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Neurophysiological and Psychological Predictors of Social Functioning in Patients with Schizophrenia and Bipolar Disorder

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Objective The aim of this study is to examine social functioning in patients with schizophrenia and bipolar disorder and explore the psychological and neurophysiological predictors of social functioning.

Methods Twenty-seven patients with schizophrenia and thirty patients with bipolar disorder, as well as twenty-five healthy controls, completed measures of social functioning (questionnaire of social functioning), neurocognition (Verbal fluency, Korean-Auditory Verbal Learning Test), and social cognition (basic empathy scale and Social Attribution Task-Multiple Choice), and the childhood trauma questionnaire (CTQ). For neurophysiological measurements, mismatch negativity and heart rate variability (HRV) were recorded from all participants. Multiple hierarchical regression was performed to explore the impact of factors on social functioning.

Results The results showed that CTQ-emotional neglect significantly predicted social functioning in schizophrenia group, while HRV-high frequency significantly predicted social functioning in bipolar disorder patients. Furthermore, emotional neglect and HRV-HF still predicted social functioning in all of the subjects after controlling for the diagnostic criteria.

Conclusion Our results implicated that even though each group has different predictors of social functioning, early traumatic events and HRV could be important indicators of functional outcome irrespective of what group they are.

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Key Words Social functioning, Schizophrenia, Bipolar disorder, Childhood trauma, Mismatch negativity, Heart rate variability.

INTRODUCTION

Social functioning, which refers to the degree to which a person adjusts to daily-life domains such as work and interpersonal relationship,[1,2] has been regarded as a treatment outcome, as well as a diagnostic criterion, in psychiatric disorders. Previous studies have shown that patients with schizophrenia and bipolar disorder typically have poorer functioning than healthy controls.[3-5] In particular, dimensional approaches have argued that schizophrenia and bipolar disorder patients have commonalities of clinical symptoms, family history, biological and genetic factors.[6-8] This may suggest that both patient groups share similar predictors of impaired social functioning.

A large number of studies have investigated the relationship between cognitive impairment and social functioning in patients with schizophrenia and bipolar disorder.[9-12] In a recent meta-analysis,[13] the association between verbal fluency and community functioning exhibited the largest effect size in schizophrenia patients. Moreover, a review stated that neurocognitive domains, such as verbal memory and executive function, are positively associated with psychosocial functioning in bipolar disorder patients, even after controlling for mood-related symptoms.[14] In addition, social cognition, which includes emotional perception, social perception, theory of mind, and attributional style, has also shown a positive association with social functioning in bipolar patients, as well as schizophrenia patients.[15-21]

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Furthermore, other studies have explored the relationship between traumatic childhood experiences and social functioning in schizophrenia and bipolar disorder.[3,22-24] While the high prevalence of childhood trauma has been consistently reported in schizophrenia and bipolar disorder,[25-27] the causal relationship between childhood traumatic events and social functioning has been explored recently.[2,28,29] A previous study revealed that early trauma in psychosis patients affected long-term functional outcome, which was mediated by depressive symptoms.[28] However, little is known about the specific relationship between early trauma and functional outcomes in bipolar disorder.[30]

In addition, neurophysiological factors may predict social functioning in schizophrenia and bipolar disorder. In this study, the mismatch negativity (MMN) and heart rate variability (HRV), which are considered as objective measures related to automatic responses[31] and autonomic nervous system,[32] were employed. These two markers have been long investigated as potential predictors of patient's functional outcome.[33,34] MMN is an auditory event-related potential (ERP) component related to pre-attentive sensory memory.[35] Recent findings have demonstrated that MMN is typically reduced in schizophrenia and bipolar disorder,[34,36-39] and MMN deficits are associated with poor functioning in schizophrenia.[40,41] Another notable factor is HRV, which is a reliable and quantitative measurement of autonomic nervous system activity.[42] A growing number of studies have reported HRV dysfunction in schizophrenia and bipolar disorder.[42-48] Previous studies have demonstrated that HRV is related to emotional regulation[49,50] and emotion recognition.[51] Fujibayashi and his colleagues[33] reported that low functioning schizophrenia patients show reduced autonomic nervous system activities compared to high functioning group. Another study revealed that HRV predicts subjective well-being, mediated by executive emotional regulation, in college students.[52]

In sum, even though a growing body of evidence has shown that cognitive impairments, childhood maltreatment, and neurophysiological factors are associated with functional outcomes in schizophrenia and bipolar disorder, few studies have examined the predictive effect of psychological and neurophysiological factors on the social functioning of both patients simultaneously. Therefore, the present study aimed to perform an exploratory examination of the predictor of psychological and neurophysiological components on social functioning in schizophrenia and bipolar disorder. We hypothesized that social functioning would be impaired in schizophrenia and bipolar disorder relative to healthy controls and explored which psychological and neurophysiological factors would significantly predict functional outcomes in each group.

METHODS

Participants

A total of 82 subjects between the ages of 20 and 64 years participated in this study. The subjects included patients with schizophrenia [n=27, age: 42.48±11.86 (range: 21−60)] and bipolar disorder [n=30, age: 39.70±12.61 (range: 20−63)] as well as healthy controls [n=25, age: 42.48±12.60 (range: 23−64)]. All patients were assessed by a psychiatrist for Axis I disorders based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (SCID).[53] Psychiatric symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS)[54] for patients with both diseases and the Young Mania Rating Scale (YMRS)[55] for bipolar disorder. No patient had a lifetime history of central nervous system disease, alcohol or drug abuse, mental retardation, or head injury with loss of consciousness. Patients with schizophrenia were being treated with atypical antipsychotics, and patients with bipolar disorder with mood-stabilizing agents (lithium, topiramate, lamotrigine, and sodium valproate), with or without atypical antipsychotics. Twenty-five healthy controls (HCs) were recruited from the local community through newspaper advertisements and flyers. Subjects with identifiable neurological disorders, head injury, or any personal or family history of psychiatric illness were excluded following an initial screening interview. Volunteers were then interviewed using the SCID for Axis II Psychiatric Disorders and excluded if they were found to have any disorder. All subjects signed a written informed consent form approved by the Institutional Review Board of Inje University Ilsan Paik Hospital (2015-07-23).

Psychological measures

Social functioning

To evaluate social functioning, the questionnaire of social functioning (QSF)[56] was performed for all participants. The QSF consists of 16 items, which include frequency (8 items) and satisfaction (8 items) of social behaviors such as working and relationships, rated using a five-point Likert scale (ranging 1−5) where a higher score indicates greater social functioning. The Cronbach's alpha for the current sample was 0.83.

Neurocognition

To assess neurocognition, a verbal fluency test[57] and the Korean-Auditory Verbal Learning Test (K-AVLT)[58] were employed. In the verbal fluency test, subjects state the names of as many animals as possible within 60 s. This evaluates verbal production and semantic memory abilities. The K-AVLT, which is included in the Rey-Kim Memory Test, is a verbal memory test consisting of five immediate recall trials (trials

1−5), plus delayed recall and recognition trials. The immediate recall score is the sum of words (trials 1−5) recalled correctly. The delayed recall score indicates the number of words recalled correctly after a delay period of 20 min. The delayed recognition score involves indicating the chosen words in the original list (15 words) spoken by the examiner among a list of 50 words after delayed recall.

Social cognition

The Basic Empathy Scale (BES)[59] and Social Attribution Task-Multiple Choice (SAT-MC)[60,61] were used. The BES consists of 20 items rated using a five-point Likert scale (scoring 1−5), in which a higher score indicates higher empathic ability. The SAT-MC consists of a 64-s animation that shows a social drama played by a large triangle, small triangle, and small circle. The animation is shown twice, and 19 multiple-choice questions about the actions are answered by the participants after the second viewing. The Cronbach's alpha for the BES in the current sample was 0.86.

Childhood trauma

Experience of childhood trauma was measured using the Childhood Trauma Questionnaire (CTQ).[62] The CTQ consists of 28 items rated using a five-point Likert scale (scoring 1−5) in which higher scores indicate greater experience of childhood trauma. Subscales include physical, emotional, and sexual abuse, as well as physical and emotional neglect. Each subscale consists of five items, and an additional three items were utilized for validity, including minimization and denial. The Cronbach's alpha for the CTQ in the current sample was 0.88.

Neurophysiological measures

Heart rate variability

HRV was measured using a 5-min single-channel (3-lead) electrocardiogram (ECG) signal. The ECG electrode sensors were attached to the left and right wrists and left ankle. After each subject was given approximately 5 minutes of rest in order to adapt to the experimental conditions, recordings were performed in the seated position at complete rest using the SA-3000P HRV analyzer (Medicore Co., Ltd, Seoul, Korea). The analyzer detected signals at 500 Hz, and the ECG signal was amplified and digitized. The following HRV parameters were calculated using frequency domain spectral analysis: low-frequency power (LF; 0.04−0.15 Hz), high-frequency power (HF; 0.15−0.4 Hz), and the LF/HF ratio. HF is considered an index of parasympathetic modulation, whereas LF is often proposed to reflect both sympathetic and parasympathetic activity.[63,64] Furthermore, the LF/HF ratio can be used as a tool to assess cardiovascular autonomic regulation.[64]

Recording and preprocessing of electroencephalography

The subjects were seated in a comfortable chair in a sound-attenuated room. They were required to watch a Charlie Chaplin movie displayed on a computer screen (Mitsubishi, 22-inch CRT monitor) without paying attention to the auditory stimuli. The auditory stimuli consisting of sounds at 85 dB SPL and 1000 Hz were delivered via MDR-D777 headphones (Sony, Tokyo, Japan). Deviant tones lasting 100 ms were presented randomly, interspersed with standard tones lasting 50 ms (probabilities: 10% and 90%, respectively). A total of 750 auditory stimuli were presented with an interstimulus interval of 500 ms. The experiment took about 10 min to complete. The stimuli were generated using E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA).

EEG recording was synchronized to stimulus presentation onset by E-Prime. EEG data was recorded using 64 Ag-AgCl electrodes mounted on a Quik-Cap using an extended 10−20 placement scheme. The ground electrode was placed on the forehead and the physically linked reference electrodes were attached to both mastoids. The vertical electrooculogram (EOG) channels were positioned above and below the left eye, and the horizontal EOG channels were recorded from the outer canthus of each eye. The electrode impedance was kept below 5 kΩ. EEG data were assessed using a NeuroScan SynAmps amplifier (Compumedics USA, Charlotte, NC, USA) with a sampling rate of 1000 Hz and a 0.1−100 Hz band pass filter.

The recorded EEG data were preprocessed using CURRY 7 (Compumedics USA). A trained person with no prior information regarding the data origin removed gross artifacts such as movement artifacts by visual inspection. Artifact rejection related to eye movement or eye blinks was conducted using the mathematical procedure implemented in the preprocessing software of CURRY 7. The data were filtered using a 0.1−30 Hz bandpass filter and epoched from 100 ms pre-stimulus to 600 ms post-stimulus. The epochs were subtracted from the average value of the pre-stimulus interval for baseline correction. If any remaining epochs contained significant physiological artifacts (amplitude exceeding±75 μV) in any site over 62 electrodes, they were excluded from further analysis. Only artifact-free epochs were averaged across trials and subjects for ERP analysis. The MMN wave was generated by subtracting the standard ERP wave from the deviant ones. MMN amplitude was measured as the mean voltage between 130 and 280 ms at nine electrode sites (F3, Fz, F4, FC3, FCz, FC4, C3, Cz, and C4), because the frontocentral electrodes show larger MMN amplitudes. The time window for MMN amplitudes was based on visual in-

spection of the grand-averaged waveforms at FCz. The number of epochs of deviant and standard stimuli used in the analysis did not significantly differ between patients with schizophrenia or bipolar disorder and healthy controls (deviant stimuli: 65.96±6.55 vs. 66.90±7.10 vs. 67.60±9.13, p=0.739, standard stimuli: 589.56±60.20 vs. 596.47±62.96 vs. 604.56±82.07, p=0.733, respectively).

Statistical analysis

A chi-squared test and one-way analysis of variance (ANOVA) were employed to examine differences in demographic variables between the three groups. Preliminary analyses identified a non-normal distribution for HRV-LF and LF/HF ratio in the bipolar disorder group and for CTQ-sexual abuse in the healthy controls. As a result, log transformation was performed on these variables. Furthermore, MMN amplitudes at the nine electrodes were averaged to represent and interpret the results more suitably than using each electrode. A partial Pearson's correlation analysis was conducted between QSF and other variables, including psychological measures, HRV, and MMN. For the patient groups, variables such as sex, age, duration of illness, and medication (i.e., equivalent doses of chlorpromazine and sodium valproate) were chosen as covariates based on the previous studies.[2,65,66] For the healthy controls, age and sex were used as covariates. All factors significantly associated with the QSF (p<0.05) on the partial correlation analysis were included in a hierarchical multiple regression model. This was to identify significant predictors of social functioning in each group. Additionally, for exploratory purposes, the partial correlation analysis and the hierarchical regression analysis were performed with the data of all subjects. In this case, variables including group, sex and age were included as covariates. All analyses included a bias-corrected bootstrap 95% confidence interval (CI) based on 5,000 resampling. Statistical analyses were performed using SPSS 21 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic and psychological characteristics

Comparisons of demographic and psychological characteristics between the three groups are shown in Table 1. There were no significant differences with respect to sex, age, or education. The QSF scores were significantly lower in patients with schizophrenia and bipolar disorder than in healthy controls. Moreover, patients with schizophrenia and bipolar disorder showed significantly lower scores on verbal fluency and the K-AVLT (delayed recall, delayed recognition) than healthy controls. Furthermore, the scores of the SAT-MC were significantly lower in patients with schizophrenia and bipolar disorder than healthy controls. Regarding CTQ scores, patients with bipolar disorder showed significantly higher scores for physical abuse than schizophrenia patients and healthy controls. Additionally, patients with schizophrenia and bipolar disorder showed significantly higher scores for sexual abuse than healthy controls.

Neurophysiological measures: HRV and MMN

The ANOVA revealed no significant differences in HRV between the three groups. The average MMN amplitude for all nine channels for each group are shown in Table 1. The results revealed a significant main effect of group for average MMN (F=11.48, df=2, p<0.001). Post-hoc tests revealed that the patient groups showed significantly smaller MMN amplitudes than healthy controls (-1.51±0.98 μV, -2.12±1.38 μV, and -3.33±1.76 μV for schizophrenia, bipolar disorder, and healthy controls, respectively).

Correlations between QSF and other variables

Table 2 presents the results of the partial correlation analysis. In patients with schizophrenia, QSF was significantly correlated with HRV-LF/HF ratio and CTQ-emotional neglect. In patients with bipolar disorder, QSF was significantly correlated with HRV-HF. In healthy controls, QSF was significantly correlated with BES, CTQ-emotional neglect, and MMN. In all of eighty-two subjects, QSF was significantly associated with K-AVLT (delayed recall, delayed recognition), BES, CTQ-emotional neglect, physical neglect, and HRV-HF.

Multiple hierarchical regression analysis

Results of the hierarchical regression model in each group are presented in Supplementary Table 1, 2, 3 (in the online-only Data Supplement). In the schizophrenia group, CTQ-emotional neglect significantly predicted social functioning after controlling for sex, age, medication (CPZ, mood stabilizer), and duration of illness (B=-0.862, p=0.033). In the bipolar disorder group, HRV-HF significantly predicted social functioning after controlling for sex, age, medication (CPZ, mood stabilizer), and duration of illness (B=0.026, p=0.010). In healthy controls, MMN significantly predicted social functioning after controlling for sex and age (B=-2.072, p=0.033). Also, CTQ-emotional neglect and HRV-HF significantly predicted social functioning in all subjects (CTQ-emotional neglect: B=-0.477, p=0.023; HRV-HF: B=0.015, p=0.004) (Supplementary Table 4, in the online-only Data Supplement).

DISCUSSION

This study aimed to identify psychological and neurophys-

iological factors that could predict social functioning in patients with schizophrenia and bipolar disorder, as well as in healthy controls. Overall, childhood trauma, especially emotional neglect, was a significant predictor of social functioning in schizophrenia, while HRV-HF was a significant predictor of functional outcome in bipolar disorder. In healthy controls, social functioning was significantly predicted by MMN. Also, CTQ-emotional neglect and HRV-HF signifi-

Table 1. Demographic characteristics of all study participants

	Schizophrenia[a] (N=27)	Bipolar disorder[b] (N=30)	Healthy controls[c] (N=25)	p	Post-hoc (LSD)
Age (years)	42.48±11.86	39.70±12.61	42.48±12.60	0.620	
Sex				0.704	
Male	11 (40.7)	10 (33.3)	11 (44.0)		
Female	16 (59.3)	20 (66.7)	14 (56.0)		
Education (years)	13.52±2.56	12.33±3.71	14.24±3.27	0.092	
Number of hospitalizations	3.22±3.86	4.34±10.66		0.608	
Duration of illness (years)	11.22±7.70	10.10±6.81		0.562	
Onset age (years)	31.22±10.80	29.70±11.45		0.609	
Dosage of medication (CPZ equivalent, mg)	518.58±657.94	343.33±475.04		0.251	
Dosage of medication (equivalent to sodium valproate dose, mg)	83.33±250.00	752.57±443.20		<0.001	
PANSS					
Positive	13.78±8.49	9.37±3.01		0.015	
Negative	15.41±4.85	9.47±3.75		<0.001	
General	30.63±10.32	24.40±6.72		0.011	
Total	59.81±21.59	43.23±11.87		0.001	
YMRS		5.86±6.73			
Verbal fluency	15.00±5.21	15.07±5.25	19.40±6.12	0.006	a<c, b<c
KAVLT-trial 5	8.48±2.82	10.47±2.92	11.52±1.69	<0.001	a<b, a<c
KAVLT-delayed recall	6.15±3.70	8.10±3.73	9.96±1.81	<0.001	a<b<c
KAVLT-delayed recognition	10.44±2.98	11.77±2.66	13.92±1.26	<0.001	a<b<c
BES	67.72±8.47	70.97±10.75	73.08±9.17	0.103	
SATMC	8.73±5.02	12.20±3.99	13.56±4.69	<0.001	a<c, b<c
CTQ					
Emotional abuse	9.11±4.85	10.30±5.41	8.00±4.20	0.225	
Physical abuse	8.63±3.62	11.03±5.61	8.04±2.78	0.024	a<b, c<b
Sexual abuse	8.26±3.83	7.90±3.84	6.04±2.01	0.046	c<a, c<b
Emotional neglect	11.00±5.14	13.53±6.10	10.92±3.67	0.099	
Physical neglect	8.48±3.20	9.80±4.05	7.68±3.25	0.087	
HRV					
LF	209.50±214.66	187.03±273.17	275.53±262.59	0.416	
HF	174.75±209.06	169.29±226.63	129.40±117.24	0.656	
LF/HF ratio	2.18±2.02	2.46±3.36	2.62±1.82	0.817	
MMN (total average)	-1.51±0.98	-2.12±1.38	-3.33±1.76	<0.001	c<a, c<b
QSF	49.33±9.34	48.70±11.19	55.20±6.90	0.027	a<c, b<c

CPZ: chlorpromazine, PANSS: Positive and Negative Syndrome Scale, YMRS: Young Mania Rating Scale, KAVLT: Korean Auditory Verbal Learning Test, BES: Basic Empathy Scale, SATMC: social attribution task-multiple choice, CTQ: childhood trauma questionnaire, HRV: heart rate variability, LF: low frequency, HF: high frequency, MMN: mismatch negativity, QSF: questionnaire of social functioning

Table 2. Partial Pearson's correlations between QSF and neurocognition, social cognition, childhood trauma, HRV, and MMN (Bootstrapping=5000)

Patients with schizophrenia (N=27)	r	p	Healthy control subjects (N=25)	r	p
QSF–Verbal Fluency	0.209	0.351	QSF–Verbal Fluency	0.112	0.609
QSF–KAVLT trial 5	0.173	0.441	QSF–KAVLT trial 5	0.083	0.705
QSF–KAVLT recall	0.241	0.281	QSF–KAVLT recall	-0.051	0.818
QSF–KAVLT recognition	0.141	0.531	QSF–KAVLT recognition	-0.327	0.128
QSF–BES total	0.418	0.053	**QSF–BES total**	**0.553**	**0.006**
QSF–SATMC	0.203	0.364	QSF–SATMC	0.043	0.844
QSF–CTQ_EA	-0.089	0.694	QSF–CTQ_EA	0.097	0.659
QSF–CTQ_PA	0.108	0.632	QSF–CTQ_PA	-0.109	0.622
QSF–CTQ_SA	0.139	0.537	QSF–CTQ_SA	-0.303	0.160
QSF–CTQ_EN	**-0.554**	**0.008**	**QSF–CTQ_EN**	**-0.444**	**0.034**
QSF–CTQ_PN	-0.270	0.224	QSF–CTQ_PN	0.074	0.739
QSF–HRV LF	-0.083	0.714	QSF–HRV LF	0.070	0.750
QSF–HRV HF	0.243	0.276	QSF–HRV HF	-0.180	0.411
QSF–HRV LF/HF	**-0.448**	**0.037**	QSF–HRV LF/HF	0.109	0.619
QSF–total MMN	0.190	0.396	**QSF–total MMN**	**-0.638**	**0.001**
Patients with bipolar (N=30)	r	p	All participants (N=82)	r	p
QSF–Verbal Fluency	0.067	0.750	QSF–Verbal Fluency	0.155	0.174
QSF–KAVLT trial 5	-0.295	0.153	QSF–KAVLT trial 5	0.054	0.639
QSF–KAVLT recall	0.097	0.645	**QSF–KAVLT recall**	**0.238**	**0.035**
QSF–KAVLT recognition	0.249	0.231	**QSF–KAVLT recognition**	**0.268**	**0.017**
QSF–BES total	0.145	0.490	**QSF–BES total**	**0.241**	**0.032**
QSF–SATMC	-0.275	0.183	QSF–SATMC	-0.022	0.846
QSF–CTQ_EA	-0.278	0.179	QSF–CTQ_EA	-0.199	0.078
QSF–CTQ_PA	-0.250	0.229	QSF–CTQ_PA	-0.156	0.169
QSF–CTQ_SA	-0.379	0.062	QSF–CTQ_SA	-0.178	0.117
QSF–CTQ_EN	-0.111	0.597	**QSF–CTQ_EN**	**-0.300**	**0.007**
QSF–CTQ_PN	-0.101	0.630	**QSF–CTQ_PN**	**-0.243**	**0.005**
QSF–HRV LF	0.285	0.167	QSF–HRV LF	0.171	0.131
QSF–HRV HF	**0.558**	**0.004**	**QSF–HRV HF**	**0.311**	**0.005**
QSF–HRV LF/HF	-0.247	0.233	QSF–HRV LF/HF	-0.045	0.694
QSF–total MMN	-0.186	0.373	QSF–total MMN	-0.217	0.055

The rows shaded in gray show the distinction among separate domains. The bold type highlights significant p-values (p=0.05). QSF: questionnaire of social functioning, KAVLT: Korean auditory verbal learning test, CTQ: childhood trauma questionnaire, EA: emotional abuse, PA: physical abuse, SA: sexual abuse, EN: emotional neglect, PN: physical neglect, BES: basic empathy scale, SATMC: social attribution task-multiple choice, HRV: heart rate variability, LF: low frequency, HF: high frequency, MMN mismatch negativity

cantly predicted functional outcome in all of eighty-two subjects after controlling for the diagnostic criteria.

Firstly, the social functioning of schizophrenia patients was negatively associated with HRV-LF/HF ratio and CTQ-emotional neglect. Further analysis revealed that only CTQ-emotional neglect was a significant predictor of social functioning. The increased HRV-LF/HF indicates the higher sympathetic nervous activity in comparison to parasympathetic nervous activity, which may result in less flexible autonomic system.[67] In regard to the possible relation between HRV-LF/HF and stress regulation, an extensive review reported that an increase in the HRV-LF/HF ratio may reflect impaired stress regulation.[68] This may insinuate the negative association between HRV-LF/HF ratio and social functioning in schizophrenia patients in our study. Also, previous studies have consistently shown a negative association between childhood trauma and functional outcomes in schizophrenia, as well as in high-risk offspring.[2,3,24,69-72] For instance, Aas et al.[69] reported that having a high prevalence of emotional neglect in childhood was associated with less improvement in global

functioning over course of one-year follow-up in a first-episode psychosis sample. In line with previous findings, our result shows that early emotional neglect could negatively affect social functioning in patients with schizophrenia. It would be advisable for clinicians to carefully elucidate any history of childhood abuse or neglect in patients with schizophrenia.

In patients with bipolar disorder, the social functioning was significantly associated with HRV-HF. The HRV-HF remained a significant predictor of functional outcome in bipolar disorder. HRV-HF has been regarded as a measure of cardiac parasympathetic neural activity[73] and a reflection of emotional regulatory capacity.[50,74] Given that low variability in heart rate indicates abnormal or insufficient adaptability of the autonomic nervous system,[32] reduced HRV-HF implies a difficulty in regulating one's emotional arousal, which could result in impaired functioning. It was reported that HRV is related to subjective well-being, mediated by executive emotion regulation.[52] Other previous studies, which have shown the positive correlation between HRV-HF and social cognition,[51,75] also support our results that HRV-HF is associated with social functioning. It seems that patients with reduced HRV-HF have difficulty in interpreting social information, which lead to impaired functioning.

However, the result of our study did not show any significant differences in HRV parameters between the three groups, which is contrary to previous studies reporting that HRV in bipolar disorder is reduced relative to that in healthy controls.[76,77] Considering that HRV in bipolar disorder was reduced during euthymia and depression compared to mania,[78] the current affective state in bipolar disorder might affect difference in HRV. Our results suggest that to enhance functional outcomes in patients with bipolar disorder, interventions focusing on increasing adaptive emotional regulation would be needed.

In healthy controls, social functioning was significantly associated with childhood trauma-emotional neglect, empathy, and MMN. Among those variables, MMN predicted functional outcomes in healthy controls. A significant association between emotional neglect and social functioning indicates that emotional support and security from a caregiver in childhood is important in acquiring social skills and forming relationships with others. Emotional neglect in childhood is known to influence social dysfunction in adulthood through the oxytocin level and attachment system in the general population.[79] Empathic ability was also correlated with social functioning in healthy controls. A deficit in cognitive or emotional empathy could contribute to impairment in social functioning.[80] Individuals with higher empathic ability were known to have larger social networks,[81] which are associated with future life satisfaction and quality of life.[82] On the other hand, lower empathic level is associated with depressive symptoms,[83] which could result in poorer social functioning.[84] Several studies have shown a significant association between deficit MMN and functional impairment in schizophrenia,[34,40,41] as well as in healthy controls.[85] Given that MMN reflects a predominantly automatic process,[85] the present result indicates that neurophysiological measures assessing pre-attentive detection could be used as an indicator of functional outcomes in healthy controls.

After controlling for the diagnostic criteria, CTQ-emotional neglect and HRV-HF still significantly predicted social functioning in all of eighty-two subjects. This result shows that early traumatic events strongly affect later functional outcome. The main implication for caregivers that can be drawn from this finding is the importance of emotional support and security during early childhood in preventing impaired functioning during adulthood. Also, HRV-HF could be used as a biological marker of social functioning level regardless of whether they are clinical or healthy control. Given that HRV-HF is an indicator of emotional self-regulation,[86] emotional regulation training is expected to help people develop effective social interaction skills.[87]

Some limitations of the current study should be noted. Firstly, as subjective functioning measures were used, there is the possibility that patients' self-report would not reflect the objective evaluation of a clinician. Second, the sample size was relatively small, thus further a study with larger sample is needed to generalize our results. To conclude, our results suggest that social functioning in patients with schizophrenia and bipolar disorder, as well as healthy controls, could be associated with different neurophysiological and psychological factors. Additionally, emotional neglect in childhood and HRV-HF were significant predictors of functional outcome irrespective of what group they are, thus these factors should be regarded as important markers of social functioning.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2019.07.28.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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Supplementary Table 1. Hierarchical regression analysis predicting social functioning using BES and CTQ in patients with schizophrenia (N=27) (Bootstrapping=5000)

Step	R^2	ΔR^2	ΔF	B	t	p
1.	0.135	0.135	0.652			0.662
Sex				1.151	0.276	0.770
Age				-0.279	-1.418	0.206
Dosage of medication (CPZ)				0.003	0.765	0.553
Dosage of medication (mood stabilizer)				-0.011	-0.925	0.296
Duration of illness				0.533	1.578	0.059
2.	0.487	0.353	6.536			0.007
Sex				0.897	0.265	0.780
Age				-0.255	-1.408	0.203
Dosage of medication (CPZ)				0.001	0.416	0.729
Dosage of medication (mood stabilizer)				-0.005	-0.540	0.567
Duration of illness				0.523	1.868	0.066
HRV-LF/HF				-1.509	-1.801	0.073
CTQ-EN				**-0.862**	**-2.575**	**0.033**

CPN: chlorpromazine, CTQ: childhood trauma questionnaire, EN: emotional neglect, HRV: heart rate variability, LF: low frequency, HF: high frequency

Supplementary Table 2. Hierarchical regression analysis predicting social functioning using neurocognition, CTQ, and HRV in patients with bipolar disorder (N=30) (Bootstrapping=5000)

Step	R^2	ΔR^2	ΔF	B	t	p
1.	0.299	0.299	2.045			0.108
Sex				2.042	0.453	0.637
Age				**-0.471**	**-2.628**	**0.016**
Dosage of medication (CPZ)				-0.002	-0.390	0.742
Dosage of medication (mood stabilizer)				-0.006	-1.249	0.306
Duration of illness				**0.767**	**2.354**	**0.035**
2.	0.517	0.218	10.404			0.004
Sex				3.702	0.960	0.312
Age				-0.308	-1.930	0.097
Dosage of medication (CPZ)				0.001	0.274	0.798
Dosage of medication (mood stabilizer)				-0.007	-1.903	0.087
Duration of illness				0.566	2.001	0.064
HRV-HF				**0.026**	**3.226**	**0.010**

CPZ: chlorpromazine, HRV: heart rate variability, HF: high frequency

Supplementary Table 3. Hierarchical regression analysis predicting social functioning using BES, CTQ, and MMN in healthy control subjects (N=25) (Bootstrapping=5000)

Step	R^2	ΔR^2	ΔF	B	t	p
1.	0.018	0.018	0.199			0.821
Sex				1.819	0.630	0.546
Age				0.000	0.004	0.996
2.	0.574	0.557	8.281			0.001
Sex				-1.052	-0.451	0.677
Age				0.010	0.115	0.910
BES				0.340	2.135	0.097
CTQ-EN				-0.295	-0.912	0.356
MMN (total average)				**-2.072**	**-2.893**	**0.033**

CTQ: childhood trauma questionnaire, EN: emotional neglect, MMN: mismatch negativity

Supplementary Table 4. Hierarchical regression analysis predicting social functioning using K-AVLT, BES, CTQ, and HRV in all subjects (N=82) (Bootstrapping=5000)

Step	R^2	ΔR^2	ΔF	B	t	p
1.	0.022	0.022	0.899			0.411
Sex				0.268	0.120	0.903
Age				-0.119	-1.339	0.199
2.	0.078	0.056	4.736			0.033
Sex				0.384	0.019	0.853
Age				-0.120	-0.150	0.200
Group				**2.884**	**0.237**	**0.014**
3.	0.332	0.254	4.557			0.001
Sex				0.245	0.123	0.889
Age				-0.031	-0.267	0.689
Group				1.405	0.978	0.274
K-AVLT delayed recall				0.584	1.598	0.149
K-AVLT delayed recognition				0.117	0.229	0.798
BES				0.157	1.386	0.208
CTQ-EN				**-0.477**	**-2.248**	**0.023**
CTQ-PN				-0.182	-0.613	0.493
HRV-HF				**0.015**	**2.851**	**0.004**

K-AVLT: Korean Auditory Verbal Learning Test, BES: Basic Empathy Scale, CTQ: childhood trauma questionnaire, EN: emotional neglect, PN: physical neglect, HRV: heart rate variability, HF: high frequency