophrenia is a syndrome characterized by the appearance, usually in adolescence or early adulthood, of thought, perception, and behavioral symptoms that result in devastating consequences for the individual's cognitive and social functioning. The etiology of schizophrenia is unknown, although it is widely accepted that a coincidence of heritable predisposing factors and environmental stressors is necessary to produce the disease.[1,2]

Autonomic nervous system activity, the major mediator of bodily responses to stress and emotion, has been shown to be abnormal both in resting conditions[3–5] and in response to the induction of psychological stress[6] in individuals with schizophrenia. It has recently been suggested that some of these abnormalities are shared by unaffected family members of afflicted persons, especially in the parasympathetic division of the autonomic nervous system.[7,8] In higher-order primates, including humans, emotion is closely related to social behavior, and disturbances in emotional regulation are difficult to separate from abnormal social adjustment.[9–11] This question bears a special heuristic value in schizophrenia, given the incapacitating potential of compromised social functioning. Many patients have impairment in their social skills for months to years before the onset of more obvious symptoms. This impairment remains largely refractory to available treatments, and it persists as the main barrier for

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patients' reintegration in society once their acute symptoms have abated.[9,12–14]

It is a subject of debate whether "generic" emotion processing and social cognitive processing represent distinct brain operations,[9,11,15] recruiting in turn different arousal responses, proposed to be critical bodily markers in decision making[16] and paranoid cognition processes.[17] The issue is particularly important in schizophrenia, whose most consistent brain morphologic abnormalities relate to reduction in cortical volume and thickness, with abnormalities of white matter connectivity in frontotemporal and cingulate areas.[18,19] These areas are known to be involved in the regulation of social behavior, emotion processing, and visceral function.[20,21]

Some of these structures are related to the network involved in social cognition, which primarily includes the fusiform gyrus and superior temporal sulcus (involved in face processing), the medial prefrontal cortex (involved in theory of mind), and the amygdala, which subserves emotion processing and social decision making and is involved in regulation of visceral/autonomic responses.[22] We hypothesized that abnormalities in the cerebral network subserving social cognition would be reflected in altered autonomic responses to social cognitive tasks in patients with schizophrenia and, on the basis of a previous study demonstrating alterations in social cognition performance in their first-degree relatives, that the relatives would also display abnormal autonomic activity in such settings. On the basis of previous studies documenting enhanced activation in different parts of this social cognition brain network,[23,24] we predicted that patients with schizophrenia would reveal more intense visceral responses to social cognition tasks. We also expected that their first-degree relatives would reveal similar partial abnormalities, as previously shown in autonomic nervous system studies using different stimulation paradigms.[7,8]

We used heart rate variability (HRV) analysis, a noninvasive tool that can measure vagal and sympathetic influences on the heart,[25] to probe peripheral autonomic activity. We used the Benton Facial Recognition Test[26] to ascertain participants' capacity for generic facial discrimination, to make sure that differences in performance during visual or social cognition tests were not caused by deficits in general capacity to discriminate facial features. In the analysis of autonomic activation, we used HRV during this task as a control condition.

MATERIALS AND METHODS

This was a cross-sectional study of HRV changes induced by social cognitive tasks in persons with schizophrenia, their unaffected first-degree relatives, and comparable healthy controls.

Participants

All participants were assessed at the Cognitive Neurology Section and the Psychiatry Department at FLENI Hospital, Buenos Aires. All participants gave written informed consent, as approved by the local bioethics committee.

Patients

Outpatients were invited to participate in the study if they (a) had received a *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR) diagnosis of schizophrenia, any subtype, confirmed with a Composite International Diagnostic Interview[27] administered by a consultant psychiatrist (E.Y.C.); (b) were aged 18 to 75 years; and (c) had been on the same medication regimen for at least 2 weeks. Exclusion criteria were (a) history of substance misuse (alcohol or illicit drugs) in the previous 6 months; (b) active symptoms having recently (< 2 wk) warranted antipsychotic dose adjustment or admission to the hospital, day hospital, or intensive outpatient treatment; (c) mental retardation; or (d) cardiac or neurological problems potentially confounding HRV analyses (including nonsinus rhythm or > 10 abnormal beats per minute, and causes of autonomic neuropathy or central dysautonomia such as idiopathic Parkinson disease or diabetes). Current symptom severity was assessed with the Positive and Negative Symptom Scale.[28] One patient from the recruited sample was not included because the heart rate recording could not be analyzed for technical reasons. A total of 19 patients with schizophrenia (7 female, age 29.7 ± 9.2 y, range, 19 to 55 y) were included in the study. Two patients were siblings.

Relatives

We recruited 19 first-degree biological relatives of the study patients who had schizophrenia. The relatives were from 16 families: 5 mothers, 4 fathers, 5 sisters, and 5 brothers (age, 51 ± 18.8 y; range, 21 to 75 y). Exclusion criteria were (a) lifetime diagnosis of any DSM-IV-TR Axis I psychotic disorder, as detected by a psychiatric interview with a consultant psychiatrist (E.Y.C.); (b) current treatment with antipsychotics, antidepressants, or mood stabilizers; or (c) the same cardiovascular and neurological causes of dysautonomia listed for patients in (d) above. One relative was excluded from the originally recruited sample because the heart rate recording was technically faulty.

Controls

Healthy controls were recruited from among attendees at free community health promotion lectures that had been advertised through posters and the media. Some controls were staff and some were colleagues at other institutions who volunteered to participate. Exclusion criteria were (a) a lifetime diagnosis of any DSM-IV-TR Axis I anxiety, mood, or psychotic disorder, as detected by a psychiatric interview with a consultant psychiatrist; (b) a lifetime medication history of antidepressants, antipsychotics, or mood stabilizers; and (c) history of cardiac or neurological problems potentially confounding HRV analyses (including nonsinus rhythm or > 10 abnormal beats per minute, and causes of autonomic neuropathy or central dysautonomia). We recruited a patients control group (n = 19, 8 female patients; age, 27.6 ± 6 y; range, 20 to 47 y) and a relatives control group (n = 19, 10 female individuals; age, 46.1 ± 17.9 y;

range, 25 to 69 y), so the experimental groups would be more closely matched. Participants were not taking over-the-counter or antiparkinsonian anticholinergic agents, or the cardiovascular medications α-blockers, β-blockers, or angiotensin-converting enzyme inhibitors.

Social Cognition Tasks

We used the Spanish versions of the Faces Test, Reading the Mind in the Eyes Test, Faux Pas Test, and Theory of Mind (ToM) Stories Test, as provided by their authors.

Mental Activation Control Task

The Benton Facial Recognition Test[15,26] is properly described as "visuoperceptual discrimination of unfamiliar faces," as opposed to recognition of facial identity, as its name suggests.[29] The Facial Recognition Test measures ability to recognize neutral/nonemotional faces by requiring the subject to select from a set of six 2×3-inch aligned black and white photographs the face with the same identity as the reference face.[30] Six items require 1 identity recognition response, and 16 items require 3 identity recognition responses. There is evidence that Facial Recognition Test performance is related to right hemisphere processing.[29] As no social cognition or Theory of Mind processes are known to be involved in this task, and as the test generates a generic stress condition equivalent to the social cognition tests, we used the Facial Recognition Test as a control task.

Visual Tests of Social Cognition

The Baron-Cohen Faces Test[31] consists of 20 photographs of the frontal face of an actress displaying different facial expressions, photographed under controlled and standardized lighting conditions. Each picture has 2 labels, giving participants a choice between 2 emotions (1 correct, 1 incorrect). We selected the label pairs out of a group of 20 emotions, and arranged them pseudorandomly. The participants were asked to identify the label that most appropriately described the actress's "thinking or feeling" mental state.

This test was immediately followed by the Baron-Cohen Reading the Mind in the Eyes Test,[32] in which participants were shown 36 photographs of the eyes of different actors, presented one at a time in a fixed order. Each pair of eyes was associated with a choice of 4 emotion labels (1 correct) from among a variety of emotions, arranged pseudorandomly. The participants were again asked to identify the verbal label that most appropriately described the actor's "thinking or feeling" mental state.

Verbal Tests of Social Cognition

The Faux Pas Test[33] contained 20 stories, of which half included a social faux pas and half did not. The stories were presented 1 at a time. The text of each story was printed on a single page and placed in front of the participant. The tester read the story aloud and then asked a series of questions about it. We quantified correct detections of unintentional Faux Pas (hits), correct rejects (ie, detection of non Faux Pas stories), and control questions designed to assess comprehension of the story.[34]

The Happé's ToM Stories Test[35,36] consisted of 16 short stories, half of them invoking ToM and the other half referring to physical causation (non-ToM). The ToM stories involved interaction between people and contained double bluff, mistakes, persuasion, or white lies, with 2 examples of each type presented. Each ToM story was followed by a question testing the participant's ability to make inferences about mental states, usually the actor's intentions.

Testing Session

All participants were tested between 9 AM and 2 PM, 2 to 4 hours postprandial, having abstained from smoking for 2 hours, having not consumed caffeinated beverages for at least 6 hours, and having not performed strenuous physical exercise for 24 hours. Testing was done with participants seated in a quiet room. After 10 minutes of resting time, we began the tests and the HRV recording session. We administered these blocks in a random sequence: (1) baseline rest, (2) the Facial Recognition Test, (3) the Faces Test and Reading the Mind in the Eyes Test, (4) Faux Pas Test, and (5) Happé's ToM Test. Throughout the session, we monitored the participant's respiratory rate visually to verify that it was between 0.15 and 0.4 Hz. For details on the testing sessions, see De Achával et al.[15]

HRV Analyses

We analyzed HRV on recordings of successive RR intervals of sinus node origin, as described previously.[25,37] Participants were connected to an electrocardiographic interphase that detected R-waves sampled at 1250 Hz in a surface electrocardiographic signal (as obtained from a DI, V4, or V5 lead) and fed into a computer that stored RR intervals (VariaDat HRV package, University of Entre Ríos School of Bioengineering, Argentina). Premature and lost beats were individually identified in the entire file of RR intervals. These abnormal beats were replaced with RR intervals resulting from linear interpolation.[25] Time domain (nonspectral) and frequency domain (spectral) measures of HRV were obtained.[25]

Time domain measures of HRV included mean RR interval (RR) and standard deviation of all normal RR intervals (SDNN), which estimates global HRV mediated by both sympathetic and parasympathetic influences on the sinus node. Frequency domain measures of HRV, quantified through fast Fourier transform, included low-frequency power (LF, 0.04 to 0.15 Hz) and high-frequency power (HF, 0.15 to 0.4 Hz). HF-HRV is a measure of the respiratory sinus arrhythmia; hence, it reflects solely parasympathetic influences onto the sinus node.[25] LF-HRV originates in modulation of heart rate by Mayer waves of blood pressure via the baroreceptor reflex. Thus, LF-HRV depends on both sympathetic and parasympathetic input to the sinus node, although in most instances it mainly reflects cardiac sympathetic

activity.[38,39] Important exceptions include physical exercise and congestive heart failure, characterized by marked vagal withdrawal and increased sympathetic activity.[39] We report absolute values (in ms^2) and proportion of total HRV of each component. Changes in HRV in relation to baseline are informed in terms of proportion of total HRV, to facilitate comparison between groups, because when spectral components of HRV are expressed in absolute terms, the changes in total power influence HF and LF in the same direction and prevent the precise appreciation of the fractional distribution of the energy attributable to vagal and sympathetic influences.[25]

Statistical Analysis

Discrete variables in patients, their relatives, and the controls were compared using the χ^2 test. After determining normal distribution of data with a Kolmogorov-Smirnov test, we compared demographic variables and test scores with a 1-way analysis of variance, followed by a post hoc Tukey test. A repeated-measures analysis of variance was carried out using participants group and social cognition task as factors to establish the influence of type of test and diagnosis on observed results of autonomic function, both in comparison with baseline resting conditions and when compared with the control task, using a post hoc Tukey test to compare the different groups. The effect of each social cognitive test on HRV measures as compared with baseline resting status in each group was studied with the Wilcoxon test. The Pearson correlation test was used to explore the correlations between performance in social cognition tests and HRV measures during those tests in patients with schizophrenia, unaffected relatives, and controls. Significance was assumed at $\alpha < 0.05$ and all reported results are 2 tailed. SPSS v13 software was used for all statistical analyses.

RESULTS

Patients were similar to their matched controls in age and sex, but they had fewer years of formal education (Table 1). One patient was receiving atenolol. Participants in the other groups were not receiving medications that could affect autonomic nervous system activity. Absolute measures of HRV in resting conditions were lower in patients than in comparable controls. Standard deviation of all sinus beats (SDNN, a measure of global HRV) and both major spectral components of HRV (LF and HF) were smaller in patients with schizophrenia. In contrast, fractional distribution of each component, expressed as a proportion of total HRV, showed no differences between patients and their controls.

Table 2 shows that unaffected relatives of the patients with schizophrenia were similar to their controls in all respects except years of education. In contrast, they demonstrated deficits in the performance of a series of social cognitive tests, including the Faces Test, Reading the Mind in the Eyes Test, and hits and control questions of the Faux Pas Test. In baseline resting conditions, the relative contribution of HF-HRV to total HRV was larger in unaffected relatives than in controls. The relatives' absolute values of global HRV (measured as SDNN) and HF-HRV and LF-HRV were indistinguishable from the controls.

TABLE 1. Patients and Patients' Controls: Characteristics and Baseline Heart Rate Variability Values

	Patients (n = 19)	Patients' Controls (n = 19)	*P*
Age (y)	30 ± 9	28 ± 6	0.965
Female (%)	7 (37)	8 (42)	0.740
Education (y)	13 ± 1	16 ± 2	0.010
Total PANSS	83 ± 21		
Positive subscale	15 ± 5		
Negative subscale	24 ± 9		
Novel antipsychotic (%)			
Clozapine	3 (16)		
Risperidone	8 (42)		
Olanzapine	6 (32)		
Quetiapine	2 (11)		
Antidepressant (%)			
Paroxetine	2 (11)		
Venlafaxine	1 (5)		
Citalopram	1 (5)		
Baseline HRV values			
RR interval (ms)	728.35 ± 106.07	784.44 ± 108.15	0.128
SDNN (ms)	33.00 ± 20.55	56.11 ± 22.30	0.002
LF (ln)	4.96 ± 1.53	6.39 ± 0.79	0.002
LF (% of total)	0.47 ± 0.15	0.40 ± 0.26	0.559
HF (ln)	3.96 ± 1.85	5.39 ± 1.08	0.017
Social cognition test performance			
FRT	23.2 ± 2.6	24.7 ± 1.7	0.196
Visual tests			
"Faces" Test	17.4 ± 1	18.4 ± 1.2	0.326
"RME" Test	24.3 ± 4.9	27.4 ± 3.9	0.285
"Faux Pas" test			
Hits	49.4 ± 10.8	56.1 ± 5.6	0.143
Rejects	18.9 ± 1.8	19.9 ± 0.5	0.087
Control questions	37.1 ± 3	38.9 ± 1.1	0.161
ToM stories test			
ToM stories	11.5 ± 2.2	12.9 ± 2	0.161
Non-ToM stories	11.8 ± 3.4	13.7 ± 1.9	0.105
Total score	23.2 ± 5.6	26.6 ± 3	0.061

Shown are mean ± standard deviation or number of subjects (% of total).

FRT indicates Facial Recognition Test; HF, high-frequency heart rate variability (0.15-0.4 Hz); HRV, heart rate variability; LF, low-frequency heart rate variability (0.04-0.15 Hz); PANSS, Positive and Negative Symptom Scale; RME, Reading the Mind in the Eyes; SDNN, Standard deviation of normal heart beats; ToM, Theory of Mind.

Figure 1 (top panel) shows changes in the average RR interval induced by the control task of general facial recognition capacity, and 3 visual or verbal tests of theory of mind, in patients with schizophrenia, their unaffected first-degree relatives, and the controls for each experimental group. For the tested subjects as a whole, RR interval was affected by the type of social cognitive task ($F = 6.058$, $P = 0.001$). All tasks induced a significant shortening of RR (ie, an increased heart rate) in unaffected relatives, but not in patients with schizophrenia. Total HRV, as measured by SDNN, changed with the type of task ($F = 24.9$, $P < 0.001$) and depended on the participants' group ($F = 4.436$, $P = 0.007$). Post hoc analysis revealed that the patients differed significantly from their controls ($P = 0.002$). SDNN increased in the patients during verbal ToM tests but not during visual

TABLE 2. Relatives and Relatives' Controls: Characteristics and Baseline Heart Rate Variability Values

	Relatives (n = 19)	Relatives' Controls (n = 19)	*P*
Age (y)	51 ± 19	46 ± 18	0.700
Female (%)	10 (53)	10 (53)	1.000
Education (y)	11 ± 4	16 ± 5	0.003
Baseline HRV values			
RR interval (ms)	842.47 ± 91.94	811.70 ± 95.19	0.249
SDNN (ms)	33.67 ± 12.65	39.65 ± 19.93	0.557
LF (ln)	5.07 ± 1.17	5.72 ± 1.29	0.220
LF (% of total)	0.43 ± 0.16	0.31 ± 0.26	0.213
HF (ln)	4.30 ± 1.10	4.50 ± 1.21	0.955
HF (% of total)	0.23 ± 0.12	0.11 ± 0.10	0.006
Social cognition test performance			
FRT	21.8 ± 3.0	23.2 ± 2.6	0.268
Visual tests			
"Faces" test	16.5 ± 2.9	18.1 ± 1.6	0.041
"RME" test	20.4 ± 6.4	25.7 ± 5.4	0.014
"Faux Pas" test			
Hits	46.6 ± 13.5	56.7 ± 4.2	0.009
Rejects	19.3 ± 1.4	19.8 ± 0.6	0.567
Control questions	36.0 ± 4.3	38.8 ± 1.2	0.012
ToM stories test			
ToM stories	12.1 ± 2.0	13.3 ± 1.5	0.228
Non-ToM stories	12.3 ± 2.6	14.1 ± 2.0	0.152
Total score	24.4 ± 4.4	27.4 ± 2.8	0.117

Shown are mean ± standard deviation or number of participants (% of total).
FRT indicates Facial Recognition Test; HF, High-frequency heart rate variability (0.15-0.4 Hz); HRV, heart rate variability; LF, Low-frequency heart rate variability (0.04-0.15 Hz); RME, Reading the Mind in the Eyes; SDNN, Standard deviation of normal heart beats; ToM, Theory of Mind.

ToM tests, as compared with resting conditions (Fig. 1, bottom panel). In relatives, SDNN remained similar to resting conditions throughout testing. Tests involving faces (Facial Recognition Test and visual ToM tests) brought about decreases in total HRV in both control groups, and one of the verbal ToM tests (Happé ToM Stories Test) produced modest albeit significant increases in total HRV as measured by SDNN.

Figure 2 depicts changes from baseline resting conditions induced by general facial recognition and social cognition tasks in HF-HRV (top panel) and LF-HRV (bottom panel), expressed as a proportion of total HRV. HF-HRV displayed intrasubject variability, depending on the social cognitive task ($F = 9.861$; $P < 0.001$), and was affected by the diagnostic group ($F = 4.765$; $P = 0.005$), such that patients ($P = 0.005$) and their unaffected relatives ($P = 0.023$) were different from their respective control groups. In the patients, HF-HRV decreased from baseline in all tests, whereas in their relatives HF-HRV displayed a significant withdrawal from baseline in all tests except facial recognition.

In the sample as a whole, LF-HRV variation was explained both by the cognitive task ($F = 5.551$; $P = 0.002$) and by the experimental group ($F = 3.010$; $P = 0.037$); post hoc analysis revealed that unaffected first-degree relatives were different from their controls ($P = 0.025$). When compared with baseline rest, LF-HRV in the patients with schizophrenia decreased in the Facial Recognition Test, visual ToM tasks, and Faux Pas Test, but not in the Happé ToM Test, and the LF-HRV showed no changes compared with resting conditions in their unaffected first-degree relatives.

In the controls, social cognitive tasks induced no significant changes in HRV of parasympathetic (HF) or baroreflex (LF) origin when compared with baseline resting conditions.

Figure 3 depicts changes in LF-HRV and HF-HRV values during testing compared with the control task. A significant effect of task on HRV changes was observed in LF-HRV (top panel, $P = 0.001$, effect size 0.164) and in HF-HRV (bottom panel, $P < 0.001$, effect size 0.3). A significant task × diagnosis interaction was found for LF-HRV only ($P = 0.022$). Post hoc analysis determined that the increase was higher in the patients with schizophrenia than in their controls during the ToM test ($P = 0.029$).

Figure 4 shows the correlations observed between performance in social cognition tests and HRV measures obtained whereas the tasks were being carried out. Controls displayed a significant relationship between parasympathetic activity and performance in the Faux Pas Test (top panel), whereas patients exhibited a negative correlation between ToM test performance and RR interval length (bottom panel). Even though previously published data from our group and others have suggested that social cognitive performance is lower in patients and their unaffected relatives than in controls, in the present sample this difference failed to reach statistical significance.

DISCUSSION

The main findings of this study were that (1) in patients with schizophrenia, a variety of social cognition tasks induce distinct changes in peripheral autonomic nervous system activity, in the form of abnormal decreases in both HF-HRV and LF-HRV, and (2) in first-degree relatives of individuals with schizophrenia, such abnormalities are largely restricted to HF-HRV, a specific measure of parasympathetic traffic to the heart. This study also replicates previous observations of global decreases in baseline HRV in individuals with schizophrenia,[3–6] with a maintenance of the proportion of vagal and sympathetic contributions to total HRV in resting conditions in both patients and their unaffected relatives, compared with controls.

The pattern of autonomic response to social tasks that we observed in our patients and their relatives does not seem to represent a particular case of the general arousal phenomenon induced by stress, that is, one of vagal withdrawal and increased sympathetic output, represented by decreases in HF-HRV and decreases in LF-HRV, respectively. In this regard, we recently showed that patients with schizophrenia and their unaffected first-degree relatives had a normal autonomic response to mental stress. However, patients displayed a sustained autonomic pattern characteristic of stress exposure even after the stimulus ceased.[6] Among their unaffected relatives, this abnormality was seen only in the parasympathetic division of the autonomic nervous system.[8]

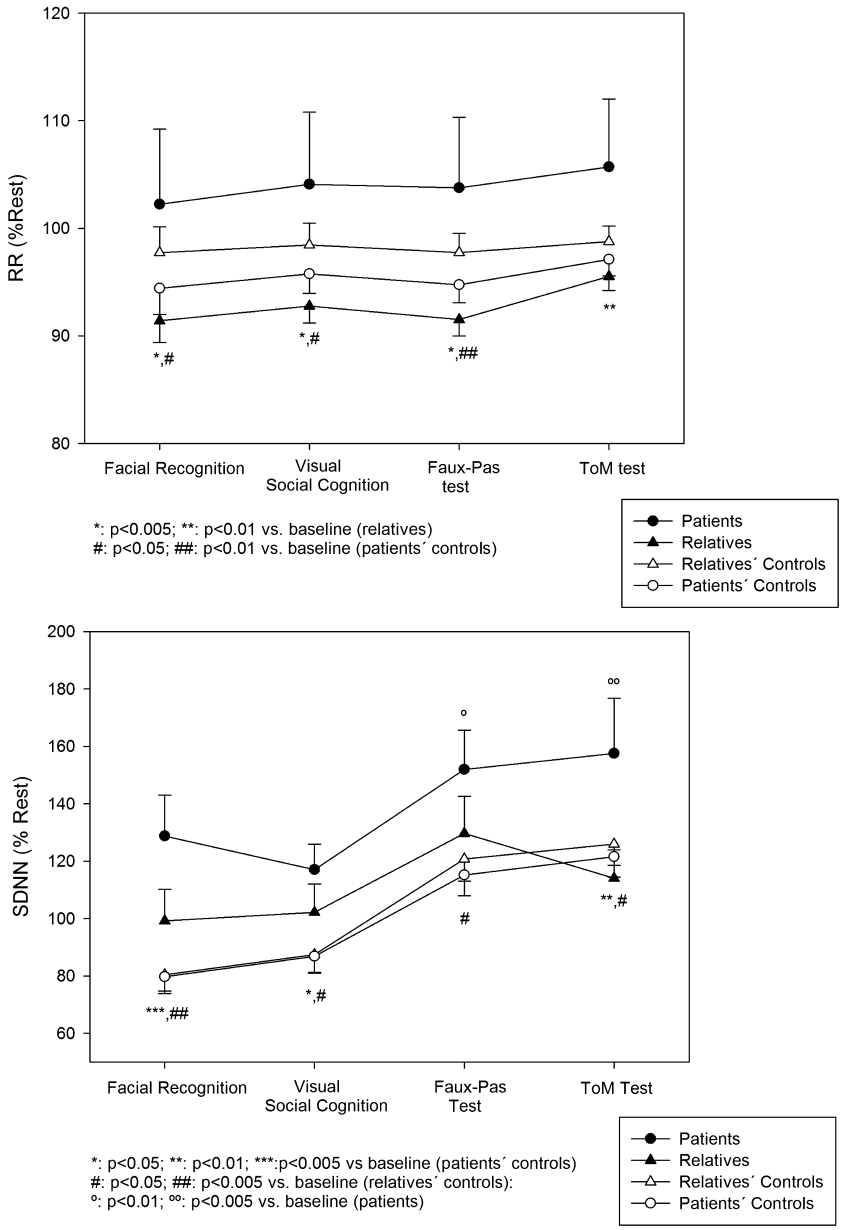

FIGURE 1. Changes in average RR (top panel) and SDNN (bottom panel) induced by social cognition tasks in patients with schizophrenia, their nonpsychotic first-degree relatives, and healthy controls matched to each group. RR indicates average normal RR interval; SDNN, standard deviation of all normal heartbeats; ToM, theory of mind.

Our current results are distinct from our recent observations on the autonomic response to stress, in that both the patients and their relatives displayed a decrease in HRV during most social tasks. In patients, both HF-HRV and LF-HRV decreased during social cognition tests (with the exception of LF-HRV during the Happe ToM test). The same abnormality was observed in unaffected relatives, but was entirely restricted to changes in HF-HRV, suggesting abnormal parasympathetic input to the heart.

Regardless of the specific pattern of autonomic changes in response to social stimuli, our current results add to mounting evidence in a variety of conditions and experimental paradigms that patients with schizophrenia show widespread autonomic function abnormalities, whereas their unaffected relatives manifest autonomic function disturbances restricted to the parasympathetic division of the autonomic nervous system.[7,8,40] However, the differences in autonomic activation during these stimulation paradigms, in contrast to generic mental stress, suggest that the abnormalities that we found in this study cannot be regarded as a general stress response in patients with schizophrenia and their unaffected relatives, irrespective of the "arousing" stimuli that they are given. Rather, the autonomic activity alterations are specific, varying with the

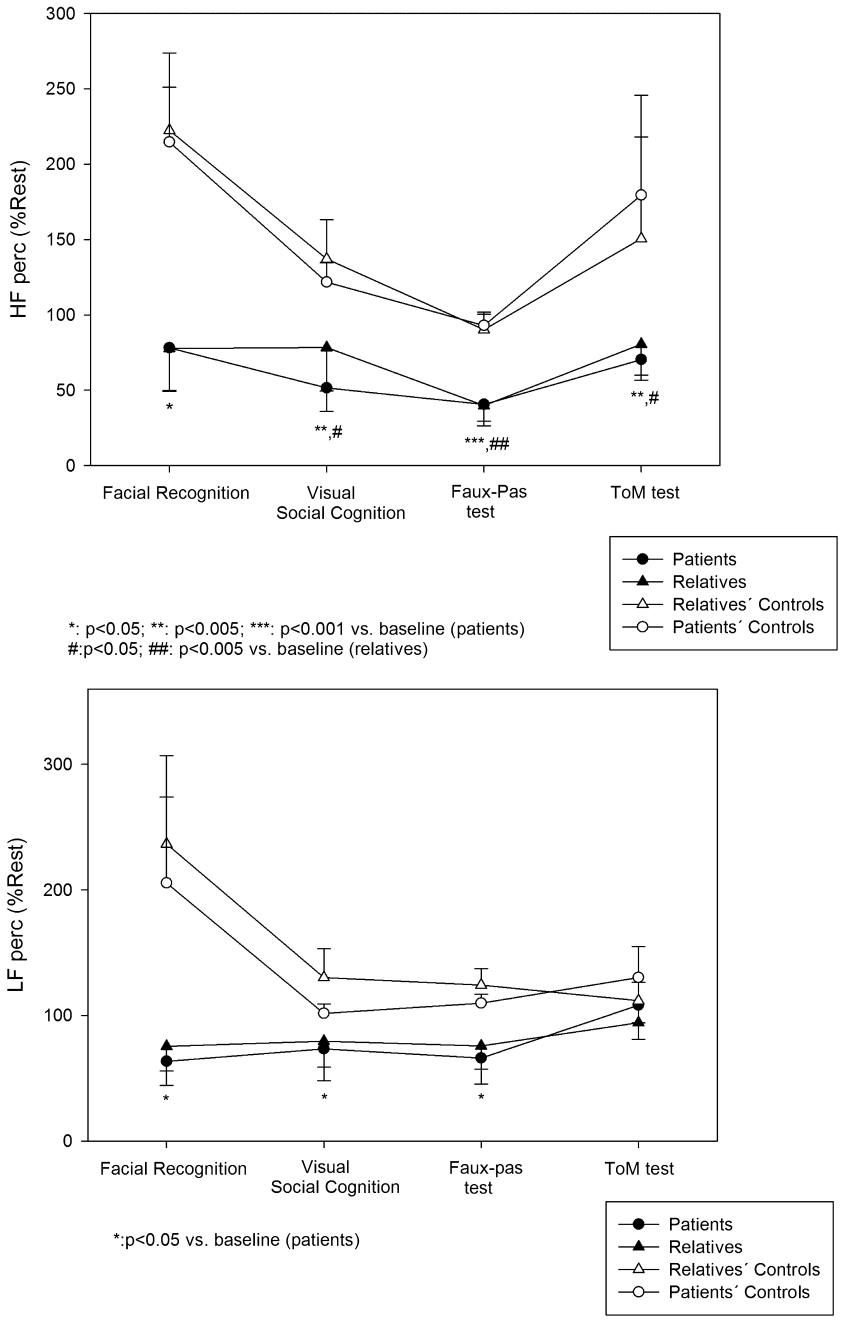

FIGURE 2. Changes in heart rate variability subcomponents in response to social cognition tasks in patients with schizophrenia, their unaffected first-degree relatives, and healthy controls matched to each group. The top panel shows changes in HF-HRV and the bottom panel shows changes in LF-HRV. HF perc indicates percentage of total heart rate variability due to high-frequency (0.15 to 0.4 Hz) variability; LF perc, percentage of total heart rate variability due to low-frequency (0.04 to 0.15 Hz) variability; ToM, theory of mind.

nature of the stimuli. In this context, our finding of an increased proportion of HF-HRV at baseline among relatives is intriguing and has not been observed in other studies; it could represent a compensatory mechanism for their parasympathetic dysfunction.

The abnormalities that we found in autonomic activation during the facial recognition control task and the visual and verbal ToM tests in patients and their relatives also showed some specificity to the test being used. In a recent report, we had observed that performance on some social tasks distinguished patients, their first-degree relatives, and controls, whereas performance on others was normal for all groups. The relatives were shown to have deficits on visual tests of social cognition—deficits that, surprisingly, were not shared by the patients themselves. In contrast, both patients and their unaffected relatives

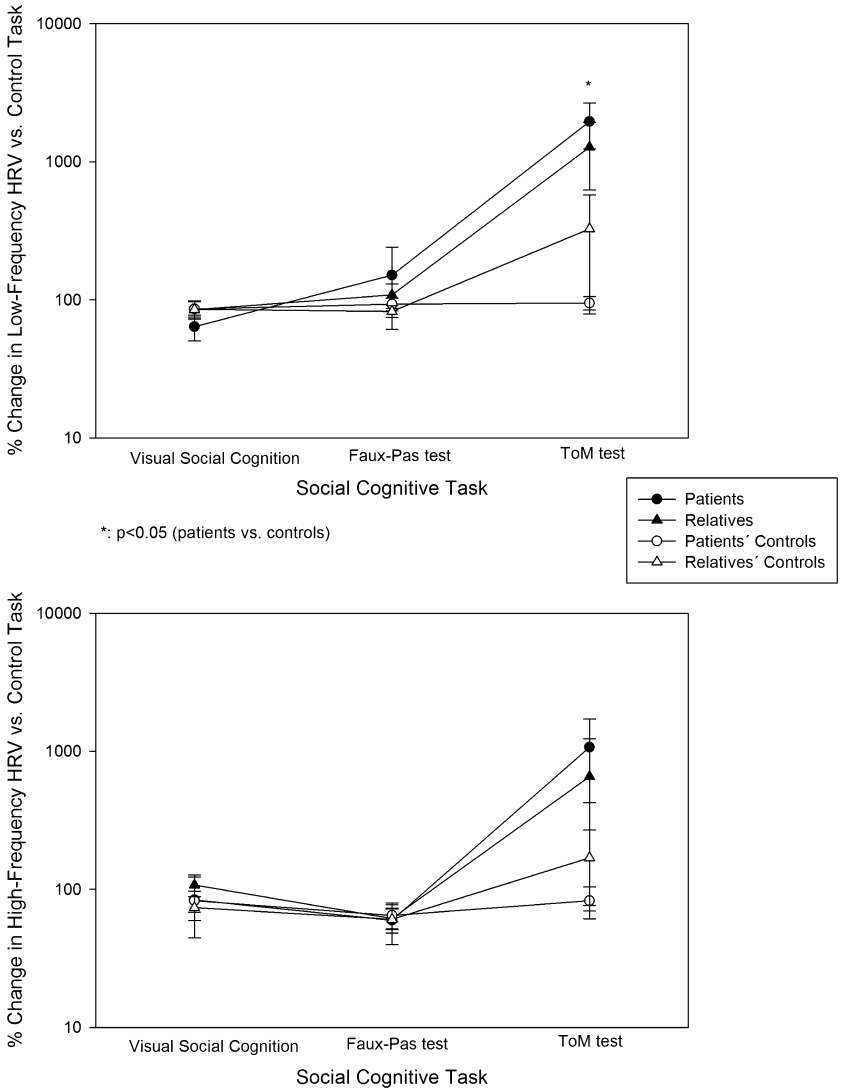

FIGURE 3. Changes in heart rate variability subcomponents in response to social cognition tasks as compared with a control task (Benton Facial Recognition Test), in patients with schizophrenia, their nonpsychotic first-degree relatives, and healthy controls matched to each group. Top panel shows changes in LF-HRV and bottom panel shows changes in HF-HRV. HF-HRV indicates heart rate variability due to high-frequency (0.15 to 0.4 Hz) variability; LF-HRV, heart rate variability due to low-frequency (0.04 to 0.15 Hz) variability; ToM, theory of mind.

showed specific deficits in their ability to detect social gaucheries in the Faux Pas Test.[15] Our current results do not seem to show a direct relationship between performance by either experimental group in the social cognition tasks, and arousal responses evoked by them. Instead, autonomic changes induced by social cognition tasks in the patients with schizophrenia encompassed both vagal and baroreflex abnormalities (even in those tests in which this group had not shown impaired performance), whereas their relatives' abnormalities were restricted to the vagal system, even on tests in which their performance was poor compared with controls.[15]

Autonomic activity has classically been seen as a balance between parasympathetic and sympathetic influences on target peripheral organs, so that when one increases the other decreases, and vice versa.[41] Although such a balance has been observed in some studies assessing how general stress affects autonomic activity in schizophrenia,[6] in this study both HF-HRV and LF-HRV decreased compared with baseline resting conditions. Situations in which both HRV components are noted to decrease simultaneously include strenuous exercise and congestive heart failure, which are characterized by parasympathetic withdrawal and markedly increased sympathetic output onto the cardiovascular system.[25,42] In these conditions, respiratory sinus arrhythmia (the origin of HF-HRV) and baroreflex modulation of the heart rate (the origin of LF-HRV, which has sympathetic and parasympathetic components) both decrease.

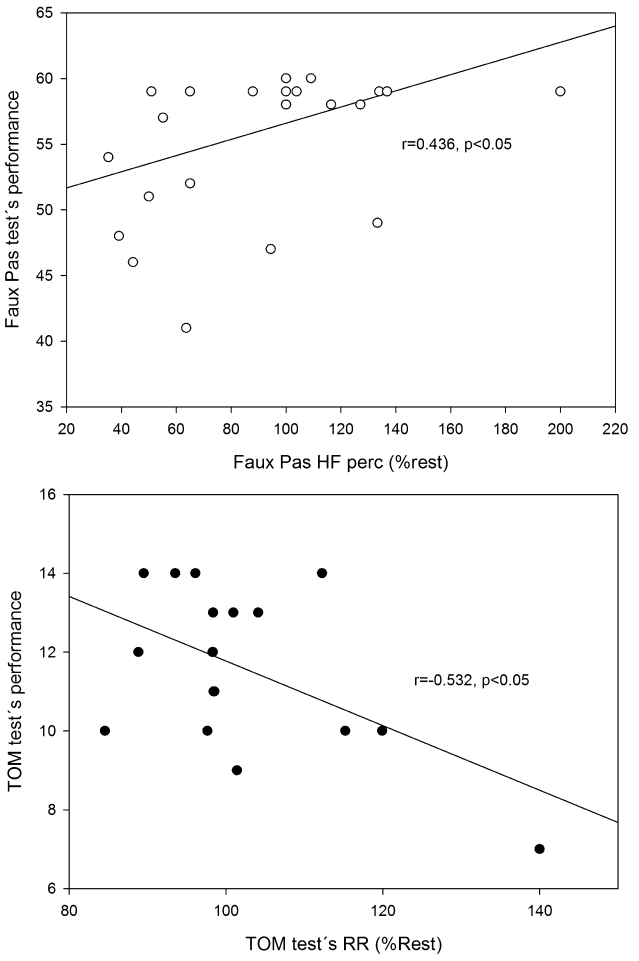

FIGURE 4. Correlations between social cognition performance and heart rate variability measures in patients with schizophrenia and healthy controls. Top panel shows the correlation between Faux Pas Test performance and Faux Pas HF perc values in controls. Bottom panel shows the correlation between ToM Stories Tests performance and ToM Stories Test's RR interval in patients. HF perc indicates percentage of total heart rate variability due to high-frequency (0.15 to 0.4 Hz) variability; RR, average normal RR interval; ToM, theory of mind.

It is possible that exposure to social tasks induces in patients with schizophrenia an autonomic profile similar to that in situations characterized by intense autonomic arousal, whereas in their relatives the abnormalities are restricted to the parasympathetic system, or else both groups show marked parasympathetic withdrawal alone (which would account for decreased HF-HRV and decreased LF-HRV at the expense of the parasympathetic component of the latter). In either case, the autonomic responses in this study were not encompassed by the traditional view of stereotyped autonomic activity that involves a general arousal response.

Autonomic nervous system response to social cognitive tasks seems to be a particular case of stimulus-specific peripheral autonomic responses, as has been demonstrated in a variety of other conditions.[20,43,44] In particular, a number of factors could explain the relationship between parasympathetic activity and social cognitive performance in healthy controls, and between higher sympathovagal balance (expressed as higher heart rate) and poorer social cognitive performance in patients. Nonspecific arousal might be related to attentional and other cognitive abilities. For example, we recently demonstrated that autonomic status explains decision-making abilities in some paradigms in healthy individuals.[45] However, the fact that in this study we found this relationship only for some tests and some experimental groups, suggests that specific mechanisms come into play, deserving further study.

A number of limitations of this study should be mentioned. First, all of the patients were receiving medication, which could have affected the HRV results. The patients and their relatives had less formal education than the controls; this could make it difficult to interpret differences observed between groups. In addition, because participants could not smoke for 2 hours before the testing session, their autonomic activity might have been affected. However, smoking abstinence is characterized by an increase in vagal cardiac control,[46] and the patients group had lower HF values at rest than did their controls. Unlike methods such as galvanic skin response, HRV does not probe sympathetic activity specifically, and, as mentioned, physiological variation in health and disease may be characterized by high sympathetic output, resulting in low LF-HRV. In addition, in this study we compared autonomic activation related to social cognitive tasks with resting conditions, not with a test of "generic" stress, as our group's previous studies have done [6,8]

In summary, our results add to the burgeoning evidence that autonomic nervous system activity is abnormal in both patients with schizophrenia and their unaffected first-degree relatives in a variety of paradigms, and that such dysfunction constitutes a potential endophenotype to guide genetic probing of susceptibility to schizophrenia. Although most patients' abnormalities affect both major divisions of the autonomic nervous system, unaffected relatives' deficits have seemed to be restricted to the parasympathetic division, in our study and a variety of previous reports.[3,5,7,8] However, our current results also indicate that in these groups the autonomic nervous system does not operate in a stereotyped manner. Rather, its activation profile depends on the environmental, emotional, and social context. It remains to be determined whether these abnormalities reflect context-specific alterations in brain activity in both patients with schizophrenia and relatives at increased genetic risk. We are using functional brain imaging techniques to establish the degree of overlap in activation of brain structures induced by different social cognition tasks in patients with schizophrenia and their nonpsychotic relatives.

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