



Published in final edited form as:

*J Neuropsychiatry (Foster City)*. 2018 ; 2(2): . doi:10.21767/2471-8548.10008.

## Peripheral Cortisol and Inflammatory Response to a Psychosocial Stressor in People with Schizophrenia

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### Abstract

**Objectives:** There is growing evidence of both hypothalamic-pituitary-adrenal (HPA) axis and immune system dysfunction in schizophrenia. Additionally, accumulating evidence has linked dysfunction in the kynurenine pathway to schizophrenia as well as to stress and inflammation. The current pilot tested changes in immune, cortisol and kynurenine and kynurenic acid responses to a psychosocial stressor in people with schizophrenia and healthy controls.

**Methods:** Ten people with schizophrenia/schizoaffective disorder and 10 healthy controls were included. Participants completed the Trier Social Stress Test (TSST) and cortisol, cytokines (IL-6 & TNF- $\alpha$ ), kynurenine and kynurenic acid were measured in the plasma at baseline 15, 30, 60 and 90 minutes following the TSST.

**Results:** Compared to baseline, at 30 minutes post TSST, mean cortisol levels had increased by 7.6 ng/ml (11%) in healthy controls but decreased by 16.3 ng/ml (25%) in schizophrenia ( $F=4.34$ ,  $df=3,38.2$ ,  $p=0.010$ ). While people with schizophrenia had a lower TNF- $\alpha$  level at baseline ( $\chi^2_{(1)}=10.14$ ,  $p=0.001$ ), no decreases or increases occurred after the TSST in either group. Both groups had a similar increase in IL-6 at 15 minutes post TSST ( $F=4.17$ ,  $df=3, 16.3$ ,  $p=0.023$ ) demonstrating an immune response to the stress in both groups. A trend towards increased kynurenine from baseline was found immediately after the TSST followed by a decrease at 60 minutes in healthy controls but no change was found in people with schizophrenia ( $F=2.46$ ,  $df=3, 49.1$ ,  $p=0.074$ ).

**Conclusion:** People with schizophrenia showed a decrease in cortisol from baseline following the TSST as compared to an elevation from baseline seen in healthy controls, supporting HPA axis dysfunction in schizophrenia. An immediate inflammatory response with IL-6 was seen in both groups following the TSST. Larger studies should examine psychosocial stress response in schizophrenia and the relationship of immune function and kynurenine pathway.

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## Keywords

Schizophrenia; Inflammation; Cortisol; Stress; Kynurenine; Kynurenic acid; TNF- $\alpha$

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## Background

The hypothalamic-pituitary-adrenal (HPA) axis is the body's primary way to adaptively respond to stress by secreting stress hormones. Psychosocial stress may play a role in major psychiatric disorders including schizophrenia and there is growing evidence of an altered HPA stress response in schizophrenia [1–3]. For example, a recent meta-analysis has shown [4] that people with schizophrenia have a dysfunctional cortisol response in anticipation of and during the Trier Social Stress Test (TSST). Importantly, Jansen et al. [5] have also reported that the attenuated cortisol response is specific to a psychosocial stressor, suggesting that a physical stressor does not produce an attenuated response in people with schizophrenia. The dysfunctional response to psychosocial stress has also been found in individuals assessed for ultrahigh risk for psychosis compared to healthy controls [6], supporting the notion that the HPA axis is disrupted even prior to the diagnosis of schizophrenia. Furthermore, several papers suggested blunted cortisol awakening response in schizophrenia, even seen in people before the onset of schizophrenia [7].

Accumulating evidence also implicates immune regulation dysfunction in people with schizophrenia [8] and the immune system has been tied to the HPA axis. For example, cortisol and ACTH have been shown to be influenced by serum cytokines in healthy controls [9]. In a study by Izawa et al. [10], the pro-inflammatory cytokine interleukin-6 (IL-6) was shown to increase in response to stress and remained elevated for up to twenty minutes post stressor in healthy controls. Taken together, these studies implicate an interaction between stress and the immune system in healthy people, but little is known about this interaction in schizophrenia. Moreover, the mechanisms mediating this relationship remain to be fully understood.

The kynurenine pathway of tryptophan metabolism is implicated in the etiology of schizophrenia. Kynurenine and its metabolite kynurenic acid are elevated in the cerebrospinal fluid and post-mortem brain of people with schizophrenia compared to healthy controls [11–16]. Cortisol and cytokines may play a role in modulating the metabolism of the kynurenine pathway [17–19]. For example, higher levels of kynurenic acid in people with schizophrenia are correlated to an increase in IL-6 [16]. Stress and anxiety, common symptoms associated with schizophrenia, have also been shown to be directly and positively related with kynurenic acid levels, such that kynurenic acid levels increase in people with schizophrenia from baseline following a psychologically stressful task [20,21].

This pilot study examined the endocrine (i.e. cortisol), immune (TNF- $\alpha$  and IL-6), and kynurenine pathway responses before, during, and after the TSST to elucidate the relationship of stress and inflammation in participants with schizophrenia and healthy controls.

## Materials and Methods

### Schizophrenia and healthy controls

Ten people (N=10) with schizophrenia or schizoaffective disorder (DSM-IV criteria) and ten healthy controls (no DSM-IV Axis I or II disorders) (N=10) were recruited for the study. Participants recruited included 5 females and 5 males in each group. Those recruited were between the ages of 18 and 64 years. Participants were excluded if they had a history of Cushing's syndrome, adrenal deficiency, or any condition or medication that may affect cortisol levels in the body, used steroids, were pregnant or lactating, or had untreated hypertension, cardiac arrhythmias, or medical condition that could not handle stress.

### Consent and screening

All participants signed informed consent and completed a screening visit to determine eligibility. Screening consisted of collecting demographic information (including race, relationship status, years of education, and smoking status), medical history, current medications, vital signs, electrocardiogram, urine pregnancy test (female only), and basic blood work. The participants completed various clinical assessments including the Structured Clinical Interview for the DSM-IV Diagnoses (SCID) [22], Brief Psychiatric Rating Scale (BPRS) (18-item) [23], Hamilton Depression Scale (HAM-D) [24], Scale for the Assessment of Negative Symptoms (SANS) [25], and the Clinical Global Impression Scale [26] to evaluate psychiatric symptoms. Participants also completed the Repeatable Battery for the Assessments of Neuropsychiatric Status (RBANS). Participants were rated at baseline also on the Perceived Stress Scale [27].

### Stress paradigm visit (Trier social stress test)

If criteria were met, participants were scheduled for a second visit to complete the Trier Social Stress Test [28]. The Trier Social Stress Test (TSST) is a stress inducing paradigm that has been proven to be a reliable and valid means of inducing a physiological stress response in various populations including healthy controls, people with depression, anxiety, and bipolar-disorder [29]. Participants were told the second visit would involve a role play scenario; however, no details regarding the role play were given in order to maintain the internal validity of the response paradigm. Upon arrival of the second visit participants had an intravenous catheter inserted in order to collect multiple blood samples for laboratory measures (peripheral cytokines, cortisol, and peripheral kynurenine and kynurenic acid).

Participants were administered the TSST and had all blood draws using the same procedures and the same time of day (2:00 pm). Briefly, this involved them being taken into a separate room to meet a "panel of judges" and watching a recording that provided instructions on the 5-minute speech they were assigned to give describing their ideal job and why they should be hired for it. Participants were also informed that after the speech they will be asked to perform a mental math task. Participants were then taken back to original premeeting room and given 10 minutes to prepare the speech, before returning to the room with the "panel of judges" to deliver their speech and complete the mental math task (test period). Immediately following the stressor, the purpose of the task was explained. Participants were asked if they were willing to complete the remainder of the study and asked to sign a form confirming that

the task was explained, and they were willing to continue. Blood was drawn at baseline prior to the TSST, and 15, 30, 60 and 90 minutes post stressor.

### Laboratory sample analysis

Serum cortisol was measured using commercial enzyme-linked immunosorbent assay kits (IBL International, Hamburg, Germany), following manufacturer's recommended protocol. Serum cytokines (IL-6 and TNF- $\alpha$ ) were sent to the Cytokine Core Lab at The University of Maryland Baltimore for analysis using Luminex® technology. Kynurenic acid and kynurenine were measured using high-performance liquid chromatography (HPLC). Briefly, serum was diluted in ultrapure water (1:2 v/v for kynurenine, 1:10 v/v for kynurenic acid) and 25  $\mu$ L of 6% perchloric acid were added to 100  $\mu$ L of preparation. After centrifugation (16,000  $\times$  g, 10 min), 20  $\mu$ L of the resulting supernatant were subjected to HPLC [30]. All laboratory measures were measured in all participants, with the exception of two participants missing cortisol levels from each group, noted in the figure to be N=8 in each group instead of N=10 for this measure only.

### Statistical analysis

Baseline group differences in demographic information, clinical ratings, cortisol, TNF- $\alpha$ , IL-6, kynurenine and kynurenic acid were assessed using Kruskal-Wallis test. Kruskal-Wallis test is used due to the small sample and nonparametric tests. Cortisol, TNF- $\alpha$ , IL-6, kynurenine and kynurenic acid were analyzed with group X time ANOVAs with repeated measures for time, controlling for baseline levels. The effects of group and time post stress on changes from baseline for these outcomes were assessed using SAS PROC MIXED to fit mixed models for repeated measures analysis of covariance. The modelling allows for missing data points, among all the data points there are 4 missing values for the data for kynurenine, 5 missing for kynurenic acid, 2 for TNF-alpha, 2 for IL-6 and 3 for cortisol. Significant interaction effects were followed up with post-hoc tests to examine the timepoint when significance was noted. Significance level was set to  $\alpha < 0.05$ .

## Results

There were no significant differences between the two groups for age, gender, race, or perceived stress at baseline study entry. Participants in the schizophrenia group scored significantly higher on the BPRS total score as expected ( $p=0.0004$ ). Comparisons between the groups on baseline physiological measures showed no significant difference in pulse or systolic Blood pressure. However, the schizophrenia group did have a significantly higher diastolic Blood pressure at baseline ( $\chi^2=5.63$ ,  $df=1$ ,  $p=0.018$ ) (See Table 1).

### Cortisol

There were no group differences in cortisol levels at baseline ( $\chi^2=1.59$ ,  $df=1$ ,  $p=0.208$ ). There was a significant interaction ( $F=4.34$ ,  $df=3,38.2$ ,  $p=0.010$ ) such that in the healthy control group cortisol initially increased (11%) after the stressor and then steadily declined over time. Conversely, cortisol levels among participants with schizophrenia decreased immediately after the stressor (25%) and then increased back to baseline with time. Post-hoc

tests revealed that cortisol levels at the 30-minute time points were different between groups ( $t=2.56$ ,  $df=36$ ,  $p=0.015$ ). See Figure 1 for illustration.

### Cytokines

TNF- $\alpha$  levels were significantly lower in the schizophrenia group at baseline (TNF- $\alpha$ : ( $\chi^2=10.14$ ,  $df=1$ ,  $p=0.001$ ), but, there were no significant main or interaction effects after stressor (see Figure 2). IL-6 at baseline did not differ between groups ( $\chi^2=1.58$ ,  $df=1$ ,  $p=0.209$ ). There was a significant main effect of time on IL-6 such that both groups had an increase after the stressor ( $F=4.17$ ,  $df=3,16.3$ ,  $p=0.023$ ) (Figure 3), with an immediate increase noted at 15 minutes, followed by a decrease but then a continued increase through the 90-minute timepoint. The interaction and main effect of group were not significant (see Figure 3).

### Kynurenine and kynurenic acid

There were no significant differences in kynurenic acid or kynurenine at baseline ( $\chi^2=0$ ,  $df=1$ ,  $p=1.0$ , ( $\chi^2=0.43$ ,  $df=1$ ,  $p=0.513$  respectively). However, kynurenine analysis revealed a marginal interaction effect ( $F=2.46$ ,  $df=3,49$ ,  $p=0.074$ ), such that kynurenine increased in the control group immediately following the stressor and then decreased at 60 minutes while kynurenine levels did not change in schizophrenia patients across time (see Figure 4). There were also no significant interaction or main effects of kynurenic acid (see Figure 5).

### Discussion

This pilot study is the first to examine differences in schizophrenia and healthy controls with regard to immune response and kynurenine/ kynurenic acid changes after a psychosocial stress. Our results indicate that people with schizophrenia have a dysfunctional HPA axis response to psychosocial stressors as indicated by an abnormal cortisol response compared to healthy controls. These findings are consistent with results reported in other studies using a psychological stressor [4,6,31,32].

While people with schizophrenia did show lower overall levels of TNF- $\alpha$  present at baseline, there were no notable changes in TNF- $\alpha$  after the TSST. This finding is in accordance with previous findings of lower levels of TNF- $\alpha$  in schizophrenia people compared to healthy controls [33]. The schizophrenia group and healthy controls showed a similar increase in serum IL-6 levels in response to the stressor. Carpenter and others [34,35] also showed an increase in IL-6 in healthy control that it increased initially, decreased and then began to increase over a 90-minute period following the TSST. While it remains unclear how long the pro-inflammatory response occurs or how robustly it changes after a psychological stressor, our pilot study demonstrates that stress contributes to the induction of a peripheral pro-inflammatory response in both schizophrenia and healthy controls. It is also interesting to note that the initial spike in IL-6 occurred prior to peak in cortisol after the stressor, suggesting the inflammatory response could contribute to or modulate cortisol release in healthy controls, but that the HPA response to IL-6 did not occur in schizophrenia. Our data suggest that immune-mediated activation of the HPA axis may function differently in people with schizophrenia compared to healthy control. Further studies to elucidate the

relationship between peripheral circulating cytokines and HPA axis function in people with schizophrenia are warranted.

Kynurenic acid and kynurenine did not significantly change during or after the TSST in schizophrenia patients, although we did find marginal evidence that after the TSST in the healthy control group kynurenine increased immediately and then declined. While previous studies have demonstrated positive correlations between cerebrospinal fluid kynurenic acid and IL-6 in people with schizophrenia at one time point and in nonstress studies [16], in the present pilot we did not see a response to kynurenic acid in peripheral blood matching the response in IL-6. We had, however, only limited power to detect these relationships. Others have shown that kynurenic acid is a potent endogenous ligand at the aryl hydrocarbon receptor (AHR) and induction of IL-6 expression is largely dependent on AHR expression [36]. Thus, this may potentially explain the results seen with kynurenine and IL-6 increasing in the healthy controls from baseline. However, interestingly IL-6 increases occurred independent of an increase in kynurenine in the schizophrenia group, suggesting other mechanisms of immune activation, independent of the kynurenine pathway, may be present. It is also noteworthy that kynurenine can cross the blood brain barrier and is the precursor to kynurenic acid, which is an antagonist at glutamatergic NMDA and nicotinic alpha 7 receptors within the CNS [37]. Thus, what is happening in the periphery may not reflect what is seen in the brain.

This study has weaknesses and strengths. The main weakness is that the pilot study is limited by its small sample size and larger studies are needed to confirm these findings. However, a significant strength of the study was the protocol benefitted from a strict design for a stress paradigm. A truly stressful environment for evaluation must be set up and can only occur if the participants are unaware that the stressor will occur, such as in this study. For this protocol, we gained IRB approval for using deceptive research practices and following the recommendations by Pascual-Leone et al. [38] for how to ethically conduct such research. Other stress-related protocols must give participants all the information on the stressful situation and environment, thereby leading to anticipatory anxiety, worry and stress. An additional limitation is the lack of a comprehensive analysis of peripheral cytokines including IFN- $\gamma$ , a cytokine known to activate the kynurenine pathway [39].

In conclusion, our pilot study supports a dysfunctional stress response to the TSST in schizophrenia. Further research is needed to elucidate the complex relationship between inflammation, stress responsivity, and alterations in the kynurenine pathway in schizophrenia which may ultimately lead to better biomarkers and treatments for this illness.

## Acknowledgement

We thank the Treatment Research Program Team for their work in performing the TSST paradigm. This study was funded in part by the NIMH Silvio O. Conte Center Grant (P50 MH 103222) and Mitsubishi Tanabe.

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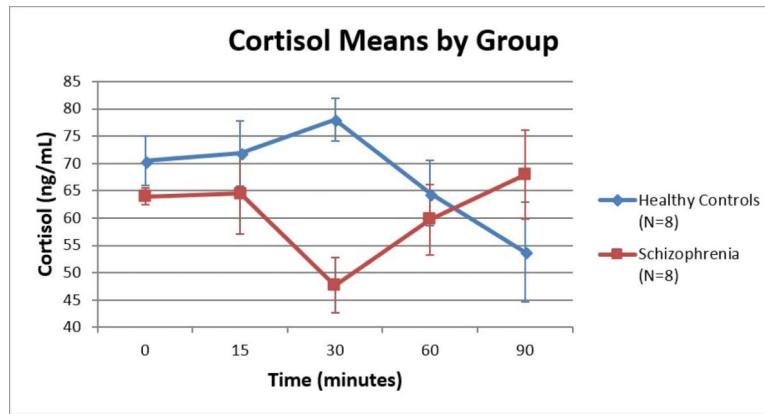
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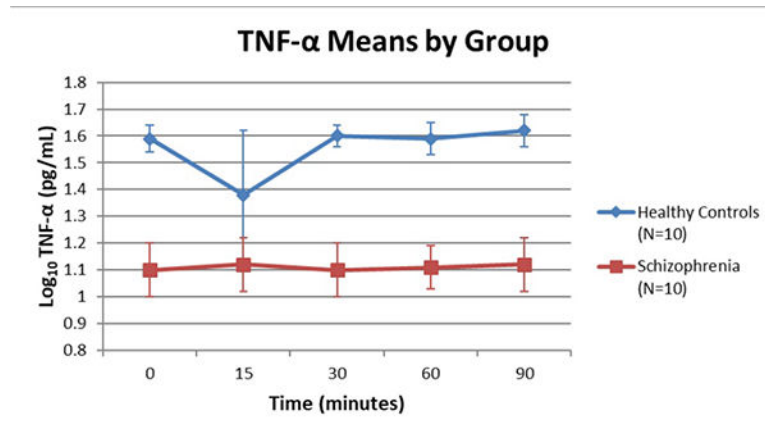
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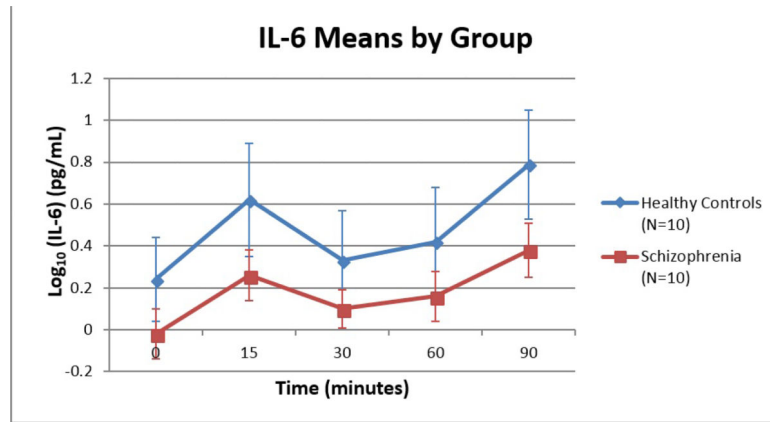




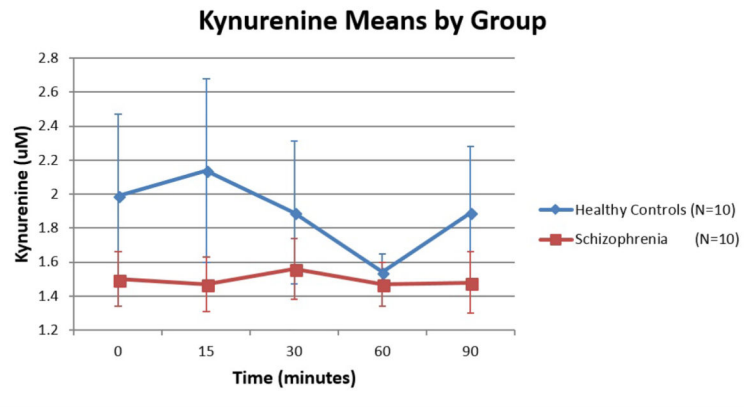
**Figure 1.** Changes in Cortisol. Group:  $F=0.39$ ,  $df=1$ ,  $11.7$ ,  $p=0.54$ ; Time:  $F=0.67$ ,  $df=3$ ,  $38.2$ ,  $p=0.57$ ; Group\*Time:  $F=4.34$ ,  $df=3$ ,  $38.2$ ,  $p=0.01$ .



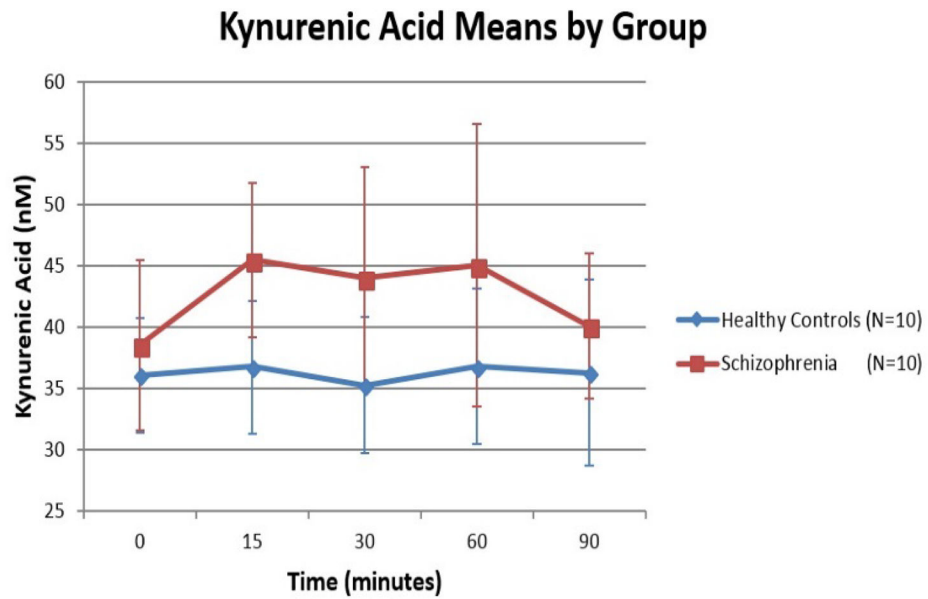
**Figure 2.** Changes in TNF- $\alpha$ . Group:  $F=0.04$ ,  $df=1, 16$ ,  $p=0.85$ ; Time:  $F=0.85$ ,  $df=3, 50.6$ ,  $p=0.47$ ; Group\*Time:  $F=0.59$ ,  $df=3, 50.6$ ,  $p=0.63$ .



**Figure 3.** Changes in IL-6. Group:  $F=0.024$ ,  $df=1$ ,  $17.5$ ,  $p=0.88$ ; Time:  $F=4.17$ ,  $df=3,16.3$ ,  $p=0.023$ ; Group\*Time:  $F=0.18$ ,  $df=3$ ,  $16.3$ ,  $p=0.91$ .



**Figure 4.** Changes in Kynurenine. Group:  $F=0.95$ ,  $df=1$ ,  $16.3$ ,  $p=0.34$ ; Time:  $F=0.64$ ,  $df=3$ ,  $49.1$ ,  $p=0.59$ ; Group\*Time:  $F=2.46$ ,  $df=3$ ,  $49.1$ ,  $p=0.07$ .



**Figure 5.** Changes in Kynurenic Acid. Group:  $F=2.05$ ,  $df=1, 15.9$ ,  $p=0.17$ ; Time:  $F=0.62$ ,  $df=3, 13.1$ ,  $p=0.62$ ; Group\*Time:  $F=0.49$ ,  $df=3, 13.1$ ,  $p=0.70$ .

Table 1

Demographic and Baseline Information.

	Healthy Controls	Schizophrenia
	<b>N=10</b>	<b>N=10</b>
Age (years)	35.4 ± 12.3	40.9 ± 14.7
Sex	Male: 50%	Male: 50%
	Female: 50%	Female: 50%
Race	Caucasian: 20%	Caucasian: 30%
	AA: 70%	AA: 70%
	Mixed: 10%	
Current Smokers	Yes: 30%	Yes: 40%
	No: 70%	No: 60%
BPRS Total Score *	19.6 ± 1.8	33.2 ± 5.3
SANS Total Score	1.0 ± 2.8	25.7 ± 9.2
HAM-D	0.67 ± 1.4	8.8 ± 5.8
CGI	1.0 ± 0.0	4.5 ± 0.8
RBANS Total Score *	86.4 ± 15.1	71.0 ± 16.0
Perceived Stress Scale	11.2 ± 9.7	14.5 ± 5.2
Systolic Blood Pressure (mmHg)	122.7 ± 21.7	117.7 ± 13.1
Diastolic Blood Pressure (mmHg) *	67.2 ± 10.8	74.9 ± 5.2
Pulse (bpm)	73 ± 14.4	83.9 ± 12.9

\* p&lt;0.05.