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Social Cognition and Functional Outcome in Schizophrenia: The Moderating Role of Cardiac Vagal Tone

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Abstract

Individuals with schizophrenia face significant challenges in daily functioning, and while social cognition predicts how well patients respond to these challenges, associated physiological mechanisms remain unspecified. The present study draws from polyvagal theory and tested the hypothesis that respiratory sinus arrhythmia (RSA), an established indicator of the capacity to self-regulate and adapt to environmental demands, combines with social cognition to predict functional outcome. Using data from 41 schizophrenia patients and 36 healthy comparison subjects, we replicated group differences in RSA and social cognition and also demonstrated that RSA and social cognition interact to predict how effectively patients manage work and independent living activities. Specifically, RSA did not enhance functional outcomes when social cognition was already strong, but higher levels of RSA enabled effective role functioning when social-cognitive performance was impaired. Jointly, RSA and social cognition accounted for 40% of the variance in outcome success, compared with 21% when evaluating social cognition alone. As polyvagal theory suggests, physiological flexibility and self-regulatory capacity may compensate for poorer social-cognitive skills among schizophrenia patients.

Keywords

schizophrenia; cardiac vagal tone; respiratory sinus arrhythmia; social cognition; functional outcome

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Functional outcomes vary widely among individuals with schizophrenia, raising important questions about how they manage the challenges of independent living and effective self-regulation across diverse settings and relationships. Polyvagal theory (e.g., Porges, 1995, 2007) provides a valuable perspective for explaining this variability, as it highlights regulatory mechanisms within the cardiovascular system that promote flexible engagement with situational demands and that support adaptive social and emotional behaviors. Well-validated in healthy individuals, polyvagal theory offers an opportunity to derive novel predictions about how cardiac vagal tone (CVT) – a physiological indicator of the capacity for behavioral flexibility – predicts performance in social and occupational roles, independently and in combination with social cognition, a well-established predictor of functional outcome in schizophrenia (Couture, Penn, & Roberts, 2006). Integrating polyvagal theory with social cognition holds considerable promise, as social-cognitive abilities in schizophrenia are associated with neural circuitry involving the medial frontal

cortex (Pinkham, Penn, Perkins, & Lieberman, 2003) as well as autonomic nervous system activity (Jáuregui et al., 2011).

According to polyvagal theory, cardiac activity is subject to multiple and dynamic interactions between central and peripheral autonomic control mechanisms, including the parasympathetic nervous system via efferent and afferent fibers of the vagus nerve which functions as a "brake." Efferent fibers, originating in the brainstem, slow heart rate (HR) by decreasing firing of the sinoatrial node (the primary cardiac pacemaker), whereas vagal afferent fibers, originating in the heart, provide feedback to the brain and facilitate regulation of cardiac activity. While efficient control of the vagal brake enables an individual to quickly engage with and disengage from the environment, poor control of the vagal brake hinders optimal interaction with the environment (Porges, 2007). CVT is commonly measured via respiratory sinus arrhythmia (RSA) which results from increases in vagal efference during exhalation that lead to HR deceleration and decreases in vagal efference during inhalation that result in HR acceleration. Therefore, greater RSA is indicative of higher CVT (Berntson et al., 1997).

In healthy individuals, high resting levels of CVT have been reliably associated with a range of adaptive behavioral processes that include coping effectively with stress (Fabes & Eisenberg, 1997), modulating emotional responses (Beauchaine, 2001), and promoting social engagement (Geisler, Kubiak, Siewert, & Weber, 2013). Conversely, lower CVT may reflect difficulties with self-regulation, physiological rigidity, and an inability to shift cardiac and neural output efficiently to environmental requirements (Porges, 1995). Consistent with this view, lower CVT has been associated with social isolation (Horsten et al., 1999), worry (Thayer, Friedman, & Borkovec, 1996), and greater reactivity to negative emotion (Beevers, Ellis, & Reid, 2011).

In relation to psychiatric disorders characterized by compromised social behaviors, such as schizophrenia, Porges (2007) proposes that disrupted neurobiological regulatory processes likely facilitate defensive rather than prosocial behaviors. Research has shown reduced CVT in schizophrenia patients, regardless of medication status, and in their healthy relatives (e.g., Bär et al., 2007, 2010; Mujica-Parodi, Yeragani, & Malaspina, 2005). Indeed, CVT has been associated with clinical ratings of global functioning in schizophrenia (Fujibayashi et al., 2009). However, the functional significance of deficits in CVT and how they interact with social cognition and other brain processes have yet to be established.

If, as suggested by polyvagal theory, CVT reflects an individual's capacity to engage flexibly with the surrounding environment, then RSA should exert a significant impact on adaptive functional outcomes for schizophrenia patients, as they perform in the workplace, interact socially, or engage in daily activities. In the course of examining this hypothesis, we also expected to replicate the well-established associations between social-cognitive processes and functional outcomes (Couture et al., 2006) while testing the more specific prediction that RSA would account for unique variance in role functioning, over and above the established contributions of social cognition. Specifically, we examined whether a relationship exists between physiological and cognitive determinants of adaptive functioning in schizophrenia by testing the prediction that RSA would moderate the effect of social

cognition on functional outcome. As available research on polyvagal theory and social cognition provide little guidance on the specific form of this interaction, we explored whether functional outcomes are optimized because *high* levels of RSA compensate for deficiencies in social cognition or whether functional outcomes are compromised because *low* levels of RSA undermine strengths in social cognition.

Method

Participants

Participants were 43 chronic schizophrenia outpatients and 36 healthy comparison subjects who all provided written informed consent. Patients met criteria for schizophrenia (*n*=39) or schizoaffective disorder (*n*=4) as assessed by the Structured Clinical Interview for the DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995). Antiparkinsonian medications were discontinued for at least 24 hours prior to testing to reduce the possibility of anticholinergic effects on the physiological measure.

Healthy comparison subjects were included in the present study to validate that the patient sample demonstrated reductions in RSA and social cognitive impairments. Inclusion criteria included no history of Axis I psychotic disorder; any Axis II Cluster A personality disorder; bipolar disorder, major depression, obsessive-compulsive disorder, post-traumatic stress disorder, or alcohol/substance dependence; or the presence of a psychotic disorder in a first-degree relative. Exclusion criteria for all participants included evidence of a neurological disorder, major head trauma, mental retardation, and limited fluency in English. Data from 2 schizophrenia patients were excluded due to beta-blocker usage, reducing the patient group to 41 participants.

Clinical Symptom Assessment

The Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984a) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984b) were administered to patients. For all participants, depression and trait anxiety were assessed with the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), and the State-Trait Anxiety Inventory (STAI; Spielberger, 1983), respectively.

Social Cognition Assessment

The Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT; Mayer, Salovey, & Caruso, 2002) assesses emotion identification, use, understanding, and management. The Relationships Across Domains Test (RAD; Sergi et al., 2009) assesses perception of social relationships based on implicit knowledge of relational models using brief vignettes. The Awareness of Social Inference Test (TASIT) Part III: Social Inference - Enriched (McDonald, Flanagan, & Rollins, 2002) evaluates beliefs and knowledge when a lie or sarcasm is depicted, including whether the meaning of a message and the intent and emotional state of the character are detected. The MSCEIT, RAD, and TASIT have strong psychometric properties and been utilized in studies of schizophrenia (e.g., Kee, Green, Mintz, & Brekke, 2003; Kern et al., 2009; Sergi, et al., 2009). Given the degree of shared variance among the three measures (r = .48, .53, and .67) and absence of differential

predictions, a social cognition composite score was derived on the basis of equally-weighted individual *Z*-scores.

Functional Outcome Assessment

The Role Functioning Scale (RFS; Goodman, Sewell, Cooley, & Leavitt, 1993) is a semi-structured interview that measures level of functioning through four subscales: work productivity, independent living/self-care, family relationships, and relationships with friends. Each subscale is measured on a scale from 1 (representing severely limited skills, defiant behaviors, or withdrawal) to 7 (signifying optimal behavior or positive relationships). The RFS has strong psychometric properties (Green & Gracely, 1987) and was administered only to patients because functioning in healthy comparison subjects would reach ceiling. Each subscale was analyzed individually and overall functional outcome was calculated as the average.

Physiological Recording and Data Reduction

Resting HR was recorded with 8mm electrodes, placed on the right and left lower ribs, near the mid-axillary line. The signal was acquired with a bandpass of 0.05 to 200 Hz and sampled at 2000 Hz. Offline, interbeat interval (IBI) series were extracted using QRSTool (Allen, Chambers, & Towers, 2007); each series was visually inspected and corrected for missed beats. The log of the variability in the high frequency band of the HR spectrum is assumed to represent vagal influences and was calculated using CMetX (Allen et al., 2007).

Procedure

Social cognition assessment generally occurred 2-3 weeks after the functional outcome interview (med = 3.1 weeks). HR recordings and self-report measures of depression and anxiety were obtained during a separate session (med = 3.9 weeks from the interview). Resting HR was obtained over 4 minutes while participants were seated in a dimly-lit, acoustically-isolated room. Participants were asked to breathe regularly, refrain from speaking, and minimize movement. They had several hours to acclimate to the laboratory environment while completing other research protocols, and refrained from vigorous activity prior to the testing session. Lunch and caffeine-free beverages were provided 1.5 hours before testing in the early afternoon. Body Mass Index (BMI) was calculated from height and weight, and health behaviors were assessed (e.g., average cigarettes smoked per day, number of days in the past week that included aerobic and anaerobic exercise).

Statistical Analyses

Group differences in demographic variables, social cognition, and RSA were evaluated with independent-samples t-tests. A hierarchical linear regression was used to evaluate the associations among social cognition, RSA, and overall role functioning in patients. To follow up, regression analyses were conducted with each of the four Role Functioning subscales as the dependent variable. For each regression analysis, the main effects of social cognition and RSA were examined followed by their interaction, which served to indicate whether CVT moderated the association between social cognition and functioning. To examine the impact of other variables potentially influencing RSA, Pearson correlations

were computed. When statistically significant, additional analyses were conducted with the relevant variable included as a covariate.

Results

As shown in Table 1, the healthy comparison sample was well matched to the schizophrenia group, although a greater proportion of European Americans were represented in the healthy sample. For patients, positive and negative symptom levels assessed by the SAPS and SANS, respectively, were generally mild to moderate. Schizophrenia patients reported higher trait anxiety (M=39.82, SD=12.14) than healthy comparison subjects (M=32.01, SD=7.34), $F(1, 71)=8.34$, p=.005, ηp2=.11, and higher depression symptoms (M=8.92, SD=9.32) than healthy participants (M=2.92, SD=3.54), $F(1, 72)=13.15$, p=.009, ηp2=.15.

As expected, schizophrenia patients exhibited lower RSA, $F(1, 75)=9.16$, p=.003, ηp2=.11, and poorer social cognition, $F(1, 75)=16.44$, p=.000, ηp2=.18, than healthy comparison subjects. Social cognition and RSA, however, did not correlate in patients, $r(39)=.11$, p=.497, or healthy participants, $r(34)=-.061$, p=.722. Consistent with prior research, social cognition predicted overall functional outcome in schizophrenia patients, β=.46, $t(38)=3.25$, p=.002. More specifically, social cognition was associated with work productivity, β=.40, $t(38)=2.80$, p=.008, independent living/self-care, β=.39, $t(38)=2.93$, p=.010, and family relationships, β=.46, $t(38)=3.22$, p=.003. However, a similar effect was not observed for relationships with friends, β=.17, $t(38)=1.10$, p=.28. RSA also showed a positive association with overall functional outcome in patients, β=.32, $t(38)=2.11$, p=.041, that was reflected primarily in independent living/self-care, β=.47, t(38)=3.29, p=.002.

Analysis of the joint contribution of RSA and social cognition to role functioning in schizophrenia patients showed that RSA moderated the relationship in overall functional outcome, β=-.91, $t(38)=-2.60$, p=.013, and in the specific domains of work productivity, β=-.86, $t(38)=-2.32$, p=.026, and independent living/self-care, β=-.89, $t(38)=-2.66$, p=.011. As illustrated in Figure 1, patients with poorer social cognitive skills required higher RSA to perform effectively at work and live independently, whereas patients with higher social cognitive performance functioned well in both domains, regardless of RSA level. Together, social cognition and RSA accounted for 39.7% of the variance in overall functional outcome and more specifically, 31.2% and 44.5% of the total variance in occupational functioning (R^2=.56, $F(1, 37)=5.36$, p=.026) and independent living (R^2=.67, $F(1, 37)=7.08$, p=.011), respectively, compared with 16.5% and 15.8% when evaluating social cognition alone within each domain. The interaction between social cognition and RSA was not observed in the more interpersonal domains of family relationships, β=-.167, $t(38)=-.42$, p=.680, and relationships with friends, β=-.603, $t(38)=-1.43$, p=.162.

Among patients, no association was detected between RSA and depression symptoms, $r(36)=.08$, p=.637, although trait anxiety tended to be negatively associated with RSA, $r(37)=-.320$, p=.051. When entered into the regression model first, however, anxiety scores did not change the significant RSA moderator finding for work productivity (β=-.86, $t(35)=-2.32$, p=.026) or independent living/self-care (β=-.89, $t(35)=-2.76$, p=.009). Additionally, no relationship was found between RSA and proxy variables associated with

physical health, including BMI, $r(32)=-.02$, $p=.910$, anaerobic exercise, $r(34)=-.11$, $p=.523$, or aerobic exercise, $r(34)=-.06$, $p=.736$. There was a trend association between RSA and cigarette use, $r(34)=-.31$, $p=.069$, although when entered into the model first, smoking did not alter the moderator finding for work productivity ($\beta=-.85$, $t(30)=-2.15$, $p=.040$) or independent living skills ($\beta=-.98$, $t(30)=-2.93$, $p=.006$). Furthermore, accounting for SAPS and SANS symptom severity did not alter the significance of the findings. Likewise, although functional outcome and HR assessments were not completed concurrently, accounting for number of days between assessments did not alter the significance of the findings.

In considering potential effects of medication, analyses were repeated using chlorpromazine (CPZ) equivalent dosages as a covariate (Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010). When entered first into the regression model, CPZ equivalent dosage did not change the significant RSA moderation finding for work productivity ($\beta=-.86$, $t(38)=-2.24$, $p=.032$) or independent living/self-care ($\beta=-.93$, $t(38)=-2.99$, $p=.005$). Given that atypical antipsychotic medications may produce repolarization abnormalities on the electrocardiogram with therapeutic dosing (see Burns, 2001), analyses were repeated to account for possible tachycardia and other abnormalities related to agents with high relative a2-adrenergic receptor antagonism (e.g., clozapine and risperidone) and high relative M1-muscarinic receptor binding (e.g. clozapine and olanzapine). When a2-adrenergic receptor binding for each participant's medication was accounted for within the model, the RSA moderator finding remained significant for work productivity ($\beta=-.84$, $t(38)=-2.23$, $p=.032$) and independent living/self-care ($\beta=-.87$, $t(38)=-2.58$, $p=.014$). Similarly, accounting for M1 receptor binding did not change the significant results for work productivity ($\beta=-.77$, $t(38)=-2.08$, $p=.045$) and independent living/self-care ($\beta=-.85$, $t(38)=-2.47$, $p=.019$).

Discussion

Given that RSA has been established as a measure of self-regulatory processes in a range of contexts, the present study sought to examine the contribution of cardiovascular modulation of vagal tone to functional outcome in schizophrenia, independently and in combination with social cognition. Consistent with prior research, schizophrenia patients exhibited dampened levels of resting vagal tone (e.g., Bär et al., 2007; Mujica-Parodi et al., 2005) and poorer social cognition (e.g., Green et al., 2012a) relative to healthy comparison subjects. Beyond replicating that social cognition is predictive of functional outcome in schizophrenia (e.g., Horan et al., 2012), the present study found the association to be significantly moderated by RSA. Specifically, functional outcome among schizophrenia patients with poor social cognition, including work productivity and independent living skills, was found to be largely contingent upon RSA. In contrast, performance of occupational and daily living activities in schizophrenia patients with strong social cognitive skills was independent of RSA. Thus, while functional outcome was best for patients who exhibited strong social cognition, self-regulatory capacity and psychological flexibility, as indexed by RSA, may compensate for poorer social cognitive abilities in individuals with schizophrenia. These findings remained statistically significant after evaluating the potential influence of clinical characteristics, proxy measures of physical health, antipsychotic medications, and

medication dosage. Furthermore, RSA and social cognition were unrelated, suggesting independent yet interacting contributions to functional outcome.

These novel results are consistent with current theories of vagal activity, which posit that individual differences in CVT reflect the capacity to self-regulate in response to the external environment, with higher levels promoting behavioral and psychological adaptability (e.g., Thayer & Lane, 2000). Specifically, findings from the present study suggest that schizophrenia patients with poorer social cognitive skills may be less capable of achieving goal-directed behaviors, and thus may require high RSA to perform at work and to live independently and engage in self-care. Conversely, independent living and work aspects of functional outcome for patients with better social cognition may be tied less closely to RSA.

These findings may also serve to extend an empirical model recently derived by Green and colleagues (2012b), indicating that the success with which schizophrenia patients confront daily living requires not only abilities reflected in social cognition but also the motivation to apply these abilities. Reduced social cognitive abilities, in turn, can lead to repeated discouragement that eventually results in dysfunctional attitudes, such as defeatist beliefs. Results of the present study suggest that by promoting flexible engagement with the environment, high levels of RSA may serve to mobilize adaptive behaviors over the course of daily living and help to overcome dysfunctional attitudes.

Unlike the findings for work productivity and independent living/self-care, RSA did not interact with social cognition to predict functional outcomes in interpersonal domains. Although this result may be a methodological artifact (e.g., patients tended to rate relationships with family members as strong, truncating the range of scores), the possibility remains that this is a meaningful finding. If family members are more tolerant and forgiving of slippage in social cognition, patients may feel less threatened and defensive in these relationships, reducing their sense of discouragement while also providing feedback on effective engagement strategies. Family interaction studies are needed to test this possibility, but evidence that social cognition is inconsistently associated with relationships with friends (e.g., Kee et al. 2003) does suggest that varying domains of functional outcome pose unique demands for schizophrenia patients.

Clinical correlates of CVT have included anxiety (Thayer et al., 1996), depression (Rottenberg, 2007), and psychotic states (Toichi et al., 1999). Present results were also suggestive of a negative association between vagal tone and trait anxiety in schizophrenia, extending the literature on individuals with clinical levels of anxiety (Friedman, 2007). No relationship was detected between RSA and positive symptoms although psychotic symptoms in the present sample were relatively mild. Finally, an association between RSA and depression symptoms was not observed, possibly due to reliance on a state-specific measure or because research findings in depressed patients may reflect a relatively modest association (Rottenberg, 2007).

Although antipsychotic medications may also potentially influence cardiovascular variability (Burns, 2001), reductions in CVT have been observed in unmedicated schizophrenia patients and their first-degree relatives (e.g., Bär et al., 2007, 2010).

Furthermore, we examined the possibility of differential impacts by type of medication, accounting statistically for CPZ equivalent dosages as well as a2-adrenergic and M1-muscarinic receptor binding profiles. None of these variables affected the statistical significance of the findings.

Causal relationships between functional outcome, social cognition, and vagal tone could not be determined within the design of the present study. Another consideration is that role functioning was assessed through self-report interviews rather than more objective measures of functional capacity. Future investigations would also benefit from longitudinal assessments to infer predictive relationships over the course of schizophrenia and different phases of illness. Given the primacy of stress to clinical and functional outcomes in schizophrenia (e.g., Walker & Diforio, 1997), it will be important to determine how CVT reactivity to stress interacts with social cognition and role functioning. In addition, further research may demonstrate differential CVT reactivity to social versus non-social challenges. Future research may also seek to identify whether strategies aiming to improve baseline CVT (e.g., exercise or mindfulness meditation; see Ditto, Eclache, & Goldman, 2006) benefit functioning in schizophrenia.

In summary, this study demonstrated that an increased understanding of role functioning in schizophrenia may be achieved when social cognition is considered in conjunction with a physiological index of the capacity to self-regulate and respond flexibly to the demands of daily living. Among patients with schizophrenia, individual differences in RSA were found to moderate the well-established relationship between social cognition and functional outcome. Enhanced understanding of functional outcome in schizophrenia will likely benefit from further integration of multiple levels of analysis, as researchers continue to explore increasingly multifaceted networks of variables and their interactions.

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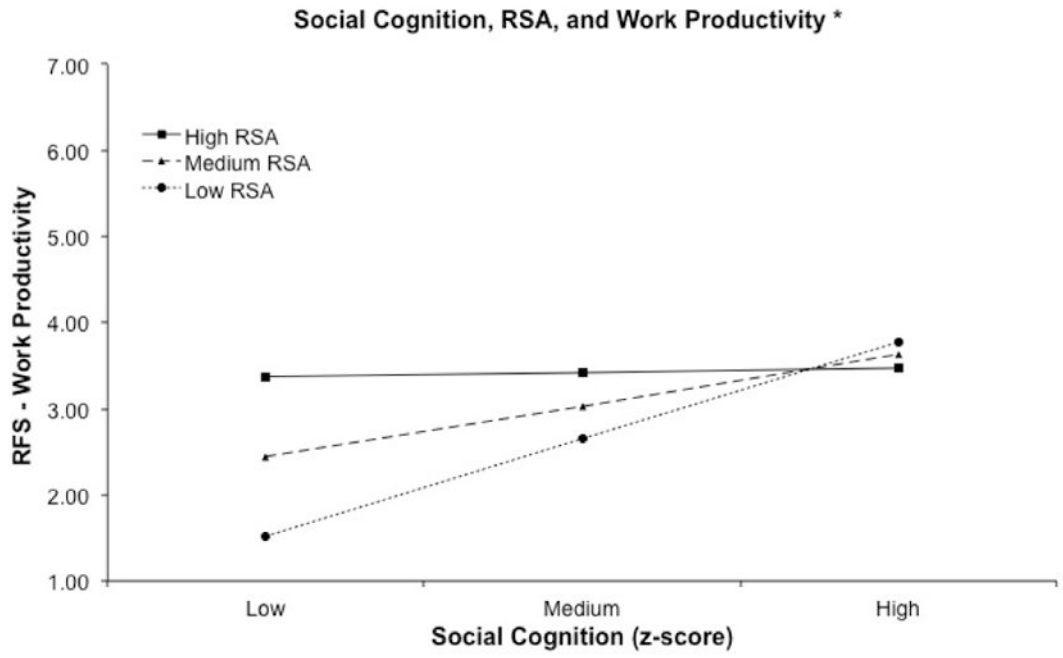

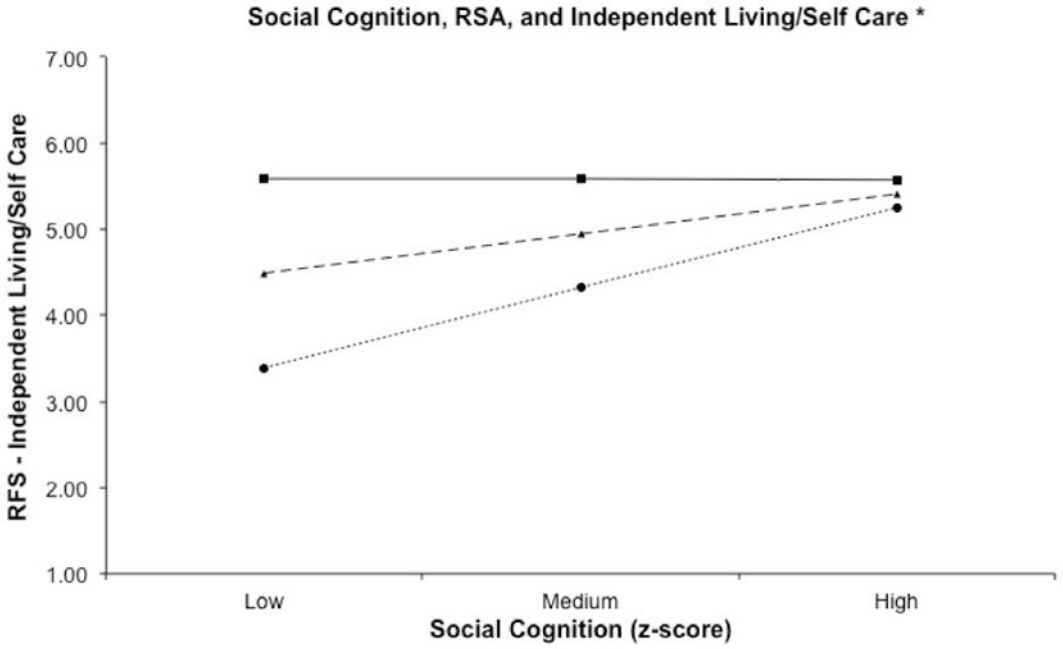

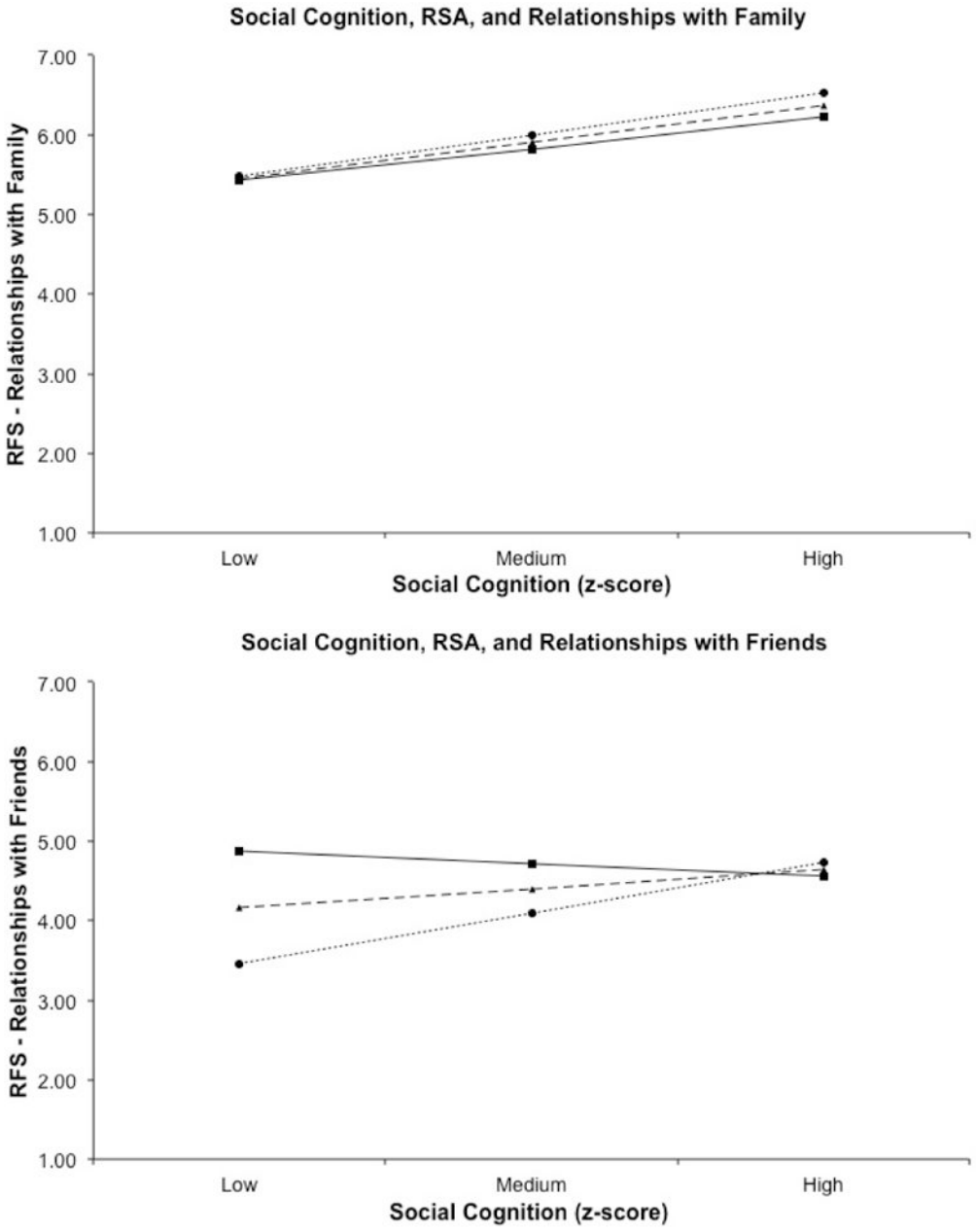

Figure 1.

Models of the interaction between social cognition and RSA on domains of role functioning. For illustration, RSA and social cognition were categorized into three levels (*Low* - one SD below the mean; *Medium* - mean; *High* - one SD above the mean). RSA moderated the relationships between social cognition & work productivity and between social cognition & independent living/self-care.

RSA: respiratory sinus arrhythmia; RFS: Role Functioning Scale; *$p = 0.05$.

Table 1

Demographic and Clinical Characteristics of Participants.

Characteristics	Schizophrenia Patients (*n*=41)	Healthy Comparison Subjects (*n*=36)
Age (years), M (SD)	33.73 *(7.87)*	33.11 *(5.50)*
Sex (Male/Female)	28/13	28/8
Education (years), M (SD)	14.02 *(1.46)*	14.64 *(1.84)*
Parental Education (years), M (SD)	15.07 *(2.94)*	15.25 *(2.10)*
Ethnicity*		
African American	9	3
Asian American	6	2
European American	15	28
Latino/Latina	6	3
Mixed	5	0
Duration of Illness (years), M (SD)	9.37 *(5.06)*	
Medications		
Aripiprazole (Abilify)	*n* = 7	
Clozapine (Clozaril)	*n* = 5	
Fluphenazine (Prolixin)	*n* = 2	
Haloperidol (Haldol)	*n* = 3	
Olanzepine (Zyprexa)	*n* = 6	
Quetiapine (Seroquel)	*n* = 3	
Risperidone (Risperdal)	*n* = 11	
Ziprasidone (Geodon)	*n* = 4	
Chlorpromazine equivalent (mg), M (SD)	436.45 *(292.10)*	
Symptom Measures		
SAPS total, M (SD)	4.10 *(3.33)*	
SANS total, M (SD)	9.04 *(5.32)*	
Beck Depression Inventory Score, M (SD)**	8.92 *(9.32)*	2.92 *(3.54)*
State-Trait Anxiety Inventory Score, M (SD)**	78.00 *(22.91)*	62.15 *(13.81)*
Role Functioning Scale (1-7)		
Work Productivity, M (SD)	2.98 *(1.71)*	
Independent Living/Self-Care, M (SD)	4.90 *(1.45)*	
Relationships with Family, M (SD)	5.90 *(1.00)*	
Relationships with Friends, M (SD)	4.37 *(1.80)*	
logRSA, M (SD)**	4.73 *(1.83)*	5.82 *(1.24)*
Health Behaviors		
Cigarettes smoked per day, M (SD)	3.53 *(8.98)*	
Aerobic Exercise, days in past week, M (SD)	1.08 *(1.70)*	
Anaerobic Exercise, days in past week, M (SD)	1.53 *(1.96)*	
Body Mass Index, M (SD)	30.95 *(8.49)*	

* $p < 0.05$;

** $p < 0.01$