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Childhood temperament is associated with distress, anxiety and reduced quality of life in schizophrenia spectrum disorders

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ABSTRACT

Schizophrenia is conceptualized as a neurodevelopmental disorder and pre-morbid differences in social function and cognition have been well-established. Less is known about pre-morbid temperament and personality. Inhibited temperament—the predisposition to respond to novelty with wariness, fear, or caution—is a premorbid risk factor for anxiety, depression, and substance use but is understudied in schizophrenia. Participants were patients with schizophrenia spectrum disorders (n = 166) and healthy controls (n = 180). Patients completed measures of childhood inhibited temperament, clinical symptoms (anxiety, depression, PANSS factors), and quality of life. Patients had significantly higher levels of inhibited temperament relative to healthy controls. In patients with schizophrenia, higher inhibited temperament was significantly associated with co-morbid anxiety disorders, greater anxiety and depression symptoms, higher PANSS Distress scores, lower PANSS Excitement scores, and lower quality of life. The current findings replicate and extend previous research with a larger sample and are consistent with vulnerability in an affective path to psychosis. In schizophrenia, higher inhibited temperament was associated with a cluster of mood and anxiety symptoms. Inhibited temperament was not associated with psychosis symptoms. Patients with high inhibited temperament may especially benefit from treatments that specifically target anxiety and depression.

1. Introduction

Schizophrenia has been conceptualized as a neurodevelopmental disorder (Murray and Lewis, 1987) based on evidence of early deviations from typical development in individuals who later develop schizophrenia. Pre-morbid differences in social functioning (Tarbox and Pogue-Geile, 2008) and cognitive abilities (Mollon and Reichenberg, 2018; Trotta et al., 2015) are commonly observed in schizophrenia. Later development of schizophrenia can be predicted by observations of social functioning in early home videos (Walker and Lewine, 1990) and teacher ratings of social functioning in childhood (Tsuji et al., 2013). Similarly, individuals who later developed schizophrenia showed a pattern of lower educational achievement and lower levels of academic functioning, as measured by standardized scores, at grade 11 (Fuller et al., 2002). Pre-morbid differences in personality have received less attention, but initial evidence suggests that the personality trait of high levels of neuroticism predicts later schizophrenia (Van Os and Jones, 2001; Lönnqvist et al., 2009). While pre-morbid differences in social functioning, cognition, and personality have often been considered to be general antecedent factors, the substantial heterogeneity in schizophrenia (Carpenter and Kirpatrick, 1988; Tandon et al., 2013) raises the question of whether the pre-morbid factors characterize all patients with schizophrenia or identify specific subgroups with altered neurodevelopmental trajectories. For example, several studies have identified cognitive subgroups. Combining measures of pre-morbid and current neuropsychological function reveals three patterns: intact functioning; deteriorated function, defined by typical pre-morbid function and current impairment; and compromised function, defined by impaired pre-morbid and current function (Weickert et al., 2000; Woodward and Heckers, 2015). The compromised subgroup has a distinct profile of reduced intracranial volume, relative to the other subgroups, suggestive of disrupted early cerebral development. Thus, it may be beneficial to identify other pre-morbid factors that account for variability in schizophrenia and may identify subgroups that emerge early in development.

A promising pre-morbid factor to consider is inhibited

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temperament. Temperament is defined as early-emerging and biologically-based individual differences in emotion, cognition, and behavior that interact with the environment to form adult personality. While premorbid personality differences have been observed in late adolescents (Van Os and Jones, 2001) and young adults (Lönnqvist et al., 2009), little is known about early-emerging temperament traits in people who later develop schizophrenia. Of the various temperament traits, one of the most fundamental individual differences is the tendency to approach or avoid novelty (Kagan et al., 1984). This trait—inhibited temperament—can be measured along a continuum ranging from individuals who are outgoing, bold, and fearless to individuals who are shy, cautious, and fearful when they encounter an unfamiliar or unexpected person, place, or object. Inhibited temperament is observable during the first year of life (Calkins et al., 1996; Kagan et al., 1998), moderately stable across development (Robinson et al., 1992; Dilalla et al., 1994; Smith et al., 2012), and heritable (Dilalla et al., 1994; Eley et al., 2003; Robinson et al., 1992). Childhood inhibited temperament confers risk for the development of anxiety disorders (Hirshfeld et al., 1992; Biederman et al., 1993; Schwartz et al., 1999; Chronis-Tuscano et al., 2009; Essex et al., 2010; Hirshfeld-Becker et al., 2010; Biederman et al., 2001); a meta-analysis of longitudinal studies found that almost half of inhibited children, a 7-fold increase in odds, developed social anxiety disorder by adolescence. Childhood inhibited temperament is also associated with an increased risk for the development of depression (Beesdo et al., 2007; Gladstone et al., 2005; Gladstone and Parker, 2006; Neal et al., 2002). For example, in the Dunedin longitudinal study, an inhibited behavioral style at age 3 was associated with depression diagnosis at age 21 (Caspi et al., 1996). Childhood inhibited temperament is also associated with later substance-use problems (Lahat et al., 2012; Williams et al., 2010). The link between inhibited temperament and multiple psychiatric disorders suggests that childhood inhibited temperament may confer broader risk for psychopathology. However, the examination of inhibited temperament in patients with more severe and persistent disorders has been understudied. This is likely due to the challenges inherent in both community samples—where prevalence rates of severe disorders is low—and longitudinal studies, where even in high-risk populations, the small sample sizes restrict statistical power.

Several lines of evidence raise the possibility that inhibited temperament is associated with schizophrenia. Inhibited temperament and schizophrenia are both characterized by social dysfunction including shyness (Goldberg and Schmidt, 2001; Degnan et al., 2014) and social anxiety (Achim et al., 2011; Clauss and Blackford, 2012). Inhibited individuals and patients with schizophrenia also share a neural signature of hyperarousal, evidenced by hyper-reactivity to neutral images (Hall et al., 2008; Blackford et al., 2011), stressful situations (Kagan et al., 1987; Ryan et al., 2004; Walker et al., 2013), and cues signaling safety (Holt et al., 2012; Barker et al., 2014). In addition, neuroimaging studies show a failure of neural habituation (Holt et al., 2005; Blackford et al., 2013; Williams et al., 2013), which may represent heightened threat detection or memory impairments (Avery et al., 2016). Given the challenges inherent in community samples and longitudinal studies, a logical first step is to measure childhood inhibited temperament in patients with schizophrenia. The Retrospective Self-Report of Inhibition (RSRI) is a well-validated measure that has been used to assess childhood inhibited temperament in two previous studies of patients with schizophrenia (Goldberg and Schmidt, 2001; Jetha et al., 2011). Goldberg and Schmidt (2001) measured childhood inhibited temperament in 23 outpatients with schizophrenia and 23 controls and found that childhood inhibited temperament scores were significantly higher in patients. However, childhood inhibited temperament was not correlated with positive or negative psychosis symptoms or quality of life. Jetha et al. (2011) later replicated higher inhibited temperament scores in a sample of 41 patients with schizophrenia and 41 controls, but did not examine correlations with symptoms. Thus, initial evidence suggests that childhood inhibited temperament may be a premorbid factor of schizophrenia.

Whether inhibited temperament is associated with heterogeneity in clinical symptoms or quality of life, and thus may identify a specific subgroup, remains unknown. Previous work suggests a subgroup of patients may have an affective pathway to psychosis that begins with heightened emotional reactivity prior to the onset of psychosis and has a more episodic course with better long-term outcomes (Myin-Germeys and van Os, 2007). The increased emotional reactivity is thought to reflect a genetic and/or environmental vulnerability for developing psychosis (Myin-Germeys and van Os, 2007). More recently, Dickinson et al. (2018) used the negative and distress subscales from the 5-factor model to examine the deficit and distress subtypes of schizophrenia. The distress subtype was characterized by high emotionality, increased anxiety and depressive symptoms, increased positive psychosis symptoms, higher cortisol levels, and more intact cognitive abilities. In contrast, the deficit subtype was characterized by diminished emotionality and enduring negative symptoms. Dickinson and colleagues proposed that these two subtypes reflect stable trait-like differences which may contribute to different pathways to psychosis. Inhibited temperament may reflect the early vulnerability within the affective pathway to schizophrenia that could result in the distress subtype of schizophrenia.

Our goals in this study are to: replicate and extend the previous finding of higher childhood inhibited temperament in schizophrenia in a larger sample; and to determine whether individual differences in childhood inhibited temperament are associated with variability in anxiety, depression, psychosis symptoms, or quality of life in patients. We predict that patients will have higher levels of inhibited temperament, replicating findings from previous studies. We predict that inhibited temperament will account for significant variability in co-morbid anxiety and anxiety and depression symptoms in patients with schizophrenia. We hypothesize that patients with higher inhibited temperament associated with more co-morbid anxiety and higher levels of anxiety and depressive symptoms. Although previous studies of inhibited temperament in schizophrenia have used the PANSS three-factor model (Goldberg and Schmidt, 2001; Jetha et al., 2011), here we use the PANSS five-factor model based on recent findings supporting a distress subtype (Dickinson et al., 2018) and because it provides greater precision by splitting the general psychopathology subscale into three distinct measures of distress, excitement, and disorganization (Jerrell and Hrisko, 2013). For the PANSS factors, we hypothesize that inhibited temperament will predict variability in the Distress factor, based on its association with anxiety and depression, and in the Positive factor, as paranoia is proposed to be linked to anxiety through alterations in threat detection associated with anxiety (Tone and Davis, 2012) and shares a temperament vulnerability with social anxiety (Schutters et al., 2012).

2. Methods

2.1. Subjects

Participants consisted of 166 patients with schizophrenia spectrum disorders (80 schizophrenia, 33 schizoaffective disorder, and 53 schizophreniform disorder) and 180 healthy controls. The Vanderbilt University Institutional Review Board approved the study and participants provided written consent. Patients were recruited from the inpatient units and outpatient clinics of Vanderbilt Psychiatric Hospital into a registered repository from 2008 through 2017 (clinicaltrials.gov; NCT00762866). Healthy controls were recruited from advertisements in the community. A Structured Clinical Interview of the DSM-IV-TR (SCID) (First et al., 2002) was conducted for all participants by trained research staff. Participants were considered for study if they were between 14–65 years old, had premorbid IQ >70, no history of traumatic brain injury, did not suffer from a chronic medical illness (e.g. HIV, cancer) or a central nervous system disorder, and did not meet criteria

for current substance abuse/dependence. Healthy control participants were excluded if they had a history of psychiatric disorders. For patients, the SCID was used to confirm diagnosis of schizophrenia spectrum and anxiety disorders. In healthy control participants, the SCID was used to rule out past or current psychiatric illness including substance abuse/dependence. Patients and healthy controls were compensated for participating the study.

2.2. Procedures

Childhood inhibited temperament was assessed with the Retrospective Self-Report of Inhibition (RSRI; Reznick et al., 1992) The RSRI is a retrospective self-report questionnaire assessing inhibited behaviors during childhood (grades 1–6) across a variety of contexts. For example, questions on the RSRI include "Did it upset you to be called up to the blackboard" and "Did you enjoy meeting new children your age?" RSRI has 30 questions and uses a Likert scale (1 = uninhibited, 5 = inhibited); the RSRI score is the average of all of the items. The RSRI has excellent reliability (Cronbach's alpha = .79) and construct validity, indicated by strong agreement between self-reports by individuals and reports from their parents and by correlations with concurrent measures (Reznick et al., 1992).

Anxiety and depression symptoms were measured using the Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995). The MASQ is a 90-item self-report measure of anxiety and depression symptoms that uses a 1–5 Likert scale (1 = not at all, 5 = extremely). The MASQ is based on the tripartite model of anxiety and depression which separates symptoms into three clusters: general distress/negative affect (shared by anxiety and depression), physiological hyperarousal (specific to anxiety), and positive affect (specific to depression). Negative affect is measured by three subscales (general distress-anxiety, general distress-depression, and general distress), anxiety is measured by the Anxious Arousal subscale and depression is measured by the Anhedonic Depression subscale.

Quality of life was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), a self-report measure of quality and satisfaction in the past week (Becchi et al., 2004). For example, the Q-LES-Q-SF asks "Taking everything into consideration, during the past week how satisfied have you been with your social relationships. The Q-LES-Q-SF has 16 Likert scale items (1 = very poor, 5 = very good) and the quality of life score is the total across all items (range 16–80). The quality of life measure was available for a subset of 59 patients.

The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was administered by a clinician to assess the severity of symptoms. A five-factor model most commonly characterizes the PANSS items (Wallwork et al., 2012) and composite scores for Negative, Positive, Disorganized, Excitement and Distress symptom factors were computed (van der Gaag et al., 2006).

2.3. Data analyses

To determine whether inhibited temperament differed between patients with schizophrenia versus healthy controls, an ANOVA was performed on inhibited temperament score with diagnosis (patients/controls) as the between-subjects factor. To determine whether levels of inhibited temperament differed across the three schizophrenia spectrum diagnoses, an ANOVA performed on inhibited temperament score with by diagnostic group (schizophrenia/schizoaffective/schizophreniform).

To determine whether individual differences in inhibited temperament explained heterogeneity in patients with schizophrenia, a series of analyses were performed within the patient group. First, a logistic regression was performed to determine if inhibited temperament predicts anxiety diagnosis (yes/no). Next, regression analyses were conducted to test for associations between the inhibited temperament score and each of the outcome measures (MASQ subscales, PANSS factors, and quality of life). Age and age of onset were covariates in all regression analyses. The standardized parameter estimates, *t*-values, effect sizes, and *p*-values will be reported for each outcome variable. All analyses were conducted using SAS software (Version 9.4, SAS Institute Inc., Cary, NC), $\alpha < 0.05$.

Table 1
Participant characteristics by diagnosis group.

	Schizophrenia (*N* = 166)	Controls (*N* = 180)	*p* value
% Male	67%	58%	0.08
% White	66%	71%	0.28
Age (SD)	29.86 (11.75)	29.42 (10.82)	0.58
Education (SD)	13.24 (2.36)	15.19 (2.33)	<0.001
Parental education (SD)	14.35 (2.97)	14.65 (2.39)	0.34
Inhibited temperament (SD)	2.37 (0.59)	1.89 (0.37)	<0.001
% Anxiety disorder	32%	–	–
MASQ			
Anxious arousal (SD)	1.75 (0.66)	1.14 (0.21)	<0.001
Anhedonic depression (SD)	2.91 (0.64)	2.18 (0.47)	<0.001
General distress-anxiety (SD)	1.99 (0.74)	1.36 (0.36)	<0.001
General distress-depression (SD)	2.34 (0.97)	1.45 (0.47)	<0.001
General distress-mixed (SD)	2.40 (0.85)	1.53 (0.46)	<0.001
PANSS			
Negative (SD)	2.29 (1.24)	–	–
Positive (SD)	2.96 (1.32)	–	–
Excitement (SD)	1.50 (0.65)	–	–
Disorganization (SD)	2.48 (1.17)	–	–
Distress (SD)	2.27 (1.02)	–	–
Quality of life	49.24 (8.95)	58.44 (5.80)	0.01

3. Results

3.1. Comparison of patients and controls

Demographic and symptoms measures for patients and controls are shown in Table 1. Patients and controls were similar in all of the demographic characteristics, except for education; patients had less education than controls, F (1, 315) = 54.96, $p < .0001$. Compared to controls, patients had significantly higher inhibited temperament scores (F (1, 344) = 82.26, $p < .0001$). As illustrated in Fig. 1, the higher

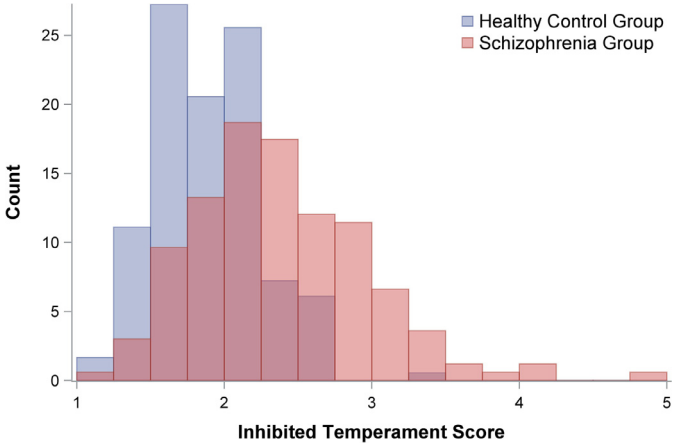

Fig. 1. Distribution of inhibited temperament scores in the healthy control and schizophrenia groups. The histograms by group illustrate that the higher mean inhibited temperament scores in patients reflect a greater variability in scores with a substantially greater number of individuals scoring in the higher range of the scale.

scores reflected a greater variability in scores (Levene's test, $F(1344) = 18.17, p < .0001$), especially towards the more inhibited end of the distribution and not merely a general shift towards higher scores. Inhibited temperament did not differ across the three schizophrenia spectrum disorder diagnoses (schizophrenia/schizoaffective/schizophreniform; ($F(2, 163) = 2.44, p = .09$), therefore, all patients were combined into one patient group for the subsequent analyses. On the symptom measures, patients had significantly higher scores on all of the MASQ measures of negative affect/general distress, anxiety, and depression, as well as lower quality of life (all $p < .05$, Table 1).

3.2. Inhibited temperament and outcomes in patients

In patients, inhibited temperament was significantly associated with having a co-morbid anxiety disorder ($\chi^2 = 19.22, p < .0001$) with a 4.64 increase in odds for each unit increase in temperament score (e.g., 3 to 4 on the 1 – 5 scale). In the regression analyses controlling for age and age of onset, inhibited temperament was significantly associated with higher scores on the MASQ anxious arousal subscale and MASQ anhedonic depression subscale. Inhibited temperament also predicted significant variance in the MASQ negative affect subscales: higher inhibited temperament was associated with more general distress-anxiety, general distress-depression, general distress-mixed. The standardized parameter estimates, effect sizes, and *p*-values are provided in Table 2 and scatterplots illustrating the relationships are provided in Fig. 2.

Within patients, inhibited temperament was associated with two of the PANSS factors. Patients with higher inhibited temperament scores had significantly higher scores on the PANSS Distress factor. Higher inhibited temperament was also associated with lower scores on the PANSS Excitement factor. Inhibited temperament did not predict variability in PANSS Disorganization, PANSS Positive, or PANSS Negative factors. The standardized parameter estimates, effect sizes, and *p*-values are provided in Table 2 and scatterplots illustrating the relationships are provided in Fig. 2.

The quality of life analysis was conducted with a subset of patients that completed the Q-LES-Q-SF. Higher inhibited temperament scores predicted significantly lower quality of life. The standardized parameter estimate, effect size, and *p*-value is provided in Table 2 and the scatterplot is provided in Fig. 2.

Table 2
Anxiety symptoms, psychosis symptoms, and quality of life by temperament.

Outcome variable	Standardized parameter estimate	*T* value	Effect size (η^2)	*P* value
MASQ				
Anxious arousal	0.43	6.05	0.17	< 0.0001
Anhedonic depression	0.45	6.31	0.19	< 0.0001
General distress-anxiety	0.45	6.30	0.19	< 0.0001
General distress-depression	0.53	7.73	0.26	< 0.0001
General distress-mixed	0.56	8.43	0.29	< 0.0001
PANSS				
Negative	− 0.06	0.44	0.00	0.50
Positive	0.04	− 0.68	0.00	0.66
Excitement	− 0.22	− 2.84	0.05	0.005
Disorganization	− 0.14	− 1.81	0.02	0.07
Distress	0.38	5.03	0.14	< 0.0001
Quality of life	− 0.45	− 3.63	0.18	0.0006

Note: Analyses adjusted for age and age of psychosis onset.

3.3. Unique contributions of inhibited temperament controlling for anxiety disorders

To address the possibility that inhibited temperament is capturing variability more parsimoniously attributable to co-morbid anxiety, regression analyses were repeated covarying for anxiety (yes/no). After controlling for anxiety disorders, inhibited temperament continued to explain a significant portion of variability in all of the anxiety and depression symptom measures (MASQ subscales, all $p < .0001$, PANSS Excitement factor ($p = .02$), PANSS Distress factor ($p = .002$), and quality of life ($p = .006$)).

4. Discussion

Inhibited temperament has been implicated in anxiety disorders, depression, and substance use; however, little is known about the role of inhibited temperament in severe and persistent mental illnesses such as schizophrenia. The first goal of this study was to test the hypothesis that patients with schizophrenia would have higher childhood inhibited temperament. The second goal of the study was to determine whether inhibited temperament was associated with a distinct set of correlates in patients with schizophrenia, providing initial evidence for subgroups. There were two major findings. First, patients with schizophrenia were significantly more inhibited than control participants, providing evidence that inhibited temperament is prominent in schizophrenia, similar to findings in other psychiatric disorders. Second, inhibited temperament was significantly correlated with mood and anxiety symptoms and quality of life, but was not associated with psychosis symptoms. Patients with the highest inhibited temperament scores were characterized by high anxiety and depression, high distress, low excitement, and low quality of life.

Patients had higher inhibited temperament scores than healthy controls, which reflected both greater variability in scores and a shift in the distribution towards more inhibited temperament. The finding that patients with schizophrenia are, on average, more inhibited than controls replicates two smaller studies (Goldberg and Schmidt, 2001; Jetha et al., 2011) and together, these studies provide compelling evidence that inhibited temperament is prominent in schizophrenia. This finding adds to a growing literature showing that inhibited temperament is associated with psychiatric disorders and provides an important extension from less severe disorders, like anxiety and depression, to severe and persistent mental illnesses, like schizophrenia. Inhibited temperament may reflect a vulnerability within patients with schizophrenia consistent with stress vulnerability models of schizophrenia (Davis et al., 2016; Zubin and Spring, 1977), a distress subtype (Dickinson et al., 2018), or an affective pathway to psychosis (Dickinson et al., 2018; Myin-Germeys and van Os, 2007). More specifically, we propose that inhibited temperament may reflect an early emerging, biologically-based vulnerability for schizophrenia with increased emotional reactivity and increased stress sensitivity that leads to a distress subtype of schizophrenia with heightened anxiety and mood symptoms. The higher levels of inhibited temperament in schizophrenia raise two questions for future research. First, “Does inhibited temperament confer increased risk for developing schizophrenia?” A meta-analytic study of prospective longitudinal studies estimated a 7-fold increase in odds for developing social anxiety disorder in inhibited children (Clauss and Blackford, 2012). Given the low prevalence of schizophrenia in the population, very large longitudinal datasets with early measures of temperament are needed to examine this question in schizophrenia. Second, “Is inhibited temperament transdiagnostic?” Future studies examining inhibited temperament across multiple disorders will be needed to determine whether inhibited temperament in more prevalent across all psychiatric disorders or only in specific disorders, for example those with high rates of anxiety.

Inhibited temperament explained significant heterogeneity across measures of negative affect, anxiety, and depression. Specifically,

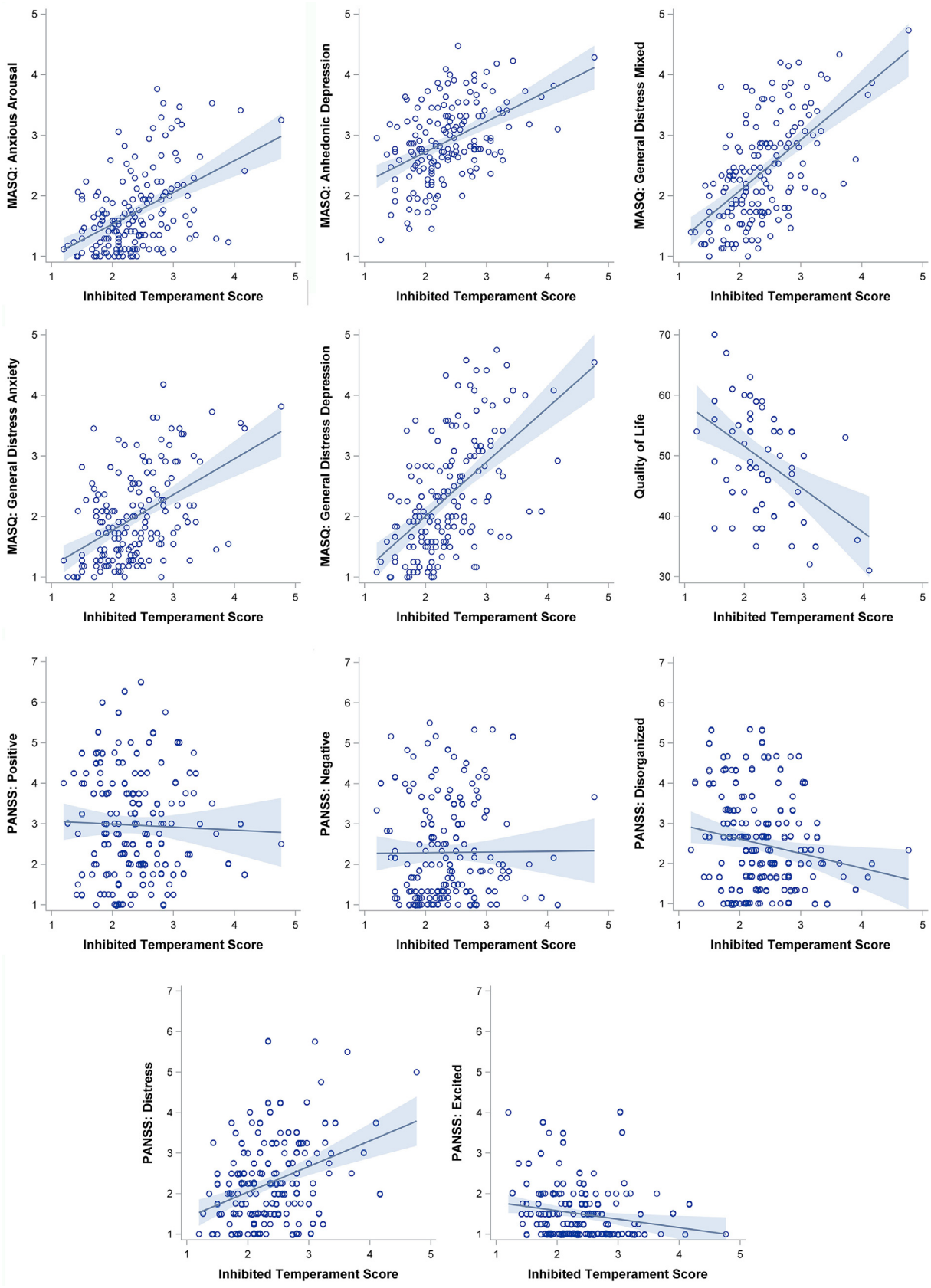

Fig. 2. Scatterplots illustrating the relationship between inhibited temperament and outcome measures. In patients with schizophrenia, inhibited temperament was positively correlated with measures of anxious arousal, anhedonic depression, general distress-mixed, general distress-anxiety, general distress-depression, and PANSS Distress. Inhibited temperament was negatively correlated with quality of life and PANSS Excited but was not correlated with PANSS Positive or PANSS Negative.

inhibited temperament was associated with higher scores on the MASQ negative affect measures, MASQ anxiety scale, MASQ depression scale, and PANSS Distress factor. Anxiety and depression symptoms are common in schizophrenia and are observed across all phases of the disease progression including in ultra-high risk individuals (Fusar-Poli et al., 2014), during the first episode of psychosis (Sutliff et al., 2015), and in chronic schizophrenia (Achim et al., 2011; Lim et al., 2015). In addition to heightened levels of anxiety in the current study, inhibited temperament was associated with a significant increase in odds of having a co-morbid anxiety disorder. The high rates of co-morbid anxiety disorders in patients has gained recent attention following a meta-analytic study that reported that 38% of patients with schizophrenia have a co-morbid anxiety disorder (Achim et al., 2011). The pattern of symptoms associated with inhibited temperament is consistent with descriptions of an 'affective pathway' to psychosis (Myin-Germeys and van Os, 2007) or a distress subtype (Dickinson et al., 2018). Heightened anxiety and depression symptoms in schizophrenia have multiple important implications for patient outcomes. Patients with co-morbid anxiety and schizophrenia have higher rate of suicide attempts, increased substance abuse, worse social adjustment, and lower overall quality of life (Pallanti et al., 2004). Depression in patients with schizophrenia is also associated with worse long-term functional outcomes (Conley et al., 2007). Despite the prevalence and importance of anxiety and depression in schizophrenia, these disorders and symptoms remain underrecognized and understudied. It will be critical for future studies of schizophrenia to include comprehensive measures of anxiety and depression in order to further our understanding of the role of anxiety and depression in functional impairment, treatment response, and long-term outcomes.

Higher inhibited temperament was associated with decreased satisfaction with quality of life. Our findings are consistent with several previous studies. One study found that in patients with schizophrenia, higher shyness was correlated with both lower quality of life and impaired interpersonal functioning (Jetha et al., 2011). In addition, patients with comorbid schizophrenia and social anxiety disorder have lower quality of life compared to patients with schizophrenia without comorbid social anxiety (Pallanti et al., 2004). Although inferences from correlations are inherently limited, inhibited temperament typically emerges early in life and has been shown to predict later social withdrawal (Pérez-Edgar et al., 2011; Walker et al., 2014) and social anxiety (Clauss and Blackford, 2012). Thus, one possibility is that inhibited temperament leads to impaired social functioning and social anxiety, which in turn leads to lower satisfaction, through either lack of social support and connectedness or potentially through negative cognitive biases impacting perception of quality of life. In a longitudinal study of patients, baseline low quality of life and emotional distress predicted poor quality of life 10 years later (Ritsner et al., 2014). Interventions targeting inhibited temperament have the potential to both reduce anxiety and depression, and improve quality of life, both of which may improve long-term outcomes.

Contrary to our hypothesis, inhibited temperament was not associated with positive symptoms. Our prediction was based on the role of attentional bias to threat and anxiety in paranoia (Tone and Davis, 2012) and based on a large epidemiological study where inhibited temperament was elevated in individuals who endorsed paranoia symptoms (Schutters et al., 2012). Of note, the one previous study that investigated inhibited temperament and PANSS scores also failed to find an association with the PANSS Positive, Negative, or General factors (Goldberg and Schmidt, 2001). Findings in studies of similar temperament and personality factors (like negative affect, neuroticism, and harm avoidance) have been mixed (for a review see Horan et al., 2008). One possibility is that the contribution of inhibited temperament is specific to affective symptoms. Another possibility is that alternative methods of characterizing symptoms that use different time scales (e.g. repeated measures over time or experience sampling methods) or different resolutions (e.g., just paranoia symptoms, or specific delusion or hallucination content) may provide a novel perspective on the relationship between inhibited temperament and positive symptoms.

The findings from the current study should be considered in the context of potential limitations. First, inhibited temperament was assessed using a self-report, retrospective measure. Self-report measures assume reliable reporting, which may be a concern in patient populations, especially populations with cognitive impairments. Patients in this study had lower levels of education than the controls, although on average they had completed one year of college. In addition, self-report has been shown to be consistent with clinician reports in patients with schizophrenia (Becchi et al., 2004) and previous studies have used the specific RSRI measure in patients with schizophrenia (Goldberg and Schmidt, 2001; Jetha et al., 2011). Another study limitation is that the data are cross-sectional. While data from other studies show a convergence between findings from cross-sectional (Gladstone et al., 2005) and longitudinal studies (Caspi et al., 1996; Chronis-Tuscano et al., 2009; Clauss and Blackford, 2012; Essex et al., 2013) of inhibited temperament and psychopathology, longitudinal studies are critical for establishing a temporal link between childhood inhibited temperament and later schizophrenia.

In summary, we show that inhibited temperament is prominent in schizophrenia and accounts for significant heterogeneity in an anxiety and depression phenotype. Thus, differences in temperament, in addition to clinical and cognitive factors, should be included in attempts to parse heterogeneity in schizophrenia. Inhibited temperament emerges early in development and is relatively stable over time; therefore, it has potential to be a premorbid risk factor that could be targeted for preventative interventions including social skill training (Jetha et al., 2007)]. In addition, patients with schizophrenia with inhibited temperament have elevated anxiety and depression symptoms and may potentially benefit from treatments focused on those symptoms such as adjunctive anxiolytic or antidepressant medications (Stroup et al., 2019).

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