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Brain-Heart Link in Schizophrenia: Cognitive Inhibitory Control Deficit in Patients Is Specifically Related to Parasympathetic Dysregulation

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Background: **This study examined the connection between two prominent deficits in schizophrenia: the deficit in parasympathetic regulation and the deficit in cognitive inhibitory control, within the framework of the Neurovisceral Integration Model (NIM).**
Study Design: **Thirty healthy controls and 30 patients with schizophrenia performed the internationally standardized antisaccade protocol while their electrocardiographic data were recorded. The interaction between the group, the cognitive inhibitory control as measured with error rate (ER) in the antisaccade task and parasympathetic activity as measured with the High Frequency power component of Heart Rate Variability (HF-HRV) was tested.**
Study Results: **Findings confirmed that decreased HF-HRV was specifically related to increased ER in patients with schizophrenia. In contrast, patient deficits in other oculomotor function measures such as reaction time and reaction time variability related to volitional movement control and cognitive stability respectively were not linked to the deficit in parasympathetic regulation.**
Conclusions: **Our study validates the theory behind NIM proposing that cognitive inhibition has common physiological substrate with parasympathetic regulation. Future research could test this brain-heart link in other mental disorders especially those with a prominent deficit in inhibitory cognitive function.**

Key words: psychosis/inhibition/heart rate variability/antisaccade/autonomic function/Neurovisceral Integration Model

Introduction

Inhibition is the process of suppressing reflexive and prepotent responses so as flexible and goal-directed behavior to be achieved.[1–3] Inhibitory processes occur at cellular, neurophysiological and behavioral levels, thus including various manifestations for similar yet different features of the same general concept.[3,4] In terms of cognition and behavior one of the most discussed forms of inhibition is "inhibitory/ cognitive control" which refers to the suppression of irrelevant responses or stimuli.[3] Inhibitory control has been linked to optimal functioning of prefrontal cortex and its connection to various subcortical regions from basal ganglia and thalamus to vagus nerve and heart.[1,5–7] Hence, it is considered as a higher-order brain function and it is related to the foundation of complex voluntary behavior.[1,3,6,7]

With consistent evidence from numerous studies, patients with schizophrenia exhibit deficits in inhibitory control.[8,9] The antisaccade task is widely recognized as a consistent and reliable measure of inhibitory control and prefrontal cortical dysfunction in schizophrenia.[10–14] In the antisaccade task participants have to suppress a reflexive saccade toward a visual target and look straight in the opposite direction instead.[15] The percentage of erroneous saccades towards the target (error rate [ER]) in the antisaccade task is related to the frontally mediated inhibitory control and the cognitive and neural mechanisms involved in the volitional control of behavior.[16]

Schizophrenia patients are reported to show increased ER.[10,12,17] This deficit in the inhibitory control of volitional saccades is observed in medicated and treatment-naïve patients, patients with recent onset of the disorder as well as in chronic schizophrenia.[16,18,19]

Along with the deficit in inhibitory control, there is also evidence showing Autonomic Nervous System (ANS) imbalance among patients with schizophrenia with decreased levels of parasympathetic activity.[20] Autonomic balance is produced by the interplay of sympathetic and parasympathetic systems. Both branches of ANS innervate and influence heart with continuous input. As a result, heart rate shows a complex variation, the heart rate variability (HRV). Specifically, hypothalamus, limbic system, and brain stem are involved in the central generation and control of heart rate, and parasympathetic cholinergic vagus nerve is responsible for the peripheral control of HRV.[21] HRV can thus be used to assess sympathetic and parasympathetic activity.[21–23] For instance, individuals with low parasympathetic activity show decreased levels of HRV.[22] A robust measure of parasympathetic activity is the power of the high frequency component of HRV (HF-HRV), which is associated with mechanical changes during respiration and is mediated by the vagus nerve.[24,25]

Findings from studies testing autonomic activity in patients with schizophrenia reveal lower parasympathetic activity (reduced HF-HRV) in medicated and unmedicated, chronic or first-episode patients.[20,23,26,27] Besides, studies comparing levels of HRV in patients with schizophrenia, their first-degree relatives and healthy controls show that both patients and relatives exhibit decreased parasympathetic activity relative to controls.[28,29] The presence of decreased parasympathetic activity in both patients and their first-degree relatives enhances the hypothesis that this feature may be a physiological trait of individuals susceptible for developing schizophrenia.[20]

A connection between HF-HRV and cognitive inhibitory control is proposed by the Neurovisceral Integration Model (NIM).[30] Based on NIM, cortical brain areas that are related to executive functions, such as the medial prefrontal and orbitofrontal cortices, the anterior cingulate, and the insula are interconnected to subcortical areas that are involved in the vagal control of the heart such as the central nucleus of the amygdala, the nucleus solitary tract, the caudal and rostral ventrolateral medulla, the vagal motor neurons in the nucleus ambiguous, and the dorsal vagal motor nucleus, forming a circuit.[31–34] Within this prefrontal cortical-subcortical circuit bidirectional communication exists via certain inhibitory pathways, allowing for selection of optimal responses to environmental demands and achievement of complex goal-oriented behavior.[30,35–38] Therefore, inhibition could be viewed as a feature with both physiological/ autonomic and cognitive/behavioral outcomes.

Put all together, the aim of the current study was to examine the connection between two prominent deficits in schizophrenia—the deficit of cognitive inhibitory control as measured with the increased ER in the antisaccade task and the deficit in parasympathetic regulation as expressed in the reduced HF-HRV. Following NIM, we hypothesized that a special connection would exist between these two deficits as an expression of a common underlying deficit in the prefrontal cortical-subcortical circuit. Hence, we tested the hypothesis that the increased ER in the antisaccade task would be specifically related to the decrease in HF-HRV in patients with schizophrenia. In parallel, we hypothesized that increased antisaccade mean reaction time (RT), increased mean RT for correction saccades after an error, and increased RT intra-subject variability (RT-ISV) that have also been confirmed in patients with schizophrenia showing deficits in the decision processes leading to the initiation of volitional movement[39–41] and cognitive stability,[42] would be unrelated to the reduced parasympathetic activity.

Methods

Sample

The sample consisted of two groups (N = 60). Thirty healthy adults (8 women, 22 men with an average age 27.06 years, SD = 4.96 years and average education level 15.9 years, SD = 1.93 years). Thirty patients with schizophrenia (7 women, 23 men with an average age 28.06 years, SD = 6.77 years and an average education level 13.5 years, SD =1.81years). There was no age ($t_{(58)}$ = .64, P = .52) or gender (X^2 = .09, P = .76) difference between the two groups but the difference for education level was significant ($t_{(58)}$ = 5.05, P < .0001).

Controls were recruited from various faculties of the National and Kapodistrian University of Athens. Patients were recruited from the Psychosis Unit of the Psychiatric Department of the National and Kapodistrian University of Athens at Eginition Hospital and the diagnosis of schizophrenia was confirmed by a trained psychiatrist according to DSM-5 criteria. Exclusion criteria for both schizophrenia patients and controls were low IQ (IQ < 70), neurological disorders or traumatic brain injury, oculomotor dysfunction, cardiovascular and thyroid disorders, medical conditions such as diabetes, treatment with beta-blockers, and antihistaminic medication, as well as the use of any drugs and alcohol 12 h prior to participation.

All patients received antipsychotic medication (mean daily dose in chloropromazine equivalents = 742.22 mg, SD = 510.71) and were in a stable phase of the disorder at the time of recruitment. Six patients received combination of antipsychotic with benzodiazepines and were asked to abstain from benzodiazepines 24 h prior to testing. One patient received combination of antipsychotics with antidepressants and mood stabilizers.

The procedures and measures of the present study were conducted under the approval of the ethics committee of Eginition University Hospital. Participants of both groups were provided with a detailed written and oral explanation of all procedures, and they were included in the study after signing informed consent.

Procedure

Testing took place in a quiet room in the Laboratory of Cognitive Neuroscience and Sensorimotor Control. Participants sat on an adjustable chair behind the eye-movement setup. Three surface electrodes were attached to the chest to obtain electrocardiographic (ECG) data. After quality of the ECG signal was checked, participants were asked to sit comfortably for the 5-minutes recording of baseline HRV. After that, task instructions were given, and participants positioned their heads on a chin rest at 74 cm in front of the computer monitor (17-inch) where stimuli were presented. After calibration and check of eye-movement data quality, participants performed the task which included five blocks of a total of 240 trials. There was 1-minute break between blocks and after each break calibration followed. After task completion, there was a recovery phase of 5 min where participants were asked to sit comfortably and relax. Participants also completed the visual analog stress rating scale before baseline, in the middle of task performance and after recovery.

Stimuli were presented using the E-Prime 3.0 software (Psychology Software Tools, Pittsburgh, PA). Eye movements were recorded from the right eye only using the ISCAN ETL-200 eye-tracking camera. Eye-movement data were sampled at 240 Hz and stored on the computer hard drive for offline data processing.

The task followed the internationally standardized antisaccade protocol[43] including 15 prosaccade practice trials followed by one block of 60 prosaccade trials, followed by 3 blocks of 40 antisaccade trials, and finally followed by one block of 60 prosaccade trials.

Each trial started with a central fixation remaining for 1 s that was displaced to the left or right with an amplitude of 10 deg of visual angle and remained on for another second. Targets were black color cross shapes (0.5 deg of visual angle) on a white background. In prosaccade blocks, participants were instructed to fixate the central target and saccade toward the peripheral target location while in the antisaccade blocks participants were instructed to saccade in the mirror location from the peripheral target. Participants were instructed to respond as fast and accurately as possible. The total duration of the task ranged between 25 and 40 min.

Oculomotor Data Processing

Eye movement position data were analyzed using MATLAB-based interactive eye movement analyses tools.[44] Position and velocity signals for the x-position eye displacement were used to define manually in each trial the onset of the first saccade toward the peripheral target in the prosaccade task and compute the RT of the saccade in millisecond. RT of correct antisaccades was measured in the same way. In case of an erroneous prosaccade toward the target in the antisaccade task the RT for the erroneous prosaccade was measured as well as the RT for the first corrective saccade towards the opposite direction from the target after the error prosaccade, if a corrective saccade was made (which was the case in about 99% of the error prosaccades). RT values for prosaccades, correct antisaccades, and error prosaccades were retained if the RT was larger than 80ms, thus excluding predictive saccades.

For each subject the following oculomotor measures were obtained:

1. Mean RT in the prosaccade task (pro-RTM) measured for each block separately and for the 2 blocks merged.
2. SD of RT in the prosaccade task (pro-RTSD) measured for each block separately and for the 2 blocks merged.
3. ER (anti-ER) in the antisaccade task (percentage of erroneous prosaccades) measured for each block separately and for the 3 blocks merged.
4. Mean RT for correct antisaccades in the antisaccade task (anti-RTM) measured for each block separately and for the 2 blocks merged.
5. SD of RT for correct antisaccades in the antisaccade task (anti-RTSD) measured for each block separately and for the 2 blocks merged.
6. Mean RT for error prosaccades in the antisaccade task (anti_er-RTM) measured for each block separately and for the 2 blocks merged.
7. SD of RT for error prosaccades in the antisaccade task (anti_er-RTSD) measured for each block separately and for the 2 blocks merged.
8. Mean RT for corrective saccades in the antisaccade task (anti_cor-RTM) measured for each block separately and for the 2 blocks merged.
9. SD of RT for corrective saccades in the antisaccade task (anti_cor-RTSD) measured for each block separately and for the 2 blocks merged.

ECG Recording and Processing

ECG signals were recorded continuously throughout the experimental procedure including the baseline and recovery periods, at 1024 Hz sampling rate[24] using the ISO-1064CE and CONTROL-1164 Braintronics System, The Netherlands. Three disposable pre-gelled Ag/AgCI electrodes (F55 SKINTACT) were placed in a standard setup: the positive electrode under the right clavicle, the ground electrode under the left clavicle, and the negative electrode on the left lower abdomen. ECG signals were

recorded using a 0.1 s time constant and a 100 Hz low-pass filter. An analog notch filter at 50 Hz was also used. The electrodes' impedance during recording was below 5 kΩ.

ECG data were inspected and analyzed offline using Kubios HRV software (version 3.3.1; Biosignal Analysis and Medical Imaging Group, Department of Applied Physics, University of Eastern Finland, Kupio, Finland). Artifacts and ectopic beats were detected using (1.) time series consisting of differences between successive RR (The time interval between two successive ECG R-waves of the QRS signal) intervals and (2.) time-varying thresholds. Correction of detected artifacts, ectopic/missed beats was applied by interpolation of RR values. The level of corrected beats did not exceed 5% to prevent significant distortion of data.

Following inspection, R-peaks were detected, and a new RR interval time series was formed. The power density spectrum was calculated for the RR interval time series in each time period using fast-Fourier transformation with the Lomb-Scargle method.[45] The logarithmically transformed values of absolute power of HF (0.15 Hz to 0.4 Hz) band were derived as a measure of HF-HRV. HF-HRV was computed for each subject for the baseline period (base_HF-HRV), the 2 prosaccade blocks, the 3 antisaccade blocks, and the recovery period (rec_HF-HRV). HF-HRV was also computed for a merged prosaccade (pro_HF-HRV) and a merged antisaccade (anti_HF-HRV) period using Kubios 3.3.1 procedure for merging time series data.[46]

Statistical Analysis

An initial exploratory analysis was performed using the oculomotor function measures for the merged blocks of the prosaccade and antisaccade tasks as well as the HF-HRV measures compared between patients and controls using *t*-tests and ANCOVA where group was the fixed factor and education level a covariate. False discovery rate (FDR) correction for multiple testing ($N = 9$ tests for oculomotor measures and $N = 4$ tests for HF-HRV measures) was used at $P < .05$.

For the correlation between oculomotor function variables and HF-HRV variables, Pearson correlation analysis was performed separately in control and patient group. FDR correction for multiple testing ($N = 7$ tests) was used at $P < .05$ to detect significant correlations. The Bayesian factors BF_{10} and BF_{01} were also measured for each correlation. The BF_{10} is a measure of the evidence in favor of the alternative hypothesis (that the 2 variables are correlated) against the null (that the 2 variables are not correlated) while BF_{01} is a measure of the evidence in favor of the null hypothesis against the alternative one. For BF calculations we used the JASP 0.1.1.1 software.

Mediation analysis was used to confirm the significant relation of the deficit in ER and the deficit in HF-HRV in patients with schizophrenia. The mediation analysis was performed in SPSS software (V26, IBM SPSS Statistics 2019) with the module PROCESS (v3.5.3).[47] ER was the dependent variable (Y), group (0: healthy controls, 1: patients) was the independent predictor variable (X) and the HF-HRV measure was the mediator variable (M).

Pearson correlations of oculomotor and HF-HRV variables with antipsychotic medication daily dose (chloropromazine equivalents) were performed. A linear regression was also performed using anti_HF-HRV and antipsychotic medication daily dose to predict antisaccade ER (anti-ER).

Results

Exploratory Analysis

Table 1 presents the results for the comparison between patients and controls in oculomotor measures in prosaccade and antisaccade tasks. There were significant deviances in all measures for patients except the mean RT for prosaccades (pro_RTSD) and error prosaccades in the antisaccade task. Table 1 also confirmed a significant decrease in HF-HRV for patients compared to controls in all time periods. HF-HRV measures were highly correlated among different periods (all Pearson correlation coefficients $r > 0.9$). For this reason and to reduce the number of tests, we performed the remaining analyses with HF-HRV values of merged prosaccade (pro_HF-HRV), merged antisaccade periods (anti_HF-HRV) that corresponded directly in time to the oculomotor performance measures, and base_HF-HRV in selected analyses.

Correlation Analysis

Table 2 presents the results of correlation analysis comparing the oculomotor function parameters that showed significant difference between patients and controls to HF-HRV measures. Only the correlation of anti-ER with anti_HF-HRV in the patient group was significant, had large effect size ($r > 0.5$) and the BF provided strong evidence in favor of the hypothesis that these variables were correlated (figure 1). All other correlations were not significant, had small effect sizes ($r < 0.3$) with the largest one being the correlation of anti-ER to anti_HF-HRV in the control group (figure 1). The BF for these correlations provided either anectodal or moderate evidence in favor of the hypothesis that these variables were not correlated (see also Supplementary Figures 1–6). Replacing anti_HF-HRV with base_HF-HRV in the correlation with anti-ER in the patient group resulted in smaller but still significant correlation (Pearson $r = -0.479$, $P = .007$).

Table 1. Oculomotor Function and HF-HRV Variable Differences Between Patients and Controls

	Controls Mean (SE)	Patients Mean (SE)	*t*-value (*df*) (*P*)	*F*-value (*df*) (*P*)
Prosaccade task				
Pro-RTM	187 (4)	200 (6)	1.78 (58) (.079)	1.93 (57) (.169)
Pro-RTSD	39 (4)	55 (4)	2.9 (58) (.005*)	4.90 (57) (.031*)
Antisaccade task				
Anti-ER	19.6 (3.3)	34.4 (4)	3.0 (58) (.004*)	8.17 (57) (.006*)
Anti-RTM	278 (5)	325 (12)	3.6 (58) (.0006*)	9.48 (57) (.003*)
Anti-RTSD	46 (2)	80 (6)	5.4 (58) (.000001*)	19.51 (58) (.00004*)
Anti_er-RTM	197 (5)	210 (7)	1.61 (57) (.112)	3.84 (56) (.055)
Anti_er-RTSD	42 (3)	60 (5)	3.52 (57) (.0008*)	6.32 (56) (.015*)
Anti_cor-RTM	96 (6)	154 (10)	4.93 (57) (.000007*)	18.09 (56) (.00008*)
Anti_cor-RTSD	54 (5)	78 (5)	3.24 (57) (.002*)	5.67 (56) (.02*)
HF-HRV				
Base_HF-HRV	6.02 (0.15)	4.73 (0.37)	3.24 (58) (.002*)	7.2 (57) (.009*)
Pro_HF-HRV	6.23 (0.18)	4.69 (0.36)	3.8 (58) (.0003*)	11.55 (57) (.001*)
Anti_HF-HRV	6.25 (0.17)	4.72 (0.35)	3.85 (58) (.0003*)	12.66 (57) (.0007*)
Rec_HF-HRV	6.14 (0.17)	4.87 (0.33)	3.39 (58) (.001*)	9.32 (57) (.003*)

Note: Means and standard errors (SE) for oculomotor function and HF-HRV variables in the control and patient groups. *T*-tests of the comparisons of these means between the two groups are provided in column 4 and *F* tests of the group differences in the ANCOVA using education as a covariate are provided in column 5.
Note: ER, error rate; FDR, false discovery rate; HF-HRV, high frequency component of heart rate variability; RTM, mean reaction time; RTSD, SD of reaction time.
*FDR corrected $P < .05$.

Table 2. Correlations of HF-HRV and Oculomotor Function Variables

	Pearson *r* (*P*)		BF_{10}/BF_{01}	
	Pro_HF-HRV	Anti_HF-HRV	Pro_HF-HRV	Anti_HF-HRV
Controls				
Pro-RTSD	−0.110 (.564)	—	0.266/3.760	—
Anti-ER	—	−0.258 (.169)	—	0.561/1.783
Anti-RTM	—	0.089 (.638)	—	0.252/3.996
Anti-RTSD	—	−0.051 (.788)	—	0.235/4.257
Anti_er-RTSD	—	−0.177 (.357)	—	0.346/2.893
Anti_cor-RTM	—	0.024 (.900)	—	0.232/4.302
Anti_cor-RTSD	—	0.006 (.975)	—	0.231/4.332
Patients				
Pro-RTSD	−0.191 (0.312)	—	0.370/2.705	—
Anti-ER	—	−0.517 (.003*)	—	13.421/0.075
Anti-RTM	—	−0.068 (.720)	—	0.241/4.144
Anti-RTSD	—	−0.141 (.457)	—	0.295/3.384
Anti_er-RTSD	—	−0.011 (.954)	—	0.227/4.400
Anti_cor-RTM	—	−0.190 (.315)	—	0.367/2.722
Anti_cor-RTSD	—	−0.152 (.423)	—	0.308/3.242

Note: Pearson correlation coefficient *r* values and *P* values for the correlations of oculomotor function variables and HF-HRV variables in the control and patient group.
Note: BF_{10}, Bayesian factor providing evidence in favor of the alternative hypothesis and against the null; BF_{01}, Bayesian Factor providing evidence in favor of the null hypothesis and against the alternative; FDR, false discovery rate; HF-HRV, high frequency component of heart rate variability; RTM, mean reaction time; RTSD, SD of reaction time.
*FDR corrected $P < .05$.

Mediation Analysis

Mediation analysis confirmed that the difference between patients and controls in anti_ER was fully mediated by the decrease in parasympathetic activation (decrease in anti_HF-HRV) (figure 2). Replacing anti_HF-HRV with base_HF-HRV produced the same results (data not shown).

Medication Effects

Table 3 shows the results of correlation analysis of the oculomotor function and HF-HRV variables with antipsychotic medication daily dose. None of the correlations reached significance and all were of small effect size ($r < 0.3$) except the standard deviation of pro_RTSD

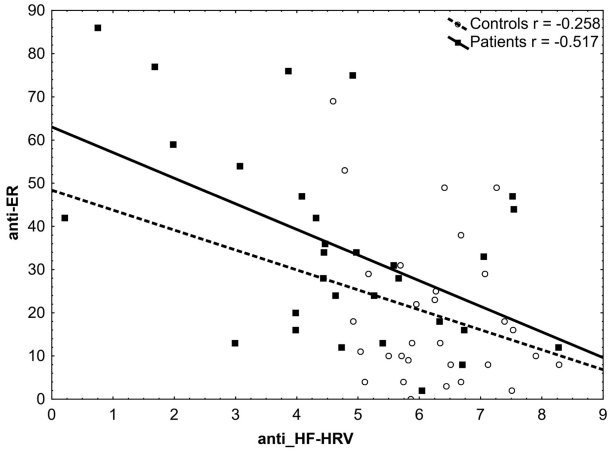

Fig. 1. Scatterplot showing the relation between antisaccade HF-HRV and antisaccade ER. Control group: open circles and dotted line for linear fit. Patient group: solid squares and solid line for linear fit. ER, error rate; HF-HRV, high frequency component of heart rate variability.

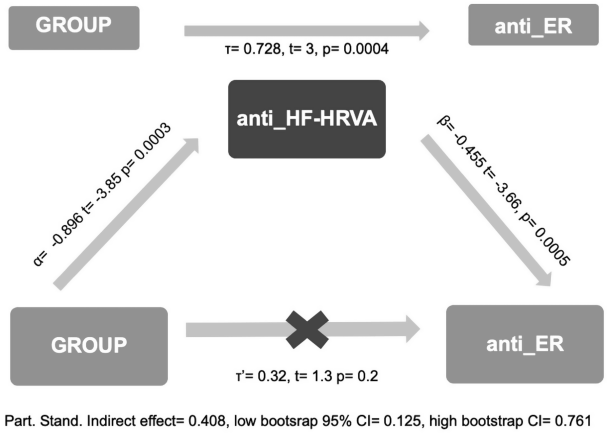

Fig. 2. Results of mediation analysis. The upper diagram represents the total model showing the group (controls vs schizophrenia) effect (τ) on antisaccade ER (anti-ER). The bottom diagram represents the mediation model with the direct group effect on antisaccade ER (τ′) and the indirect effect mediated by the antisaccade HF-HRV (α,β). ER, error rate; HF-HRV, high frequency component of heart rate variability.

which reached medium effect size. BF for these correlations provided anectodal or moderate evidence in favor of the hypothesis that these variables were not correlated except for pro_RTSD which provided anectodal evidence in favor of the hypothesis that this variable was correlated with medication dose.

Linear regression using antipsychotic medication daily dose and anti_HF-HRV to predict anti_ER in patients was significant ($F_2 = 5.37$, $P = .011$). The coefficient for HF-HRV was highly significant ($\beta = -0.491$, $t = -2.962$, $P = .006$) while the coefficient for antipsychotic medication daily dose was not ($\beta = 0.134$, $t = 0.809$, $P = .426$).

Table 3. Correlations of Oculomotor Function and HF-HRV Variables With Antipsychotic Medication Daily Dose in Patients

	Pearson *r* (*P*)	BF_{10}/BF_{01}
Pro-RTSD	0.344 (.062)	1.191/0.840
Anti-ER	0.228 (.226)	0.458/2.185
Anti-RTM	0.083 (.664)	0.248/4.026
Anti-RTSD	0.189 (.317)	0.366/2.734
Anti_er-RTSD	0.171 (.366)	0.336/2.980
Anti_cor-RTM	0.235 (.211)	0.480/2.085
Anti_cor-RTSD	0.050 (.792)	0.235/4.263
Base_HF-HRV	−0.202 (.284)	0.392/2.549
Pro_HF-HRV	−0.167 (.377)	0.329/3.036
Anti_HF-HRV	−0.191 (.312)	0.370/2.704
Rec_HF-HRV	−0.102 (.591)	0.260/3.840

Note: Pearson correlation coefficient *r* values and *P* values in parentheses for the correlations of oculomotor function and HF-HRV variables to antipsychotic medication daily dose in the patient group.
Note: BF_{10}, Bayesian factor providing evidence in favor of the alternative hypothesis and against the null; BF_{01}, Bayesian factor providing evidence in favor of the null hypothesis and against the alternative; FDR, false discovery rate; HF-HRV, high frequency component of heart rate variability; RTM, mean reaction time; RTSD, SD of reaction time.
*FDR corrected $P < .05$.

Discussion

The aim of this study was to explore the connection between 2 prominent deficits among patients with schizophrenia: the deficit in cognitive inhibitory control and the deficit in parasympathetic activity.

Regarding the oculomotor measures, our results confirmed previous results. Namely, there was no difference in mean RT of prosaccades between schizophrenia patients and controls, confirming that patients do not have deficit in the control of visually guided saccades.[12,13,41] However, patients showed increased mean RT of antisaccades and increased mean RT of corrective saccades in line with previous findings, supporting a deficit in the decision process leading to saccade initiation related to volitional saccades.[41,42,48] Patients also showed greater RT-ISV for prosaccades, antisaccades, and corrective saccades, confirming previous results that have argued for a deficit in the stability of higher-order processes in schizophrenia.[42] Finally, schizophrenia patients showed increased anti-ERs compared to controls, confirming the deficit in inhibitory control suggested by previous studies.[14,16,48,49]

Concerning the measures of autonomic function, our results are consistent with existing literature reporting autonomic abnormalities in patients with schizophrenia with decreased parasympathetic activity.[2,20,50–52] Schizophrenia patients had lower HF-HRV during prosaccade and antisaccade task performance as well as before and after the saccadic tasks, compared to healthy controls. Moreover, the measurements for HF-HRV were highly correlated in all time periods.

Confirming our hypothesis, the increased anti-ER in patients with schizophrenia indicating a deficit in inhibitory cognitive control was highly correlated with the decreased HF-HRV indicating a deficit in parasympathetic activation. The BF showed strong evidence in favor of this correlation. The relation of ER and HF-HRV was diminished in healthy controls but retained the same direction. Results from mediation analysis further confirmed that group difference in ER between patients and controls was fully mediated by the difference in HF-HRV. Mediation was evidenced by the non-significant direct effect of group on ER and the highly significant indirect effect via the HF-HRV. Based on these results, the deficits in inhibitory cognitive control and parasympathetic activation are related in a way that the presence of one in a group of patients predicts the presence of the other.

In line with our initial hypothesis, there was no relation between HF-HRV and all other oculomotor measures where schizophrenia patients showed deficit, namely increased mean RT for antisaccades and corrective saccades and increased RT-ISV in the prosaccade and antisaccade task. BF analysis also favored the absence of correlations of these measures with HF-HRV in both patients and controls.

NIM suggests that inhibition occurs at both physiological and cognitive levels and is critical for goal-directed behavior.[2,31] Specifically, it is proposed that adaptive and complex goal-directed behavior is facilitated by the inhibitory communication between prefrontal cortex and subcortical areas that are involved in autonomic balance.[2,31,32] Patients with schizophrenia show significant deficits in both cognitive inhibitory control and autonomic system. We could hence assume that these two deficits could be indicative of an impaired inhibitory cortical-subcortical neural network. Future research should investigate the dynamics and directionality of the relation between the two deficits in schizophrenia and test whether behavioral or neuropharmacological interventions aiming at one deficit could lead to the modification of the other.

Given that HF-HRV deficit in patients was stable across all time periods of recording, the relation of ER and HF-HRV measured during baseline was found to be similarly strong as the relation of ER with HF-HRV measured during the antisaccade task. Thus, one could argue that recording of few minutes resting-state ECG could provide an estimate not only of a deficit in parasympathetic regulation but also of the linked deficit in cognitive inhibitory control. HF-HRV could therefore turn out to be a robust and easy-to-use biomarker for future studies of cognition in schizophrenia, especially longitudinal ones following patients after therapeutic interventions.

It remains to be seen whether the strong relation of deficits in cognitive inhibition and parasympathetic regulation is specific only in schizophrenia or across different psychiatric conditions. Despite that, the relation between cognitive deficits and autonomic imbalance has been investigated in depressive disorders[53,54] more research is needed in other psychotic disorders like bipolar disorder and in conditions where prefrontal disinhibition is prominent such as prefrontal cortical lesions and attention deficit hyperactivity disorder.

One limitation of this study is that schizophrenia patients were medicated therefore results cannot be generalized to unmedicated patients. However, as mentioned in the introduction the deficits in ER and HF-HRV are also seen in unmedicated patients. Moreover, there was no correlation of antipsychotic medication dose to any one of the deficits in oculomotor function and HF-HRV measures. When including both HF-HRV and antipsychotic medication levels to predict the deficit in ER the medication level was not a significant predictor.

In conclusion, this is the first study to our knowledge that tested the NIM theory comparing patients with schizophrenia and controls and confirming its prediction that the deficit in parasympathetic activity is specifically related to the deficit in the cognitive inhibitory control. Taking into consideration the several deficits across the wide range of physiological, cognitive, and social domains in schizophrenia[55–57] our results suggest that the complex relationships between these deficits should be included in future models explaining the cognitive decline, a core feature of schizophrenia.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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