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Associations between Physiological Responses to Social-Evaluative Stress and Daily Functioning in First-Episode Schizophrenia

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Abstract

Schizophrenia (SZ) is associated with impaired adaptive functioning, including difficulties managing the demands of independent living, work, school, and interpersonal relationships. Prior studies have linked the physiological stress response with less effective coping in daily life. Differences in stress-response tendencies may also support heterogeneity in daily functioning in SZ. The present study examined two established measures of the stress response in patients with first-episode SZ. Salivary cortisol was included as an index of hypothalamic-pituitary-adrenal response. Vagal suppression (VS), a measure of stress-related reduction in heart rate variability, was used to assess parasympathetic flexibility. Greater cortisol response and VS to social-evaluative stress were predicted to be associated with better functioning in SZ over and above relationships with social cognition and neurocognition, two well-established predictors of functional outcome. Thirty-eight first-episode SZ outpatients and 29 healthy comparison subjects (HC) provided social cognitive, neurocognitive, and physiological measurements before and after

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Contributors

CMY, KHN, and MFG designed the project. ACR, CMY, HKH, and GAM developed the study concept. JV, KLS, and KHN recruited participants and supervised their diagnoses and functional outcome and symptom severity ratings. MFG and JL designed and supervised the social cognitive assessments. ACR wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

the Trier Social Stress Test (TSST). Although SZ and HC did not differ on VS to the TSST, patients exhibited significant associations between VS and functioning across all four domains of the Role Functioning Scale. Furthermore, greater VS predicted more effective functioning with friends, beyond the contributions associated with social cognition and neurocognition, and strengthened the positive effects of higher levels of social cognition on independent living/self-care. VS elicited by social-evaluative stress in the laboratory may reflect stress-response tendencies in daily life that are relevant for daily functioning in first-episode SZ.

Keywords

Schizophrenia; functional outcome; stress; vagal suppression; cortisol

1. Introduction

Schizophrenia (SZ) is associated with widespread impairment in daily functioning, including difficulties with living independently, performing at work and school, and maintaining relationships with family and friends. Compromised functional outcome contributes to long-term disability in SZ (Harvey et al., 2012) and poor quality of life (Heider et al., 2007). The most well-established predictor of functional outcome is social cognition (Horan et al., 2012; Martínez-Domínguez et al., 2015). However, meta-analyses suggest that social cognition alone accounts for only about 16% of the variance in community functioning in SZ (Fett et al., 2011), increasing to 25% when combined with neurocognition (Schmidt et al., 2011; Vauth et al., 2004). To achieve a more complete understanding of functional outcome and identify new targets for its enhancement, the present study examined two physiological pathways that may be critical to supporting functioning in SZ.

Adaptive functioning inherently involves managing physiological stress responses effectively, including rapid activation of the sympathetic nervous system, cortisol release, and a speedy return of cortisol to initial levels when a threat or challenge is resolved (de Kloet et al., 2005). Resting cortisol and cortisol reactivity are dissociated in SZ (Karanikas & Garyfallos, 2015), such that resting levels are typically elevated and reactivity is often blunted relative to healthy comparison (HC) participants (Brenner et al., 2009; Ciufolini et al., 2014; van Venrooij et al., 2012; cf. Mizrahi et al., 2012; Monteleone et al., 2015). Although cortisol has been studied extensively in SZ, its contribution to functional outcome remains poorly understood. Tas et al. (2018) found that chronic SZ patients who exhibited a robust cortisol response to social-evaluative stress functioned better socially than cortisol non-responders. HC studies reveal similar positive associations between acute cortisol response and interpersonal competence (Cook et al., 2012). Therefore, we expected first-episode SZ patients to exhibit overall blunting of the cortisol response to social-evaluative stress, with larger responses predicting better functional outcome.

The stress response is also facilitated by nimble parasympathetic modulation (Porges, 2003). Polyvagal theory posits that variations in time between heartbeats (“heart rate variability”) reflects the contribution of the parasympathetic nervous system to cardiac regulation through the vagus nerve (Porges, 1995, 2007). This modulatory activity can be quantified via

respiratory sinus arrhythmia (RSA; Porges, 2007). In healthy samples, higher RSA at rest is associated with reliance on more effective emotion-regulation strategies (Fabes & Eisenberg, 1997; Williams et al., 2015), more appropriate social engagement (Porges, 2007), and better cognitive performance (Thayer et al., 2009). Given these associations between RSA and cognitive and affective self-regulation, the neurovisceral integration model situates RSA as an indicator of central and autonomic nervous system integration (Thayer & Lane, 2000).

RSA is also sensitive to social stressors, which typically trigger a decrease in RSA, known as vagal suppression (VS; Porges et al., 2007). VS is a brief, adaptive response to the disruption of homeostasis; restorative functions are down-regulated in order to facilitate increased metabolic output for fight-or-flight responses (Porges et al., 1996). Blunted VS in healthy adults has been associated with negative outcomes, including anxiety (Friedman & Thayer, 1998), depression (Rottenberg et al., 2007), and general psychopathology (Shahrestani et al., 2015). Conversely, more VS during stress is linked to better emotion regulation, prosocial behavior, better social skills, and higher social status during adolescence and early adulthood (Cui et al., 2015; Graziano & Derefinko, 2013). In SZ patients, RSA at rest is typically attenuated relative to HC (Andersen et al., 2018; Montaquila et al., 2015) and has been associated with negative symptoms (Mathewson et al., 2012) and poorer adaptive functioning (Hamilton et al., 2014). It is less clear whether VS to psychosocial stress is similarly compromised in SZ. To our knowledge, only one study has evaluated whether SZ patients and healthy controls differ in RSA to social-evaluative stress. Andersen and colleagues (2018) observed diminished vagal modulation in SZ. However, it has yet to be established whether individual differences in VS in patients are linked to differences in real-world functioning. Patterns observed in healthy individuals suggest that robust VS to psychosocial stress is adaptive and portends better functioning.

The present study sought to determine whether measures of physiological response to social-evaluative stress explain differences in functional outcome during first-episode SZ. Specifically, it was expected that physiological responses to social-evaluative stress would be most relevant for social domains of functioning, such as relationships with friends and family. Given that there are social aspects to independent living (e.g., shopping) and work/school functioning (e.g., managing professional relationships), smaller associations with physiological responses to social-evaluative stress were anticipated. To assess their predictive value in SZ, we evaluated the contributions of cortisol and VS to functioning over and above social cognition and neurocognition. Single measures of physiological reactivity as well as joint contributions between cortisol response, VS, and social cognition were examined given some suggestion that cognition and physiology may interact in SZ (Hamilton et al., 2014).

2. Materials and methods

2.1. Participants

Participants were recruited through the UCLA Center for Neurocognition and Emotion in Schizophrenia and included 38 first-episode SZ outpatients and 29 HC participants; all provided written informed consent. An additional 8 SZ and 5 HC participants were excluded due to cardiovascular disease (heart disease, cardiac hypertension), beta-blocker usage, or

incomplete data. Patients met criteria for schizophrenia (n = 25), schizophreniform disorder (n = 9), or schizoaffective disorder, depressed type (n = 4) as assessed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID), Fourth Edition (First et al., 1995). Patients were within two years of diagnosis, receiving treatment through the UCLA Aftercare Research Program, and stabilized on antipsychotic medication. When clinically feasible (3 of 5 patients), antiparkinsonian medications were discontinued for 48 hours to minimize anticholinergic effects on physiological measures. HC were screened with the SCID-IV, and exclusion criteria included personal history of psychotic disorder, major depression, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, or personality disorder, and first-degree family history of any psychotic disorder. Potential participants with a history of alcohol or drug abuse in the past month or dependence in the past 6 months, neurological disorder, major head trauma, or mental retardation were excluded.

2.2. Procedure

Participants were assessed over 3-4 sessions that included functional outcome assessment, social cognitive and neurocognitive testing, and administration of the TSST. The TSST session included a 4-minute baseline electrocardiogram (EKG), EKG recording during the TSST, and salivary cortisol assessments (Figure 1). The mean time between assessment of functional outcome and the TSST was 45 days (median = 46).

The TSST (Kirschbaum et al., 1993) is a social-evaluative stressor that involves a 5-minute anticipatory phase during which participants in the present study prepared a speech advocating a not guilty verdict in response to a false accusation of shoplifting. Participants then completed 5-minute speech and serial subtraction tasks in front of an evaluative panel. Participants rated their state anxiety by completing the State Trait Anxiety Inventory (STAI; Spielberger, 1983) immediately before and after the TSST.

The TSST was scheduled in the mid-afternoon to minimize diurnal cortisol variation. Participants were instructed to avoid dental work and abstain from exercise, alcohol, and nonprescription medications in advance of the TSST and queried about current illness and medication use, which may influence cortisol response (Kirschbaum & Hellhammer, 1994). Procedures ensured that participants refrained from caffeine, nicotine, major meals, dairy, chips, acidic, or high-sugar foods, and brushing their teeth one hour before the session. Cortisol was assessed prior to the TSST and 20 minutes after TSST onset (Dickerson & Kemeny, 2004). Resting cortisol data from 2 SZ and 5 HC and reactivity data from 7 SZ and 6 HC were not available due to noncompliance with study procedures or inability to provide a saliva sample suitable for analysis. EKG was collected after 30+ minutes of acclimatization to the lab. Participants were seated in a sound-attenuated chamber and instructed to breathe normally and minimize movement.

2.3. Measures

UCLA Aftercare Research Program staff, unaware of TSST performance, administered clinical symptom, functional outcome, social cognitive, and neurocognitive measures. Clinical symptoms were assessed with the Scale for the Assessment of Positive Symptoms

(SAPS; Andreasen, 1984a) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984b).

A semi-structured interview, the Role Functioning Scale (RFS; Goodman et al., 1993), was used to assess patients' daily functioning across four domains: work/school productivity, independent living/self-care, relationships with friends, and relationships with family. RFS subscales are rated 1-7, representing a range from severely limited to optimal functioning. The RFS has strong psychometric properties in samples with chronic mental illness (Green & Gracely, 1987) and was administered only to patients because of ceiling effects in HC.

A composite social cognition score was derived from equally weighted z-scores from two established measures: relationships across domains (RAD; Sergi et al., 2009) and the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT; Mayer et al., 2002) with good validity in samples with SZ (Eack et al., 2008; Pinkham et al., 2013). The RAD employs vignettes to evaluate competence in relationship perception and implicit knowledge of relational models. The MSCEIT assesses the ability to identify, use, understand, and manage emotions. The RAD and MSCEIT have both been used extensively to assess deficits in social cognition in SZ (Green et al., 2012; Kee et al., 2009; Kern et al., 2009; Sergi et al., 2009).

The MATRICS Consensus Cognitive Battery (MCCB: Kern et al., 2008; Nuechterlein et al., 2008) is a reliable and valid measure of cognition in SZ (August et al., 2011). Social cognitive domain scores from the MSCEIT Managing Emotions branch were not included in the MCCB neurocognitive composite, as social cognitive assessment relied on the full MSCEIT and RAD. Neurocognitive composite T-scores were age- and gender-adjusted (Nuechterlein, & Green, 2017).

EKG was collected using electrodes on the right and left lower ribs. Signals were bandpassed 0.05-200 Hz and sampled at 2000 Hz. Offline, QRSTool (Allen et al., 2007) was used to visually inspect, edit for missed beats and artifact (Berntson et al., 1997), and reduce EKG to interbeat intervals (IBI). CMetX (Allen et al., 2007) was used to estimate RSA by calculating ln of band-limited (.12-.40 Hz) IBI variance. Only EKG obtained during the 4-minute anticipatory phase of the TSST were analyzed, as speech alters respiration rate which affects RSA (Quintana & Heathers, 2014). VS was calculated as RSA during TSST speech anticipation minus RSA during 4-minute baseline (Rigoni et al., 2017; Scott & Weems, 2014).

Salivary samples were collected via passive drool into Cryule vials, frozen, and assayed for salivary cortisol by a commercial vendor (Institute for Interdisciplinary Salivary Bioscience Research, Irvine, CA). The average of two assays was used for subsequent analyses. Cortisol data were excluded if raw resting values were 3 SDs above the individual's group mean (n = 1 SZ). Cortisol response to the TSST was calculated as the difference between cortisol at 20 minutes after TSST initiation and pre-TSST.

2.4 Statistical Analyses

Group differences were analyzed with t-tests, Pearson χ^2, and ANOVA. Pearson correlations and Fisher r-to-z transformations were used to characterize relationships between TSST reactivity and social and less-social RFS subscales. Hypotheses were tested with hierarchical linear regressions predicting each of the four RFS subscales from social cognition and neurocognition, each physiological measure, and their interactions. To determine whether a general deficit in the stress response was driving effects, cortisol response and VS were evaluated in the same model. To verify that effects for reactivity measures were not confounded by resting levels, cortisol and RSA at rest were subjected to the same regression analysis strategy. Neither cortisol nor RSA at rest accounted for variance in any domain of daily functioning beyond social cognition or the combination of social and neurocognition (all $p > .10$). Therefore, resting measures were not evaluated further.

3. Results

SZ and HC were well-matched on age, ethnicity, and gender (Table 1). Given that SZ influences educational attainment, SZ and HC differed on personal years of education, $t(65) = -4.19$, $p < .001$, $d = -1.03$. SZ parental education level was marginally lower, $t(65) = -2.00$, $p = .05$, $d = -0.51$. SZ SAPS/SANS symptoms were generally mild to moderate. SZ exhibited poorer social cognitive ($t(65) = -6.86$, $p < .001$, $d = -1.63$) and neurocognitive ($t(65) = -6.10$, $p < .001$, $d = -1.5$) performance than did HC (Table 2). Prior to the TSST, SZ endorsed higher state anxiety ($t(54) = 2.71$, $p = .009$, $d = .70$) than did HC. There were no group differences in resting physiology (pre-TSST cortisol: $t(57) = -0.30$, $p = .76$, $d = .09$; pre-TSST RSA: $t(65) = -1.37$, $p = .18$, $d = .035$).

The TSST effectively increased state anxiety pre-to-post TSST ($F(1, 53) = 9.49$, $p = .003$, $\eta^2_p = .15$), with HC tending to report a more substantial increase (Group x Pre-to-post: $F(1, 53) = 3.10$, $p = .08$, $\eta^2_p = .06$). A tendency emerged for blunted TSST cortisol response in SZ ($F(1, 52) = 3.92$, $p = .05$, $\eta^2_p = .07$). Although means were in the predicted direction, SZ and HC did not differ in VS to the TSST ($F(1, 65) = 2.67$, $p = .11$, $\eta^2_p = .04$).

Table 3 provides zero-order correlations between the RFS domains and predictor variables included in the hierarchical regressions. As expected, social cognition was correlated with most RFS domains. Although patients' resting cortisol levels did not correlate with functioning in any domain, resting RSA was positively associated with work productivity and had nonsignificant tendencies to correlate with family and friendship functioning. It was hypothesized that the correlations between TSST physiological reactivity and functional outcome would be stronger for the social subscales (relationships with friends and family) than the less-social domains (work/school productivity, independent living). VS was positively associated with all four RFS domains, but Fisher-r-to-z transformations revealed that there were no significant differences in the magnitude of correlations between physiological reactivity and social vs. less-social RFS subscales. With the exception of a tendency toward a positive association between stress-related change in cortisol and family functioning, cortisol responses were unrelated to RFS.

To evaluate the hypothesis that physiological stress response would explain patients' daily functioning beyond the effects of social cognition, regressions predicting each RFS subscale from social cognition, cortisol reactivity or VS, and their interaction were undertaken. Contrary to expectations, cortisol response did not enhance estimates of any subscale over and above social cognition. Social cognition and VS together accounted for a substantial 33% of variance in SZ functioning in friendships ($p = .004$), relative to 21% for social cognition alone (Table 4). As hypothesized, VS enhanced estimation of functioning in relationships with friends beyond social cognition ($\Delta R^2 = .12$, $\beta = .39$, $t(35) = 2.45$, $p = .02$). VS did not enhance estimates of work productivity. The full model accounted for 52% of the variance in independent living, including an interaction between VS and social cognition ($\Delta R^2 = .06$, $\beta = .38$, $t(35) = 2.01$, $p = .05$), such that greater VS strengthened the already positive effects of higher levels of social cognition on independent living and self-care (Figure 2). No model accounted for significant variance in family functioning.

Due to null findings for cortisol response, follow-up analyses to determine the specificity of effects were confined to VS. Regressions were repeated for each RFS subscale with overall cognition (social cognition and neurocognition) instead of social cognition alone entered in the first step. In combination, social cognition, neurocognition, and VS accounted for 36% of the variability in patients' relationships with friends ($F(3, 34) = 6.29$, $p = .002$). The role of VS remained unchanged with the cognitive composite in the model; VS continued to enhance estimates of functioning with friends beyond overall cognitive abilities, (VS: $\Delta R^2 = .13$, $\beta = .41$, $t(34) = 2.59$, $p = .014$). VS did not improve model fit predicting RFS work productivity, independent living, or family functioning. As cognition already accounted for 45% of the variance in RFS independent living, the addition of VS provided a relatively modest increase to 54% of the total variance ($p = .15$).

To evaluate the possibility that findings for VS were attributable to stress-related changes in heart rate, the same regression analyses were applied as with VS. Change in average heart rate from rest to TSST anticipation did not predict any RFS subscale over and above social cognition or the combination of social and neurocognition (all $p > .28$).

To determine whether VS or a generalized systemic deficit in stress reactivity was driving observed effects, regressions predicting RFS domains from social cognition, VS, cortisol response, and the interactions between these predictors were undertaken for participants with available cortisol response data ($n = 31$). Order of entry and results of these regressions are provided in Table 4. Regression results and the standardized β coefficients for shared predictors were similar to regressions for VS alone, such that the cortisol response predictors and interaction terms did not enhance model fit. Likewise, VS continued to predict functioning in relationships with friends over and above social cognition ($\beta = .36$, $p = .05$). For independent living, a consistent interaction between social cognition and VS, which was found in the larger sample, also emerged in the subsample with cortisol response data ($\beta = .46$, $p = .03$). Again, no variables beyond social cognition enhanced predictions of work productivity, and no models accounted for significant variance in family functioning.

4. Discussion

The present study evaluated the hypothesis that physiological responses to stress, as indexed by cortisol and VS to social-evaluative stress, would predict daily functioning in first-episode SZ. In particular, it was expected that physiological responses to social-evaluative stress would be more relevant for primarily social domains of role functioning (relationships with friends and family) than for less-social domains (work/school productivity, independent living). As predicted by polyvagal theory (Porges, 2003; 2009), findings confirmed that greater VS during the early phase of SZ is associated with better functional outcome in SZ across social and less social domains. These novel results extend studies reporting positive associations between laboratory-induced VS and social functioning in healthy adolescents and young adults (Cui et al., 2015; Graziano & Derefinko, 2013; Scott & Weems, 2014) to young adults contending with serious mental illness.

Further, VS accounted for unique variance in the quality of patients' relationships with friends over and above social cognition and neurocognition and interacted with social cognition to predict patients' independent living behaviors. A parsimonious explanation for these results is that physiological responses elicited by the TSST parallel patients' stress response tendencies in daily life. Specifically, greater VS during speech anticipation could reflect simultaneous and optimal changes in attention (Porges et al., 1973), physiological and metabolic preparation for action (Jennings et al., 2014), and/or emotion regulation (Cui et al., 2015). By efficiently downregulating parasympathetic drive, patients who demonstrated flexible VS to the TSST may also regulate more effectively when confronting stressors in the course of daily life.

Our findings resemble those of Andersen et al. (2018), as they link aberrant RSA response to social stress and poorer outcomes in SZ. It is noteworthy that individual differences in VS corresponded with clinician ratings of patients' real-world functioning, even in the absence of a significant difference in the magnitude of VS for SZ and HC groups. Present findings also support the neurovisceral integration model, which posits that the functioning and integration of the central autonomic network contributes to heterogeneity in parasympathetic flexibility and cognitive and affective self-regulation capacity (Thayer & Lane, 2000).

By including multimodal assessment of physiology at rest and in response to stress, the present study offers evidence of a specific relationship between appropriate vagal modulation during stress and better adaptive functioning. Strengthening the argument for specificity, observed relationships between VS and functioning were not attributable to task-related changes in heart rate. Evidence for a specific relationship with VS is encouraging, although it is not yet known whether context-appropriate VS can be trained or targeted by clinical interventions and whether improving VS would lead to improvement in social functioning.

The present study also builds on previous research by articulating how different indices of vagal flexibility and social cognition may be related to functional outcome across phase of illness in SZ. In a chronic sample, we observed that RSA at rest moderated the relationship between social cognition and functioning independently or in the workplace, such that

patients with the greatest impairments in social cognition required high resting RSA to perform effectively in both domains, whereas RSA was not associated with functional outcomes in patients with intact social cognition (Hamilton et al., 2014). In the present first-episode sample, similar relationships with RSA at rest were not observed. Instead, the combination of greater context-appropriate VS to stress and intact social cognition was associated with optimal independent living outcomes, indicating distinct patterns of response as a function of phase of illness. Taken together, these studies highlight the potential for interactions between social cognition and vagal flexibility to predict independent living skills and behaviors over the course of SZ.

The present investigation did not yield support for the hypothesized relationship between a blunted cortisol stress response and impaired functioning in first-episode SZ. However, we did replicate a tendency for a blunted cortisol response to the TSST in first-episode SZ (van Venrooij et al., 2012). A blunted cortisol response is associated with desensitization of the hypothalamus-pituitary-adrenal axis by repeated exposure to psychosocial stress (Brenner et al., 2009; Marcelis et al. 2004) or the combination of stress and antipsychotic medications (Mondelli et al., 2010). Therefore, cortisol stress response may be a stronger indicator of illness chronicity than a sensitive marker of functioning in SZ.

Limitations of the present study include its cross-sectional design, which precludes directional inferences and the absence of measures assessing emotion-regulation strategies used during the TSST. We propose that VS reflects self-regulation during stress, but future studies of SZ are needed to clarify relationships between VS, emotion regulation, and interpersonally effective behavior. Given the present study's reliance on the TSST, it is also unclear whether physiological responses to non-social stressors would show the same relationships with functional outcome in first-episode SZ.

Nonetheless, the present study provides initial evidence that context-appropriate VS to social-evaluative stress is associated with current functioning and social cognition in first-episode SZ. In light of these associations and evidence that VS can prospectively predict the expression of clinical symptoms such as anxiety and depression in adolescents (Greaves-Lord et al., 2010; McLaughlin et al., 2014), longitudinal studies examining the relationship between VS and functional outcome in SZ are warranted. Specifically, investigations are needed to determine whether similar relationships between VS and outcomes persist into the chronic phase of illness, whether VS predicts functioning over time or response to clinical interventions, and whether interventions targeting VS can improve clinical course.

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Conflict of interest

ACR, JL, HKH, MFG, GAM, and CMY have no conflicts to report. KHN has received research support from Posit Science, Inc., and Janssen and has been a consultant to Astellas, Biogen, Genentech, Janssen, Medincell, Otsuka, Takeda, and Teva. KLS has received funding from Janssen Scientific Affairs, LLC, through grants to KHN, has served as a consultant to Alkermes, Inc, and Medincell, Inc, and has been on speaker bureaus for Janssen Canada and Otsuka America Pharmaceutical, Inc. JV has received funding from Brain Plasticity, Inc., Genentech, Inc., and Janssen Scientific Affairs, LLC, and has served as a consultant to Boehringer-Ingelheim, GmbH, and Brain Plasticity, Inc.

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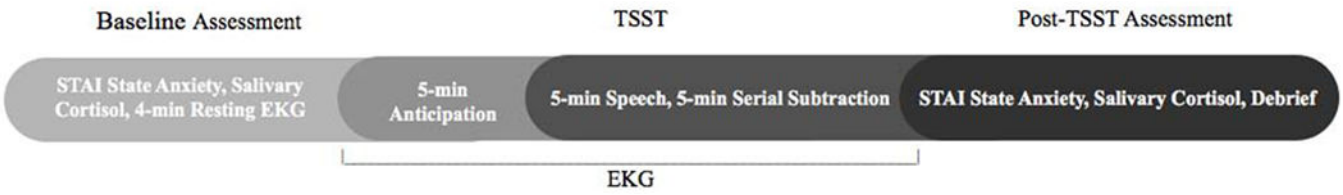

Fig. 1.
Timeline of Trier Social Stress Test (TSST) Procedure.

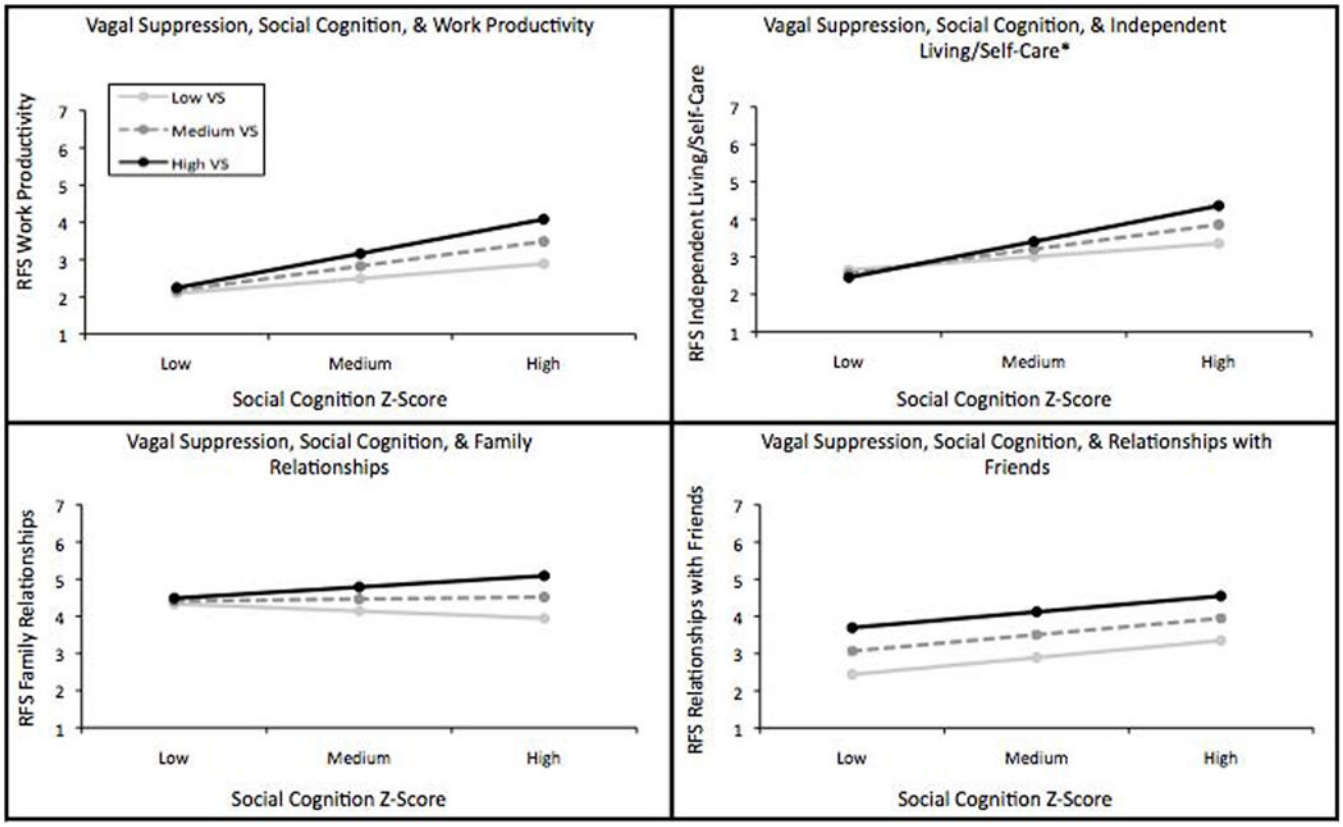

Fig. 2.

Models of the interaction between social cognition and VS on domains of daily functioning. For illustration, VS and Social Cognition were categorized into three levels (*Low*- one SD below the mean; *Medium*- mean; *High*- one SD above the mean). VS moderated the relationship between social cognition and independent living/self-care, VS: vagal suppression; RFS: role functioning scale. *p =.05

Table 1.

Demographic and Clinical Characteristics of Participants

	Schizophrenia Patients (*n* = 38)		Healthy Comparison Subjects (*n* = 29)	
Characteristic	***M***	***SD***	***M***	***SD***
Age (years)	22.16	3.55	22.72	3.38
Education (years)***	13.30	1.75	15.45	2.44
Highest Parental Education (years)t	13.50	4.54	15.52	3.39
Time Since First Psychotic Episode (days)	383.14	220.05		
Antipsychotic Dosage1 (mg/day, CPZ equiv.)	189.22	135.72		
SAPS Total Score2	6.21	4.77		
SANS Total Score3	12.52	5.68		
	N		***N***	
Gender (Female/Male)	8/30		9/20	
Race/Ethnicity				
African America	10		6	
Asian American	3		10	
European American	7		5	
Latino/Latina	16		7	
Mixed	2		1	
Smoking Status (Smoker/Nonsmoker)	4/34		2/27	

Note:

t $p = .05$,

* $p < .05$,

** $p < .01$,

*** $p < .001$.

1 Antipsychotic dosages were available for $n = 37$. CPZ equiv. = chlorpromazine equivalents;

2 SAPS = Scale for the Assessment of Positive Symptoms ($n = 33$);

3 SANS = Scale for the Assessment of Negative Symptoms ($n = 33$).

Table 2.

Cognition, functional outcome, and Trier Social Stress Test (TSST)-related changes in self-reported anxiety and psychophysiology

	Schizophrenia Patients (*n* = 38)		Healthy Comparison Subjects (*n* = 29)	
Measure	***M***	***SD***	***M***	***SD***
Social Cognition Composite (z-score)***	−1.51	1.09	0.05	0.73
MCCB Neurocognitive Composite[1] ***	29.68	12.42	46.59	9.47
Role Functioning Scale	2.95	1.68		
Work Productivity	3.34	1.21		
Independent Living/ Self-Care	4.58	1.18		
Relationships with Family	3.50	1.59		
Relationships with Friends				
Pre-TSST	39.29	14.03	31.00	8.78
STAI State[2]**	0.21	0.14	0.22	0.11
Cortisol at Rest (μg/dL)[3]t	6.26	1.13	6.61	0.90
RSA at Rest (ln ms^2)				
Post TSST	41.13	12.04	36.77	10.52
STAI State	0.02	0.12	0.14	0.31
Cortisol Response (μg/dL)[4]	0.13	0.56	0.40	0.79
Vagal Suppression (ln ms^2)[5]				

Note:

$^{t}p = .05$,

$^{*}p < .05$,

$^{**}p < .01$,

$^{***}p < .001$.

[1]MCCB= MATRICS Consensus Cognitive Battery.

[2]STAI = State-Trait Anxiety Inventory (SZ $n = 31$, HC $n = 25$).

[3]Cortisol at Rest (SZ $n = 35$, HC $n = 24$).

[4]Cortisol Response is the difference score between Cortisol at Rest and cortisol 20 minutes after TSST initiation (SZ $n = 31$, HC $n = 23$).

[5]Vagal Suppression is the difference score between RSA at Rest and RSA during the TSST anticipation phase.

Table 3.

Zero-order correlations of key variables in patients with first-episode schizophrenia

	1	2	3	4	5	6	7	8	9
1. RFS[1] Work/School Productivity	1								
2. RFS Independent Living/Self Care	.78***	1							
3. RFS Relationships with Family	.51***	.52***	1						
4. RFS Relationships with Friends	.80***	.69***	.55***	1					
5. Social Cognition Composite (z-score)	.51***	.67***	.21	.46**	1				
6. RSA at Rest (ln ms^2)	.33*	.15	.29t	.30t	.27	1			
7. Vagal Suppression (ln ms^2)	.41*	.46**	.33*	.52***	.48**	.41*	1		
8. Cortisol at Rest (μg/dL)[2]	−.13	−.12	−.26	.03	−.01	−.08	.06	1	
9. Cortisol Response (μg/dL)[3]	−.04	−.02	.32t	.28	.02	.07	.12	−.16	1

Note: Total $n = 38$,

[1] RFS; Role Functioning Scale;

[2] Cortisol at Rest, ($n = 35$);

[3] Cortisol Response ($n = 31$);

t $p < .10$,

* $p < .05$,

** $p < .01$,

*** $p < .001$

Table 4.

Hierarchical regressions predicting domains of daily functioning from social cognition, vagal suppression and cortisol response, and hypothesized interactions.

Predictors	Work Productivity		Independent Living		Relationships with Family		Relationships with Friends	
	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β
Step 1: Social Cognition z-score	.26**	.51**	.43***	.66***	.04	.21	.21**	.46**
Step 2: Vagal Suppression	.04	.21	.03	.19	.07	.29	.12*	.39*
Step 3: Vagal Suppression x Social Cognition z-score	.02	.24	.06*	.51*	.04	.32	.00	−.02
Step 4: Cortisol Response	.00	−.05	.00	.01	.10	.32	.06	.25
Step 5: Social Cognition z-score x Cortisol Response	.01	.26	.00	.00	.00	−.08	.00	−.12
Steps 1-3: Total R^2	.32**		.52***		.15		.33**	
Steps 1-5: Total R^2	.35*		.52**		.28		.41*	

Note: For steps 1-3, total $n = 38$; for steps 1-5, total $n = 31$.

* $p \leq .05$,

** $p < .01$,

*** $p < .001$.