UNDERSTANDING THE QUALITY OF LIFE AMONG INDIVIDUALS WITH SCHIZOPHRENIA

UNDERSTANDING THE QUALITY OF LIFE AMONG INDIVIDUALS WITH SCHIZOPHRENIA: AN EXPLORATION OF RISK AND RESILIENCE FACTORS

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy

McMaster University DOCTOR OF PHILOSOPHY (2023) Hamilton, Ontario, (Psychology, Neuroscience, and Behaviour; Psychology Research and Clinical Training Stream)

TITLE: Understanding the Quality of Life among Individuals with Schizophrenia: An Exploration of Risk and Resilience Factors

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NUMBER OF PAGES: 157

LAY ABSTRACT

Individuals with schizophrenia have been shown to experience reduced quality of life (QoL). Many studies have tried to understand what factors lead to reduced QoL, with one of them being individual differences in personality. This dissertation focused on the personality trait of shyness and addressed two main questions: 1. Are we correctly measuring shyness in people with schizophrenia? 2. What other factors influence the relation between shyness and QoL among individuals with schizophrenia? I first examined whether the meaning of shyness was equivalent between adults with schizophrenia and nonclinical controls. I then examined two different biological factors (i.e., neural and hormonal) related to stress responses to see if they influenced the relation between shyness and QoL in adults with schizophrenia. The answers to these questions have theoretical and practical implications for helping us understand who is at increased and decreased risk for experiencing hindered QoL, and possible targets for intervention.

ABSTRACT

The objective of this dissertation was to examine the relation between shyness and quality of life (QoL) among adults with schizophrenia in a series of three studies. I first began by understanding whether commonly used measures of shyness and sociability were reliable in this population (Study 1). Next, I examined two moderating variables related to stress-responses subserved by the central (Study 2) and peripheral (Study 3) nervous systems.

Study 1, used self-report questionnaires of shyness and sociability to determine whether individuals with schizophrenia responded to these questionnaires in the same way as healthy controls. Studies 2 and 3 used linear regression analyses to determine whether passive neural responses (ERP's) to social stimuli (emotional faces) and hormonal levels (baseline salivary cortisol and testosterone), respectively, moderated the relation between shyness and QoL.

I found that individuals with schizophrenia responded to self-reported shyness and sociability items in a similar way as their nonclinical peers, suggesting that self-reported shyness and sociability are equivalent across populations (Study 1). Study 2, found that individuals who were shy and displayed a hyposensitivity to the processing of fearful faces displayed the lowest QoL. Those who were shy and took longer to process happy faces also demonstrated hindered QoL. Finally, individuals who were shy and had relatively lower baseline salivary cortisol levels also had the lowest QoL. In all circumstances, individuals who were relatively less shy were not susceptible to factors relating to the central and peripheral nervous system.

The results of these three studies show that interpretations of findings using self-reported measures of shyness and sociability can be made with confidence in this population. The results also provide support that factors related to processing stressful stimuli can influence the relation

between shyness and QoL, thereby further increasing our understanding of this nuanced relation. Theoretical and practical implications of these findings are discussed.

Key words: Schizophrenia, Shyness, Temperament, Quality of life, Measurement Invariance

ACKNOWLEDGEMENTS

One thank you simply does not encompass the depth of my gratitude towards my two supervisors, Drs. Louis Schmidt and Heather McNeely. Dr. Schmidt, thank you for your constant support throughout my dissertation. The conversations we had in designing and implementing the research have helped me feel confident and excited about the work that was done. Thank you for allowing me to explore my own specific interests while still guiding me when appropriate. Dr. McNeely, thank you for the encouragement and discussions throughout the years. Your support in my exploration of research topics and clinical interests have made me the clinician scientist that I am today. Thank you both for encouraging me and being present throughout the years; my PhD experience would not have been the same without the two of you. Additionally, I would like to thank my committee members Drs. Michelle Jetha and Jelena King for their ongoing advice and support throughout the years. I have truly felt fortunate and grateful to be surrounded by encouraging and insightful mentors throughout my academic journey.

Thank you to the participants in the studies whose time and commitments have made this research possible. I enjoyed meeting and getting to know each and every one of you. Thank you to my co-authors for assisting me with the preparation of the manuscripts. Thank you to the Child Emotion Lab members and students who have volunteered with data collection for Chapter 2; your tireless efforts will not be forgotten. Thank you to the members of the Schizophrenia Outpatient Clinic and Cleghorn Clinic at St. Joseph's Healthcare Hamilton for allowing me to invite clients to contribute to the research program.

I would also like to thank my husband, Michael Goncalves, for supporting me throughout my academic journey. It has been a long one and your patience and loving support by my side has helped me carry forward throughout the years. Thank you to my family for supporting me

and inquiring about my research along the way. Most importantly, thank you to my brothers for being the reason why I entered this field. Thank you for being the first to teach me about the importance of quality of life among individuals with schizophrenia. Thank you for always being present in my life and showing me the importance of looking beyond clinical symptoms. To you, I will always be grateful.

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LIST OF ABBREVIATIONS

AQ-S	Autism Spectrum Quotient Short Form
ASD	Autism Spectrum Disorder
CBSHY	Cheek and Buss Shyness Scale
CBSOC	Cheek and Buss Sociability Scale
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision
EEG	Electroencephalogram
EOG	Electrooculogram
ERP	Event-Related Potential
HiREB	Hamilton Integrated Research Ethics Board
HPA	hypothalamic-pituitary-adrenal
HPS	Hamilton Program for Schizophrenia
Hz	Hertz
M	Mean
MC	Monte Carlo
MGCFA	Multiple Group Confirmatory Analysis
MI	Measurement Invariance
MLR	Robust Maximum Likelihood Estimation

MREB	McMaster Health Sciences Research Ethics Board
ms	Milliseconds
n	Sample Size
PANNS	Positive and Negative Syndrome Scale
PTSD	Posttraumatic Stress Disorder
QoL	Quality of Life
r	Pearson Correlation Coefficient
RMSEA	Root Mean Square Error of Approximation
SD	Standard Deviation
SEM	Standard Error of the Mean
SPSS	Statistical Package for the Social Sciences
SRMR	Standardized Root Mean Residual
X^2	Chi-Square Statistic
α	Cronbach's Alpha
β	Beta

DECLARATION OF ACADEMIC ACHIEVMENT

This dissertation consists of five chapters. The first chapter is a general introduction of the dissertation topic. The following three chapters (Chapters 2, 3, and 4) are empirical articles that have been previously published in a scientific journal. The last chapter (Chapter 5) is a general discussion that summarizes important findings, limitations, and future directions. The author of this thesis is first author, and her primary supervisor, Dr. Louis Schmidt, is last author on all publications.

Khalesi, Z., & Schmidt, L. A. (2020). Personality in special populations: Insights from schizophrenia. In V. Zeigler-Hill & T.K. Shackelford (Eds.), *Encyclopedia of Personality and Individual Differences* (pp. 3802-3805). Cham: Springer International Publishing.

Chapter 1 conceptualizes background information for the dissertation. It includes information published in a book chapter listed above. Z. Khalesi wrote the chapter under the guidance of L. Schmidt, who provided key revisions.

Khalesi, Z., Brook, C. A., Jetha, M. K., McNeely, H. E., Goldberg, J. O., & Schmidt, L. A. (2021). Revisiting shyness and sociability in schizophrenia: A psychometric examination of measurement invariance and mean level differences. *Journal of Personality Assessment*, *103*(6), 833-841.

Chapter 2 examined whether individuals with schizophrenia displayed measurement invariance when responding to self-report questionnaires assessing for shyness and sociability temperaments. Z. Khalesi conceptualized the study, collected data from individuals with schizophrenia, and wrote the majority of the study. C. Brook performed the data analysis, completed the data analysis, and wrote a portion of the methods and results sections of the

manuscript. M. Jetha provided valuable feedback on the drafts. H. McNeely supervised data collection among adults with schizophrenia and provided valuable feedback on the drafts. J. Goldberg provided valuable feedback on the drafts. L. Schmidt provided feedback on the study design and the drafts.

Khalesi, Z., Jetha, M. K., McNeely, H. E., Goldberg, J. O., & Schmidt, L. A. (2022). Shyness, emotion processing, and objective quality of life among adults with schizophrenia: An ERP study. *International Journal of Neuroscience*, 1-9, in press.

Chapter 3 examined the role of passive neural responses of emotional stimuli on moderating the relation between shyness and quality of life among adults with schizophrenia. It includes information published in the article above. Z. Khalesi conceptualized the study, conceptualized the data analysis, completed the data analysis, and wrote the majority of the manuscript. M. Jetha provided expertise on neural responses, wrote a portion of the manuscript, provided key edits on drafts and had previously collected the data. H. McNeely provided valuable revisions to the drafts. J. Goldberg had previously supported the data collection and provided valuable revisions on the drafts. L. Schmidt provided feedback on the study design, previously supported data collection, and provided revisions on the drafts.

Khalesi, Z., Jetha, M. K., Poole, K. L., Goldberg, J. O., Van Lieshout, R. J., & Schmidt, L. A. (2019). Shyness, hormones, and quality of life among adults with schizophrenia. *International Journal of Neuroscience*, *129*(5), 470-480.

Chapter 4 examined the role of hormones on moderating the relation between shyness and quality of life among adults with schizophrenia. Z. Khalesi conceptualized the study,

completed the data analysis, and wrote the majority of the manuscript. M. Jetha provided key edits on drafts and had previously collected the data. K. Poole performed the data analysis, completed the data analysis, and wrote a portion of the methods and results sections of the manuscript. J. Goldberg had previously supported the data collection and provided valuable revisions on the drafts. R. Van Lieshout provided valuable revisions to the manuscript. L. Schmidt provided feedback on the study design, previously supported data collection, and provided revisions on the drafts.

CHAPTER 1:

GENERAL INTRODUCTION

Chapter link:

Khalesi, Z., & Schmidt, L. A. (2020). Personality in special populations: Insights from schizophrenia. In V. Zeigler-Hill & T.K. Shackelford (Eds.), *Encyclopedia of Personality and Individual Differences* (pp. 3802-3805). Cham: Springer International Publishing.

Schizophrenia is a chronic illness that is often associated with major debilitating factors such as early morbidity, hindered social functioning, and hindered quality of life (Jääskeläinen et al., 2012; Katschnig, 2000; Lambert & Naber, 2004; Tolman & Kurtz, 2012). It affects approximately 1% of the population with reports stating that the average number of individuals living with schizophrenia increases by 3% a year (Public Health Agency of Canada, 2020). The impacts of this disorder not only affect the individual, but also the family and, on a larger scale, society. For example, the economic burden associated with the disorder has been estimated at 1,112 million dollars per capita (Blomqvist et al., 2006). Although many psychiatric and psychological treatments exist, there is no known "cure" for this illness, with some individuals experiencing symptoms for chronic and extended periods, while others may only experience a short period of symptoms (Cohen et al., 2008).

While outcome measures have traditionally focused on symptom improvement in this population, more recent studies have examined the importance of assessing subjective and objective quality of life (QoL) amongst individuals with schizophrenia (Hofer et al., 2005). Subjective QoL refers to the individual's perceived life satisfaction and well-being in different domains of their life, while objective QoL refers to the individual's ability to perform activities and engage in relationships (Lehman, 1988). Objective QoL, specifically, has been shown to be indicative of overall participation is society and is predictive of future relapse amongst individuals with schizophrenia (Boyer et al., 2013).

Due to the large heterogeneity in the presentation and prognosis of this illness, it is important to understand which factors may account for the phenotypic differences observed. Indeed, there are multiple factors which can contribute to the duration and severity of

schizophrenia such as age, gender, duration of untreated illness (Barrowclough & Hooley, 2003; Beaucham et al., 2006; Szymanski et al., 1995). More recently, personality traits have been examined as factors that may influence the severity of symptoms, response to treatment, and impact on quality of life.

Personality constructs are understood as a lens by which individuals view and react to the world. They reflect a characteristic pattern of thinking, feeling, and behaving in response to external situations (Andersen & Bienvenu, 2011). A well-established theoretical model of personality (i.e., McCrae & John, 1992) describes 5 main constructs: Neuroticism, Extraversion, Openness, Conscientiousness, and Agreeableness. These personality constructs are thought to be in part genetically-determined and relatively stable throughout adulthood, often predating the onset of a diagnosis (McCrae & Costa, 1994), though recent findings have shown that life experiences can sometimes shape and modify personality traits observed (Debast et al., 2014). Research examining links between personality and mental disorders has consistently shown that high levels of neuroticism are most frequently associated with several common mental disorders and may represent a non-specific generalized risk (see Ormel et al., 2013, for a review). Temperament (e.g., shyness and sociability), on the other hand, represents the early features of personality that are present at birth and can be considered as the building blocks to personality traits (Mathewson et al., 2017). Temperament factors have been found to be stable despite intervention techniques. For example, findings showed that shyness and sociability remained stable after social skills training among individuals with schizophrenia (Jetha et al., 2007). By understanding an individual's temperament, we may predict how the individual will potentially interpret and respond to particular situations. For example, individuals who are shy often experience fear or inhibition in the context of novel social situations and/or social evaluation.

Such responses can be cognitive (negative interpretation of surroundings and perceived judgements), affective (heightened physiological response), and/or behavioral (withdrawing from the situation) (Crozier, 2005); these responses shape the individual's experiences and responses to essentially all life experiences including the experience and response to symptoms of a psychotic illness. Personality and temperament traits often predate the onset of illness and may influence the severity of symptoms, response to treatment, and impact on quality of life (Jetha, Goldberg & Schmidt, 2013; Kentros et al., 1997; Ridgewell et al., 2007; Swann et al., 2002; Widiger, 2011).

Some personality traits are more likely to be present in individuals experiencing first episode psychosis as compared to healthy peers or non-afflicted family members (Beaucham et al., 2006; Couture et al., 2007; Simonsen & Newton-Howes 2018). This trend also continues for individuals further along their illness, suggesting that they are relatively stable and independent of the psychopathology (Beaucham et al., 2006). For example, very early into the illness, the following personality traits differentiate those with first episode psychosis from healthy controls: high levels of neuroticism, openness, and agreeableness as well as low levels of extraversion, and conscientiousness. These personality characteristics appear to be immutable to treatment (i.e., Cognitive Behavioural Therapy for Psychosis) and remain relatively stable over time (Beaucham et al., 2006). It appears as though individuals with schizophrenia who exhibit high levels of neuroticism and low levels of extraversion may be at particular risk for increased symptoms as well as poor treatment outcomes (Beaucham et al., 2006).

When examining personality traits among individuals with schizophrenia who have continued to experience more than one psychosis episode and ongoing symptoms, similar personality profiles emerge. Lysaker and colleagues (1999) also found that certain personality

traits are associated with the pathology and symptomology of schizophrenia. Their results indicated that extraversion was associated with lower levels of positive, negative and emotional discomfort while endorsing higher levels of excitement symptoms as measured by the PANSS (Kay et al., 1987). Moreover, those who were high on the neuroticism trait also reported higher levels of positive and emotional discomfort symptoms. These findings remain consistent across multiple studies with adults with schizophrenia (e.g., Boyette et al., 2013; Boyette et al., 2015; Lysaker & Taylor, 2007; Lysaker et al., 2003; Miskovic et al., 2018). In addition to low extraversion and high neuroticism, these studies demonstrated that all of the big five personality traits, except for openness, were associated with symptom severity. That said, only high neuroticism was associated with *greater* symptom severity (Boyette et al., 2013) and lower response levels to psychological treatment (Boyette et al., 2015). Moreover, individuals with high risk for developing schizophrenia (e.g., family members of those with schizophrenia) also reported higher levels of neuroticism relative to healthy controls, but at lower levels than those with schizophrenia (Boyette et al., 2013). This suggests that some personality traits, such as neuroticism, may be a risk factor that contributes to the development and maintenance of schizophrenia symptoms. Meanwhile, some personality traits, such as extraversion, may be a protective factor that leads to lower symptom expression and better prognosis (Beaucham et al., 2006; Boyette et al., 2013; Boyette et al., 2014; Boyette et al., 2015; Camisa et al., 2005; Lysaker & Taylor, 2007).

It is thought that the personality traits of neuroticism and introversion are, in part, comprised of the temperamental trait of shyness (Briggs, 1988). Shyness has been conceptualized in terms of a three-component model: somatic-emotional, behavioural, and cognitive components (Cheek & Watson, 1989) that represent the different characteristics

observed in shy individuals in response to novel social stimuli. The somatic-emotional component refers to the physiological and affective-emotional responses observed (e.g., blushing or feeling upset in a novel social situation). The behavioural component refers to the observed behaviours such as quietness, difficulty engaging and sustaining conversations, gaze aversion, withdrawal, and avoidance of social situations. Lastly, the cognitive model refers to the thoughts and worries experienced during social interactions (e.g., fears of rejection, self-consciousness) (Cheek & Watson, 1989). These components outline a stable set of characteristics that are present in early development and stable across time and context (Mathewson et al., 2017). Understanding how shyness may influence an individual's response to psychopathology, such as psychosis or schizophrenia, can help make sense of the heterogeneity often observed within this population. That is, do adults with schizophrenia differ in their presentation based on previous temperament factors that may influence the way they interpret and react to the social stimuli around them?

Indeed, increasing evidence has found that individuals with schizophrenia are more likely to report higher levels of shyness than healthy controls (Goldberg & Schmidt, 2001). This pattern is also seen with individuals at clinical high risk for developing schizophrenia and first episode psychosis patients, suggesting that these temperamental traits were present before the onset of the illness. Additionally, among adults with schizophrenia, shyness has been found to predict poorer subjective quality of life reports, with estimates accounting for up to 16% of the variability for QoL (Ritsner et al., 2003; Ritsner & Blumenkrantz., 2007). Those with higher levels of shyness report poorer subjective QoL (Ritsner et al., 2003; Ritsner & Blumenkrantz, 2007). Some studies have also examined the impacts of temperament and personality on objective QoL, which focuses on the ability to perform activities and engage in relationships. A

similar pattern is observed where temperament and personality such as shyness or inhibition was associated with hindered objective QoL (Goldberg & Schmidt, 2001; Jetha et al., 2013a; Sörgaard et al., 2001). These findings suggest that temperament traits such as shyness may interact with the psychopathology presentation to differentially influence outcomes in QoL.

Despite the associations found between shyness and quality of life among adults with schizophrenia, there remains a large amount of variability that is not accounted for. This discrepancy of variability may suggest that other moderating variables exist that may help further explain the general relation observed. Due to the impact of temperament on physiological reactions of individuals (i.e., blushing, increased heart rate) (Poole & Schmidt., 2021; Sriranjan et al., 2022; Tang et al., 2021), it is likely that individual differences in peripheral and central nervous system responses to stressful events or stimuli could impact the relation observed. Examining facets of these responses using salivary cortisol levels and physiological measures such as event related brain potentials (ERPs) which comprise different biological levels could provide clearer information about the associations among shyness, physiological responses, and outcomes among adults with schizophrenia.

Although evidence supporting the associations between personality constructs and psychopathology among adults with schizophrenia exist, the specific measures' reliability has not been examined across different populations. That is, it is unknown whether individuals with schizophrenia are interpreting and responding to the questionnaires the same way as the healthy controls that the measure was initially developed against. Understanding whether these measures are reliable across populations is of upmost importance in order to secure confidence in the conclusions drawn from previous research.

1.0. Overview of Dissertation

The following three empirical chapters aim to address the measurement issues observed within the field that although critical, have been understudied as well as moderating factors that might help us more fully understand the relation between shyness and quality of life among stable adult outpatients with schizophrenia. All participants across the studies were associated with outpatient clinics for schizophrenia spectrum disorder and were diagnosed by a psychiatrist with a primary diagnosis of schizophrenia spectrum disorder. The first empirical chapter deals with critical issues related to measurement. The latter two empirical chapters examine the relation between temperamental factors and quality of life outcomes as well as the moderating influences of the central and peripheral nervous system's response to stressful events on this relation.

In the first empirical chapter (i.e., Chapter 2), I examined a large sample consisting of stable adults with schizophrenia who responded to widely-used measures assessing temperament traits of shyness and sociability. Responses from these measures were compared with healthy controls and analyses addressing reliability through measurement invariance were conducted. Findings suggested that adults with schizophrenia interpreted and responded to temperament measures in the same way as healthy controls. These findings indicate that the measures used within this population are reliable and can be interpreted with confidence and trustworthy comparisons can be made using these measures between people with schizophrenia and healthy controls.

In Chapter 3, I examined the central nervous system's response to stressful social stimuli using ERP measures (i.e., early neural responses to emotional faces) and whether these responses moderated the relation between shyness and quality of life. I found that that those patients who

scored higher on shyness and demonstrated hyposensitivity in the early visual processing of fearful emotional faces (i.e., reduced attention and slower processing at the P1 and N170 stage for emotional faces) were at higher risk for deficits in cognitive, affective, and motivational domains in relation to quality of life. However, I did not find the same robust findings for intrapersonal quality of life outcomes. This study demonstrated the importance of understanding stress response factors on central measures when examining the relation between temperament and quality of life among adults with schizophrenia.

In Chapter 4, I followed up on this line of research by examining the influence of the peripheral nervous system's response to stress using endocrine variables (i.e., salivary cortisol levels) on the relation between temperament and quality of life among adults with schizophrenia. Here I found that baseline cortisol levels moderated the relation between shyness and quality of life. Among individuals with relatively low baseline cortisol, higher shyness was associated with deficits in cognitive, affective, and motivational domains in relation to quality of life. These findings suggest that relatively lower baseline cortisol levels, which have been implicated in nonclinical samples of people who are shy and the negative downstream effects resulting from HPA axis dysregulation, are important factors to examine when trying to understand the relation between temperament and quality of life among adults with schizophrenia.

In Chapter 5 of the dissertation, I then provide a general discussion of the theoretical and practical implications of this series of studies along with limitations and avenues for future research.

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CHAPTER 2:

REVISITING SHYNESS AND SOCIABILITY IN SCHIZOPHRENIA: A PSYCHOMETRIC EXAMINATION OF MEASUREMENT INVARIANCE AND MEAN LEVEL DIFFERENCES

Chapter link:

Khalesi, Z., Brook, C. A., Jetha, M. K., McNeely, H. E., Goldberg, J. O., & Schmidt, L. A. (2021). Revisiting shyness and sociability in schizophrenia: A psychometric examination of measurement invariance and mean level differences. *Journal of Personality Assessment*, *103*(6), 833-841. 10.1080/00223891.2021.1895183

Revisiting Shyness and Sociability in Schizophrenia:

A Psychometric Examination of Measurement Invariance and Mean Level Differences

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Abstract

Although there is a long and rich empirical history of demonstrating differences on psychological self-report measures between people with schizophrenia and healthy controls, the question of whether both groups respond to psychological measures in the same way has gone largely unexplored. That is, is there measurement equivalence, or invariance, across the samples? To our knowledge, there have been no published studies on measurement equivalency in personality measures across groups diagnosed with and without schizophrenia. Here we examined the question of measurement invariance on two widely used questionnaires assessing temperament, the Cheek and Buss Shyness and Sociability Scales (CBSHY and CBSOC, respectively) between 147 stable adult outpatients with schizophrenia and 147 healthy age- and sex-matched controls. Results supported measurement invariance of the CBSHY and CBSOC across our clinical and non-clinical groups. These findings suggested that stable adult outpatients with schizophrenia and age- and sex-matched controls respond to the shyness and sociability items in the same way. We found that adults with schizophrenia reported higher levels of shyness and lower levels of sociability than healthy controls, consistent with prior studies. Findings are discussed concerning their relevance more broadly to self-report assessments of personality and psychological traits in clinical populations.

Keywords: schizophrenia, measurement invariance, psychometric, shyness; sociability, personality

Introduction

Schizophrenia is a complex and persistent mental disorder that is often associated with poor outcomes, such as low levels of quality of life, low remission rates, and low rates of functional recovery, including limitations in return to work or school and independent living (Harvey & Bellack, 2009; Moriarty et al., 2001; Murray & Van, 1998; Robinson et al., 2004; Strauss & Carpenter, 1974). Despite this typically poor prognosis, there exists considerable heterogeneity within this population, suggesting that individual difference factors, such as temperament, may influence the vulnerability, course and prognosis of the illness (Eklund et al., 2003; Fresán et al., 2015; Jetha et al., 2013; Khalesi et al., 2019; Ritsner & Blumenkrantz, 2007; Ritsner et al., 2003). One growing area of interest is the relation between individual differences in temperament and the onset, maintenance, and prognosis of schizophrenia spectrum disorders.

Temperament is considered to reflect differences in emotional responsiveness, mood, and behavior of an individual and is defined by varying characteristics or constructs (Rothbart et al., 2000; Rothbart & Mauro, 1990). Some of these temperament characteristics, such as shyness and sociability, respectively, have been implicated as potential risk and resilience factors for schizophrenia prognosis (Khalesi et al., 2019). For instance, individuals with schizophrenia often report higher average levels of shyness, or constructs related to shyness such as behavioral inhibition, than healthy populations (Feola et al., 2019; Goldberg & Schmidt, 2001; Jetha et al., 2013; Khalesi et al., 2019; Ritsner et al., 2003). Retrospective reports also indicated there were higher than average levels of shyness or behavioral inhibition in childhood among those who developed schizophrenia, suggesting that these temperament characteristics were present prior to schizophrenia onset (Feola et al., 2019; Goldberg & Schmidt, 2001; Ritsner & Blumenkrantz, 2007; Ritsner et al., 2003). Such premorbid temperament factors also predicted future outcomes

of adults with schizophrenia; those with higher levels of shyness or behavioral inhibition, either as children or currently, also experienced lower levels of subjective quality of life as adults (Feola et al., 2019; Khalesi et al., 2019; Ritsner & Blumenkrantz, 2007; Ritsner et al., 2003) and higher levels of psychiatric symptoms than individuals with schizophrenia who reported lower levels of shyness or behavioral inhibition (Feola et al., 2019). Finally, individuals with schizophrenia who have higher levels of sociability or extraversion traits report higher levels of life satisfaction and a better prognosis (Beauchamp et al., 2006), providing further evidence of the influence of temperament on psychopathology expression and quality of life. Taken together, these studies underscore the value of further exploration of how temperament traits may impact the lives and recovery of individuals with schizophrenia.

Although temperament and personality measures have been used in the study of clinical populations such as those with mood and anxiety disorders (Brown et al., 1992; Clark et al., 1994; Poole et al., 2017), relatively little is known about whether individuals with a schizophrenia diagnosis respond in the same way to personality measures as other clinical samples or as compared to typically developing, nonclinical individuals. That is, are we actually measuring the same construct across these different populations? Previous research has not addressed this question directly but rather has explored validity issues through a clinical lens, examining whether unawareness of illness or impaired insight might influence the self-reporting of personality traits in schizophrenia patients; such investigations have examined comparisons between patient scores and clinician ratings and concluded that self-report measures were generally valid for most personality and symptom domains (Bell et al., 2007). An alternative psychometric approach to addressing this validity question is to evaluate the measurement invariance (MI) of a scale across populations of interest to determine whether the same

underlying construct is being measured across clinical and nonclinical groups (Van De Schoot et al., 2012).

Evaluating MI of a questionnaire has important implications for group comparisons because it establishes the generalizability of a scale across different populations and across time. To our knowledge, no study has evaluated MI of any measure used to assess differences between individuals with schizophrenia and healthy controls. Despite this void, a study by Murray and colleagues (2014) did examine MI of the Autism Spectrum Quotient Short Form - AQ-S (Hoekstra et al., 2011) between individuals diagnosed with Autism Spectrum Disorder (ASD) and healthy controls. While their results supported metric invariance (i.e., inferring that the construct had a similar meaning across both groups), they were unable to establish scalar invariance (i.e., inferring that the groups were not responding to the items in the same way), likely making group mean comparisons between individuals with ASD and healthy controls untrustworthy (Murray et al., 2014). A lack of evidence for scalar invariance in particular has implications for interpreting results in clinical research. In practice, much of the research with clinical populations, including studies assessing personality traits in association with schizophrenia, has used self-report tools to compare means among different groups without first testing for MI (Guillem et al., 2002; Jetha et al., 2013; Kurs et al., 2005; Szöke et al., 2002). Despite the fact that testing for MI in psychological measures across groups or across time is necessary to establish meaningful comparisons (Putnick & Bornstein, 2016), it seems very few studies examining clinical-nonclinical group mean differences, if any, have reported tests of MI beforehand.

As a first step toward investigating this issue, we examined whether the two distinct constructs of shyness and sociability, in separate analyses, were being assessed as the same

underlying phenomenon across participants with or without a diagnosis of schizophrenia. To accomplish this goal, we evaluated the measurement equivalence of the Cheek and Buss Shyness Scale (CBSHY) and Cheek and Buss Sociability Scale (CBSOC) (Cheek & Buss, 1981), previously well-established and validated measures (Bruch et al., 1989; Hopko et al., 2005), across our clinical and nonclinical groups through two different invariance testing approaches, multiple group confirmatory factor analysis (MGCFA) and the alignment method. Previous studies using the CBSHY, CBSOC (Goldberg & Schmidt, 2001; Jetha et al., 2013) and related shyness scale constructs (Feola et al., 2019) have reported higher levels of shyness and lower levels of sociability in stable adults with schizophrenia as compared with control adults, but MI was not tested in these studies. In contrast, recent work has established MI in the CBSHY and CBSOC across sex and age in healthy, nonclinical individuals (Brook & Schmidt, 2019, 2020; Kwiatkowska & Rogoza, 2017). Yet, to our knowledge, no one has tested for MI in the CBSHY or CBSOC across clinical and nonclinical samples. We hoped to establish measurement invariance across these two scales to substantiate this previous work and provide support for our own investigation into the validity of mean differences in shyness and sociability between healthy controls and stable outpatient adults with schizophrenia, matched on age and sex. Furthermore, we hope to highlight an oversight in clinical research practice; measurement equivalence assessments of self-report measures should become standard practice before valid mean level comparisons can be made across groups of interest.

Method

Participants and Overview

A convenience sample comprised of primarily white participants who were either clinically diagnosed with schizophrenia (n = 147, age range = 21 to 77 years, 64.4% male) or

roughly age-matched controls (n = 147, age range = 17 to 86 years, 46.3% male) was drawn from four, larger and more comprehensive, independent studies that shared similar protocols regarding self-report questionnaire completion. The two studies researching schizophrenia were based on the first (Khalesi, in progress) and third (Jetha et al., 2007) authors' dissertation data, respectively: one study only recruited participants with schizophrenia (n = 105), whereas the other study recruited participants with schizophrenia (n = 42) and controls (n = 81). In both of those studies diagnoses were conducted by a psychiatrist upon entry to the respective clinic and based on DSM-IV-TR and DSM-5 criteria (American Psychiatric Association, 2000). The remaining non-clinical participants were drawn from two different research projects (Brook & Schmidt, 2019, 2020) and were matched to patients based on sex and age (n = 25 and n = 41, respectively). Overall, there were more men than women in the sample (55.3% males) and there was a discrepancy between the economic backgrounds of the healthy controls and participants with schizophrenia as indicated by a median family income of approximately $88,610 CAD (Statistics Canada, 2017) and $15,000 CAD, respectively. Despite the large discrepancy between the two groups, the lower average income of the schizophrenia group was expected because the majority of the participants with schizophrenia were receiving financial support from disability healthcare subsidies. Missing data were negligible, with sex missing on one participant. All of the studies were conducted in either a university or clinical setting within the same city of Hamilton, Ontario. Ethics approval for each of the four studies was gained from both University and/or Hospital Research Ethic Boards prior to their start. The following research ethics boards and their respective codes are provided for the four studies used: MREB 2010-170.2, HiREB 2010-480.1, HiREB 2004-332, and HiREB 3980. All participants provided written consent, and

participants with schizophrenia also completed the capacity to consent tool to take part in the primary research program (Jeste et al., 2007).

Measures

Demographics. All participants reported on their age and sex.

Shyness. The five highest-load shyness items (Bruch et al., 1989)1 from the original 13-item self-report Cheek and Buss Shyness Scale – CBSHY (Bruch et al., 1989; Cheek & Buss, 1981) were used to measure the construct of shyness on a 5-point Likert scale between 1 = *strongly disagree* to 5 = *strongly agree* (Table 1). Higher scores indicated higher levels of shyness, for example, in response to items such as, "*I find it hard to talk to strangers*."

Sociability. Sociability was measured with the five items of the Cheek and Buss Sociability Scale (CBSOC) using a 5-point Likert scale (Bruch et al., 1989; Cheek & Buss, 1981). Higher scores reflected higher levels of sociability, for example, in response to items such as, "*I find people more stimulating than anything else*."

Plan of Analysis

Historically, the CBSHY and CBSOC scales were developed by Cheek and Buss (1981) to investigate whether shyness was just low sociability. In fact, the scales were found to be

[1] We selected the 5 shyness items *a priori* based on their factor loadings from the study by Bruch et al. (1989). This shorter shyness scale was used to minimize participant burden, increase compliance, and make the number of items identical to the original Cheek and Buss (1981) sociability measure. The 5-item shyness scale has been used on many occasions over the years with nonclinical samples (see Brook & Schmidt, 2019 for details). We previously demonstrated that this 5-item shyness measure was conceptually and empirically linked to subscales of harm avoidance and novelty seeking - from the much lengthier Cloninger Temperament Character Inventory (TCI), which is routinely used with patients with schizophrenia - in a sample of stable outpatients with schizophrenia (Jetha et al., 2013). The rationale for the Jetha et al. (2013) was to provide the clinical community with a brief measure of shyness rather than the lengthy TCI in order to reduce patient burden and increase compliance. However, a limitation of Jetha et al. (2013) was that measurement invariance was not tested.

distinct dispositional traits and have been studied as such since this time (Bruch et al., 1989; Cheek & Buss, 1981). Before testing for MI in the two scales, we ran confirmatory factor analyses (CFA) to verify that the CBSHY and CBSOC one-factor models each had acceptable fit to the data in both the schizophrenia and control status groups. Good and acceptable model fit to data was determined through several fit statistics, including a nonsignificant χ^2 test (this test may be significant due to various reasons including its sensitivity to sample size), a root mean square error of approximation close to RMSEA ≤.080 and ≤.060, a comparative fit index of CFI ≥. 950 and ≥.900, and a standardized root mean residual of SRMR ≤ .050 and ≤.080, respectively (Browne & Cudeck, 1993; Hooper et al., 2008; Hu & Bentler, 1999; Kline, 2011). Aside from using global fit statistics to determine model fit, we also examined local fit through standardized residuals (i.e., the standardized difference between the model implied and sample variance-covariance matrices) to assess whether any specific element of the model fit poorly. Values within the range of ±2.00 were considered to be nonsignificant discrepancies.

Subsequently, once good fit had been established in the individual group models for both scales, we tested for MI across status group through multiple group confirmatory analysis (MGCFA). We originally planned to compare groups across clinical status by sex because sex differences are well documented within personality research and may confound the assessment of MI in the shyness and sociability measures across status (Schmitt et al., 2008), however, our sample size was not sufficient. The MGCFA involved a series of nested or increasingly restrictive model comparisons beginning with configural model invariance (requiring the same construct dimensionality across the groups), followed by metric model invariance (requiring the addition of the same loadings to be constrained across groups), and ending with scalar model invariance (requiring both the same loadings and intercepts/thresholds to be constrained across

groups). Configural invariance was determined by measuring overall good model fit across both groups simultaneously (see previous paragraph for cutoff criteria). To assess metric and scalar invariance, a comparison was made between the nested models to establish that there was no significant change in model fit, explicitly between the configural and metric models, and the metric and scalar models. Recommended critical values for non-significant change in model fit included a $\Delta\chi^2$ associated with a $p > .05$, ΔRMSEA $\leq .015$, ΔCFI $\leq .010$, and ΔSRMR $\leq .030$ for the loading level and $\leq .010$ for the intercept/threshold level (Chen, 2007; Cheung & Rensvold, 2002).

Although the traditional MGCFA methodology is commonly used to test MI among groups, frequently the scalar invariance test fails, leading to multiple model adjustments to obtain good fit. The alignment method is an alternative method for testing approximate invariance that avoids multiple model adjustments and imposes a different set of restrictions to minimized parameter noninvariance. Basically, only the simplest configural model is estimated with the least amount of noninvariance resulting in a solution of a "few large noninvariant parameters and many approximately invariant parameters" – further details of the underlying statistics of this methodology can be found elsewhere (Asparouhov & Muthén, 2014; Marsh et al., 2017; Muthén & Asparouhov, 2014). Following Muthén and Asparouhov's rule of thumb, trustworthy approximate invariance was supported if 25% or fewer parameters were found to be noninvariant (for example in the CBSHY, five items by two groups by two parameters – loadings and intercept – equals a total of twenty possible noninvariant parameters). As a follow-up to the alignment analysis, a Monte Carlo (MC) simulation study was run using starting values from the real data analysis to verify how well the shyness or sociability means were estimated. A correlation of .980 or higher between the generated and estimated means was considered

supportive of trustworthy alignment results. Our intent was to follow up any MGCFA significant change fit statistics with the alignment or approximate invariance method.

Finally, we assessed the internal consistency of both the shyness and sociability scales across the whole sample and by schizophrenia status (i.e., those with or without a schizophrenia diagnosis) through Cronbach's alpha and McDonald's omega. While the former statistic has been most frequently reported in the literature, there is some question as to its susceptibility to change in measurement error, which the omega coefficient takes into account (Dunn et al., 2014). All the above analyses were computed in Mplus 8.4 using robust maximum likelihood estimation (MLR) because it does not assume multivariate normality (Wolf et al., 2013).

Results

Descriptives

Within their respective scales, the CBSHY and CBSOC items displayed similar mean levels and univariate normality for each status group (Table 2). In general, the mean levels of the CBSHY items were lower for the control group than the schizophrenia group. In contrast, the mean levels of the CBSOC items were higher for the control group as compared to the schizophrenia group. Across each scale separately, moderate correlations were found among the items in both status groups (Table 3). One exception to this pattern was found between items 6 and 7 of the CBSOC; the relation was strong at .779. Samples sizes for group comparisons fell within guidelines for the investigation of a simple SEM measurement model (n_{male} = 162 and n_{female} = 131; $n_{control}$ = 147 and $n_{schizophrenia}$ = 147) and also were supported by the results of a MC power analysis of > .80 (Muthen & Muthén, 2002).

Scale factor structure by Group Status

Shyness. A CFA on the schizophrenia one-factor CBSHY model led to good global and local fit (Table 4, all standardized residuals $p > .05$), and subsequently was used as the schizophrenia baseline model in the MGCFA. For the control one-factor CBSHY model, global and local fit were adequate except for the RMSEA (Table 4, all standardized residuals $p > .05$), which indicated there was likely some misfit between the data and model, despite evidence suggesting that the RMSEA might also perform poorly in models with small degrees of freedom (Kenny et al., 2015). Nonetheless, based on the modification indices and similarity in item meaning, CBSHY item 2 ("When I'm in a group of people, I have trouble thinking of the right things to talk about") and item 4 ("I feel inhibited in social situations") appeared to be modeling a relation outside their association with the latent shyness factor. A revision of the control model with a correlated error between these two items led to overall good global and local fit (Table 4). Consequently, this modified model was used as the control baseline model to explore MI in the CBSHY.[2]

Sociability. The global and local fit for the schizophrenia and the control one-factor CBSOC models were unacceptable. Both models had poor fit with respect to the $\chi 2$ and the RMSEA

[2] We modified the *control* group CFA models for both shyness and sociability to obtain acceptable fit with respect to the RMSEA because our values were higher than conventional critical values would dictate. However, some evidence and discussion in the literature has suggested that models with very low degrees of freedom and relatively small sample sizes produce artificially biased and large RMSEA values, and consequently, the RMSEA should *not* be reported under these conditions (Kenny et al., 2015). In our analyses, degrees of freedom were small (df = 5) and the sample size was not large ($n = 147$). Nonetheless, because the RMSEA is an extremely popular model fit statistic in the literature, we introduced correlated errors into our *control* group model for both the shyness and sociability CFAs based on modification indices and similarity in item meaning (Bandalos, 2018) to obtain adequate/good fit as a prerequisite for running MGCFAs. In an effort to allay concern about post hoc modifications through the introduction of correlated errors, we ran our shyness and sociability analyses without the specified correlated error terms and found our measurement invariance results were the same.

(Table 4, each model had one standardized residual $p < .05$). The modification indices indicated that the poor fit stemmed from one discrepancy, specifically between the CBSOC items 1 and 2. A closer look revealed that there was a greater similarity in meaning and wording of the two items with each other than with the remaining items in the scale ("I like to be with people" and "I welcome the opportunity to mix socially with people"). In addition, the bivariate correlation between these two items was strong in comparison to the other sociability item correlations (Table 3). This evidence suggested that the two items were likely covarying for reasons outside the sociability model, and thus, we reran the CFA specifying a correlation between the error terms of CBSOC items 1 and 2. This re-specified model had good fit and the one-factor model with a correlated residual was subsequently used for both status groups in the MI analysis (Table 4; all standardized residuals $p > .05$).

Multi-group Measurement Invariance

Shyness Across Group Status. Configural global and local model fit to the data across status in a MGCFA was good (Table 5, all standardized residuals within ± 2.00). Furthermore, the MGCFA results showed there was no significant difference in model fit among the configural, metric and scalar models, except for a significant ΔRMSEA between the configural and metric models (Table 5). However, because the $\Delta\chi 2$ was nonsignifcant across the nested models, we concluded that the same CBSHY model was being assessed across the two status groups. Thus, we provided evidence to suggest that those with schizophrenia as compared to our control participants responded in a similar way to the shyness questionnaire. The results also indicated that those with schizophrenia had significantly higher mean levels of shyness than our controls (Table 6, $W(1) = 5.875$, $p = .015$).

Sociability Across Group Status. Configural and local fit to data was very good across clinical status in a MGCFA (Table 4, all standardized residuals within ± 2.00). However, the change in fit statistics between the configural and metric models, and the metric and scalar models, was not fully supportive of MI in the CBSOC between status groups (Table 5). To better understand the noninvariance, we followed up the MGCFA with the alignment method and found no evidence of noninvariance (0%) in the sociability measure across status (see Supplementary for alignment results). The MC simulation study also supported this conclusion by finding a perfect correlation between the generated and estimated sociability means. Thus, both those with schizophrenia and the control participants likely responded in the same way to the sociability questionnaire, and we found evidence to suggest that those with a diagnosis of schizophrenia as compared to those without a diagnosis had lower mean levels of sociability (Table 6, $W(1) = 21.926$, $p < .001$).

Reliability

Cronbach's alpha and McDonald's omega reliability coefficients for the shyness and sociability scales displayed high internal reliability (Table 6) when measured in the entire sample and by status group.

Discussion

In the past, researchers have examined the association between individual differences in temperament among individuals with schizophrenia to better understand the effects of personality and emotion on both the development and the prognosis of this mental disorder. Yet, it is unclear whether those diagnosed with schizophrenia respond to temperament measures in the same way as healthy controls. Comparisons between clinical and nonclinical groups may be biased by measurement error and thereby compromise the assessment of valid comparisons of

personality constructs. To address this concern, we assessed whether individuals with schizophrenia responded to questionnaires assessing shyness and sociability in the same way as community controls by evaluating the MI of the CBSHY and CBSOC scales across the two groups. The evidence indicated that there was MI in the measures of CBSHY and CBSOC across individuals with schizophrenia and healthy controls. Given that MI is considered a critical prerequisite before mean comparisons can be made on the same underlying construct, we were assured psychometrically of making valid and unbiased comparisons across our clinical and nonclinical groups.

After establishing MI on the personality measures, we compared the two groups separately on shyness and sociability. With respect to shyness, we found that those with schizophrenia had significantly higher mean levels of shyness than the comparison group of healthy controls. These findings were consistent with past results showing that patients with schizophrenia had higher levels of shyness, on average, than healthy controls (Bandalos, 2018; Goldberg & Schmidt, 2001; Jetha et al., 2013). Other researchers also have found that these temperament traits were resistant to change after a social skills training intervention was implemented in a schizophrenia sample, further corroborating the stability of these personality traits and implicating their continued impact on social functioning and quality of life (Feola et al., 2019; Goldberg & Schmidt, 2001; Jetha et al., 2013; Jetha et al., 2007). Thus, the results from the present study supported and validated work that had previously linked individual differences in shyness with individual differences in social functioning in participants with schizophrenia.

In terms of sociability, we found that the control adults had significantly higher mean levels of sociability than stable adults with schizophrenia. These results were consistent with

previous research reporting that individuals with first episode psychosis had lower mean levels of extraversion, a personality trait closely related to the temperament construct of sociability (John & Srivastava, 1999), than healthy controls (Beauchamp et al., 2006; Couture et al., 2007). Similarly, adults with chronic schizophrenia also showed lower levels of extraversion, on average, than healthy controls (Lysaker et al., 1999), suggesting a pattern of stability across the lifespan. Moreover, patients with schizophrenia exhibited lower mean levels of sociability as measured by the CBSHY in comparison to healthy adults (Goldberg & Schmidt, 2001; Jetha et al., 2013). Consequently, the results from this study replicated earlier findings, validating previous research that linked individual differences in sociability with individual differences in levels of social functioning.

Finally, there has been a scarcity of research evaluating MI within special populations in general, and schizophrenia in particular. We found only one paper that examined MI of a quality of life scale among patients with schizophrenia (Kyeunghae Lee et al., 2010). However, without a healthy control comparison group, the interpretation of the results lacked evidence to validate that their sample's responses to the questionnaire were comparable to those of a healthy population. Another two studies examined a self-report clinical disorder questionnaire specifically purposed for its relevance to the schizophrenia population, namely the schizotypal personality questionnaire (Raine & Benishay, 1995), but reported MI using only a single-group convenience sample taken from the general community (Fonseca-Pedrero et al., 2011; Ortuño-Sierra et al., 2013) without comparisons to a clinical sample of individuals with schizophrenia. While these studies are important in understanding the properties of specific clinical tools, they do not address the broader question that clinical and nonclinical participants respond to subjective self-report items on established personality measures in the same way. Our study,

however, provided psychometric evidence for the first time that stable outpatients with schizophrenia were responding to the CBSHY and CBSOC scales in a similar way to control participants. In turn, this provided empirical assurance that meaningful and unbiased mean comparisons were being made between our clinical and nonclinical samples.

Limitations

While we have shown that the CBSHY and CBSOC are invariant across our population of participants with schizophrenia and healthy controls, we recognize several limitations to our study. First, limited sample size is often an issue in clinical research and one that affected our study. Despite our relatively large pool of participants overall, measurement models as studied through CFAs require large sample sizes (Kline, 2011). This could be of particular concern in clinical research in which sample sizes are typically small. In relation to our study, a larger sample size would have provided us more power for our analyses to examine other factors. For instance, we were not able to examine MI in the CBSHY or CBSOC across our two status groups by sex, which has important implications for future clinical research trying to research unbiased sex effects across status groups. In addition, with larger sample sizes, we could have used age bins in order to better establish MI across various developmental stages. Second, although this study was a first crucial step for the clinical field, this research only assessed the MI of two questionnaires, the CBSHY and CBSOC. In fact, future studies ought to examine the MI of other well-established clinical questionnaires that have been frequently used to examine group differences between schizophrenia and healthy populations, such as social cognition and social anxiety, to verify that mean level differences are actually meaningful and not due to measurement error. Third, we did not use the full 13-item Cheek and Buss Shyness Scale (Cheek, 1983; Cheek & Buss, 1981), but used only the 5-highest loaded shyness items of the

Cheek and Buss Shyness Scale reported in (Bruch et al., 1989). Although the 5-item shyness scale has been used in many studies over the years in nonclinical studies (Brook & Schmidt, 2019) and clinical studies involving stable outpatients with schizophrenia (Goldberg & Schmidt, 2001; Jetha et al., 2013), caution should be exercised as to whether the present findings would be replicated when using the full 13-item shyness scale. Last, in order to be confident of the generalizability of these results within the schizophrenia field more broadly, further research could examine whether there are group differences between first episode psychosis patients, chronic stable patients with schizophrenia (our sample), and more acutely ill inpatients with schizophrenia, as those populations may not respond to the measures in the same way.

Conclusion

To our knowledge, this is the first study to evaluate the properties of MI of personality measures in schizophrenia compared with community controls. Indeed, MI is considered a critical prerequisite before meaningful mean comparisons can be made between groups across the same underlying construct; true differences may be obscured by measurement error across different ages, samples, contexts and time. Yet, while much of the clinical research on schizophrenia depends on mean comparisons between clinical and nonclinical samples to further the understanding of the development and prognosis of this complex and chronic mental health condition, MI has not been at the foundation of this important work. To ensure that the construct of interest has substantive meaning across populations, MI testing should be included alongside traditional tests of reliability and validity.

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Table 1. Items of the Shyness and Sociability Scales

	Items	
Shyness	CBSHY 1	I find it hard to talk to strangers
	CBSHY 2	When I'm in a group of people, I have trouble thinking of the right things to talk about
	CBSHY 3	I feel nervous when speaking to someone in authority
	CBSHY 4	I feel inhibited in social situations
	CBSHY 5	It takes me a long time to overcome shyness in new situations
Sociability	CBSOC 1	I like to be with people
	CBSOC 2	I welcome the opportunity to mix socially with people
	CBSOC 3	I prefer working with others rather than alone
	CBSOC 4	I find people more stimulating than anything else
	CBSOC 5	I'd be unhappy if I were prevented from making many social contacts

Note. CBSHY is the Cheek and Buss Shyness Scale and CBSOC is the Cheek and Buss Sociability Scale.

Table 2. Descriptives for the Shyness and Sociability Scale Items by Status ($n_{control}$= 147, $n_{schizophrenia}$ =147)

		Control				Schizophrenia			
	Item	*M*	*SD*	Skew	Kurtosis	*M*	*SD*	Skew	Kurtosis
Shyness	CBSHY 1	1.150	1.139	.754	-0.291	1.490	1.295	0.313	-1.063
	CBSHY 2	1.340	1.059	.560	-0.190	1.612	1.285	0.385	-0.845
	CBSHY 3	1.435	1.063	.220	-0.933	1.585	1.266	0.311	-0.874
	CBSHY 4	1.340	1.085	.350	-0.924	1.524	1.168	0.454	-0.545
	CBSHY 5	1.197	1.079	.469	-0.342	1.592	1.271	0.221	-1.130
Sociability	CBSOC 1	3.027	0.910	-.648	-0.177	2.327	1.273	-0.351	-0.891
	CBSOC 2	2.796	1.094	-.650	-0.321	2.224	1.287	-0.251	-1.049
	CBSOC 3	2.306	1.098	-.133	-0.632	1.986	1.277	-0.092	-0.983
	CBSOC4	2.333	1.090	-.216	-0.709	1.946	1.282	0.102	-0.993
	CBSOC 5	2.689	1.239	-.700	-0.525	2.054	1.446	-0.135	-1.335

Note. Items were measured on a 5-point Likert Scale from 1 = "Not at all" to 5 = "Extremely". Higher scores indicated more shyness or sociability. CBSHY is the Cheek and Buss Shyness Scale and CBSOC is the Cheek and Buss Sociability Scale.

Table 3. Correlations Among the Shyness and Sociability Scale Items by Status ($n_{control}$= 147, $n_{schizophrenia}$ =147)

		1	2	3	4	5	1	2	3	4	5
Shyness	CBSHY 1	-	.493	.598	.542	.607					
	CBSHY 2	.555	-	.454	.710	693					
	CBSHY 3	.464	.453	-	.544	.583					
	CBSHY 4	.559	.543	.630	-	.686					
	CBSHY 5	.592	.565	.508	.671	-					
Sociability	CBSOC 1						-	**.757**	.495	.594	.502
	CBSOC 2						**.773**	-	.516	.645	.555
	CBSOC 3						.571	.573	-	.608	.436
	CBSOC 4						.528	.651	.539	-	.551
	CBSOC 5						.319	.406	.402	.497	-

Note. The correlations for the control and schizophrenia groups are above and below the diagonal, respectively. Shyness and sociability items are numbered between CBSHY 1 to 5 and CBSOC 1 to 5, sequentially. Correlation between items 6 and 7 is bolded to indicate that the magnitude of the overlap is large as compared to the other more moderate correlations. CBSHY is the Cheek and Buss Shyness Scale and CBSOC is the Cheek and Buss Sociability Scale

Table 4. CFA Fit Statistics for the Shyness and Sociability Models by Status ($n_{control}$= 147, $n_{schizophrenia}$ =147)

	Status	χ^2	*df*	*p*	RMSEA [90% CI]	*p*	CFI	SRMR
Shyness	Control	13.325	5	.021	.106 [.038, .178]	> .05	.966	.039
	Control[a]	4.323	4	> .05	.024 [.000, .129]	> .05	.999	.022
	Schizo	6.188	5	> .05	.040 [.000, .127]	> .05	.993	.025
Sociability	Control	16.780	5	.005	.127 [.063, .196]	.027	.958	.035
	Control[b]	2.442	4	> .05	.000 [.063, .099]	> .05	1.000	.014
	Schizo	17.382	5	.005	130 [.067, .119]	> .05	.932	.048
	Schizo[c]	8.163	4	> .05	.084 [.000, .167]	> .05	.997	.029

Note. χ^2 = chi-square, df = degrees of freedom; RMSEA = root mean square error of approximation;
CI = 90% confidence intervals for the RMSEA; CFI = comparative fit index; SRMR = standardized root
mean square residual.
[a]revised model with shyness item 2-item 4 correlated error.
[b,c]revised model with sociability item 1-item 2 correlated error.

Table 5. MGCFA Measurement Invariance for Shyness and Sociability Scales: Group Comparison Goodness-of-fit Indices by Status ($n_{control}$ = 147, $n_{schizophrenia}$ =147)

	Model	χ^2	*df*	*p*	RMSEA [90% CI]	*p*	CFI	SRMR	ΔRMSEA	ΔCFI	ΔSRMR
Shyness	Configural	10.513	9	> .05	.034 [.000, .102]	> .05	0.996	.024	-	-	-
	Metric	12.235	13	> .05	.000 [.000, .178]	> .05	1.000	.027	-	-	-
	Scaler	16.822	17	> .05	.000 [.000, .074]	> .05	1.000	.033	-	-	-
	Confi vs Metric	0.532	4	> .05	-	-	-		**.034**	.004	.003
	Metric vs Scaler	4.815	4	> .05	-	-	-		.000	.000	.006

Sociability	Configural	11.142	8	> .05	.052 [.000, .117]	> .05	0.993	.023	-	-	-
	Metric	12.839	12	> .05	.022 [.000, .088]	> .05	0.998	.038	-	-	-
	Scaler	28.019	16	.032	.071 [.021, .114]	> .05	0.973	.062	-	-	-
	Confi vs Metric	1.837	4	> .05	-	-	-		**.030**	.005	.015
	Metric vs Scaler	15.881	4	**.003**	-	-	-		**.049**	**.025**	**.024**

Note. MGCFA = multi-group confirmatory factor analysis for measurement invariance testing; χ^2 = chi-square, df = degrees of freedom; RMSEA = root mean square error of approximation; CI = 90% confidence intervals for the RMSEA; CFI = comparative fit index. Confi = configural; significant changes in model fit between nested models were **bolded**.

Table 6. Means, Standard Deviations and Bootstrap Corrected Reliability Coefficients with 95% Confidence Intervals of the Shyness and Sociability Scales: By Entire Sample (N = 294) and by Schizophrenia Status ($n_{control}$= 147, $n_{schizophrenia}$ =147).

		Mean (SD)	Alpha (CI)	Omega (CI)
Shyness	Entire Sample	1.427 (0.957)	.868 [.834, .894]	.868 [.836, .893]
	Control	1.293 (0.885)	.874 [.830, .904]	.875 [.830, .905]
	Schizophrenia	1.561 (1.006)	.859 [.814, .897]	.860 [.814, .896]
Sociability	Entire Sample	2.369 (0.991)	.860 [.826, .887]	.858 [.821, .885]
	Control	2.630 (0.876)	.862 [.819, .895]	.861 [.812, .895]
	Schizophrenia	2.107 (1.031)	.843 [.788, .886]	.842 [.782, .884]

Note. All comparisons for shyness and sociability status groups were significantly different at the 5% level.

Sociability Invariance Results in the Alignment Optimization Metric

Table S1

Approximate Measurement Invariance

(Noninvariance) for Intercepts

and Loadings Across Diagnosis Status

Item	Threshold	Loadings
CBSOC 1	1 2	1 2
CBSOC 2	1 2	1 2
CBSOC 3	1 2	1 2
CBSOC 4	1 2	1 2
CBSOC 5	1 2	1 2

Note. All sixteen parameters are invariant but if one or more were **noninvariant,** then there would be a ()s around the group number. Group 1 = control, Group 2 = schizophrenia.

Table S2

The Sociability Alignment Results: Fit Statistics in the Alignment Optimization Metric for Group Comparisons Across Diagnosis Status* ($N_{control}$= 147, $N_{schizophrenia}$ = 147).

Group Comparison	Parameter	Items	# Groups Invariant	R^2	Fit Function Contribution	Weighted Average Estimate
Schizophrenia Diagnosis (2 groups)	Threshold	CBSOC1	2	0.890	-0.600	2.459
		CBSOC2	2	1.000	-0.316	2.227
		CBSOC3	2	0.637	-0.500	1.891
		CBSOC4	2	0.699	-0.503	1.833
		CBSOC5	2	0.961	-0.371	2.093
	Loadings	CBSOC1	2	0.786	-0.411	0.724
		CBSOC2	2	0.971	-0.324	0.827
		CBSOC3	2	0.998	-0.317	0.554
		CBSOC4	2	0.855	-0.331	0.909
		CBSOC5	2	0.000	-0.457	0.747

Note. # Groups Invariant = number groups with measurement invariance for intercepts and/or loadings for each item – # noninvariant in bold; R^2 = variance explained in the factor/sociability mean for each measurement parameter across groups, higher values related to more variance explain on scale 0-1 scale; Fit Function = optimization function/process that minimizes the amount of measurement noninvariance based on pairwise group comparisons of thresholds/loading parameters, larger number indicates greater contribution to noninvariance; Weighted Average Estimate = the average threshold/loading for invariant items across the two groups. The FIXED alignment method was used in which the factor/shyness mean was fixed to 0 and factor variance was fixed to 1.

*The model for sociability scale used in the alignment method contained a correlated error between CBSOC item 1 and 2.

CHAPTER 3:

SHYNESS, EMOTION PROCESSING, AND OBJECTIVE QUALITY OF LIFE AMONG ADULTS WITH SCHIZOPHRENIA: AN ERP STUDY

Chapter link:

Khalesi, Z., Jetha, M. K., McNeely, H. E., Goldberg, J. O., & Schmidt, L. A. (2022). Shyness, emotion processing, and objective quality of life among adults with schizophrenia: An ERP study. *International Journal of Neuroscience*, 1-9, in press.

Shyness, Emotion Processing, and Objective Quality of Life among Adults with Schizophrenia: An ERP Study

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Abstract

Although individual differences in temperament have been shown to influence Quality of Life (QoL) among individuals with schizophrenia, there exists large heterogeneity in such outcomes suggesting moderating factors. Here we used event-related potential (ERP) methodology to examine whether the processing of facial emotions moderated the association between shyness and objective QoL among adults with schizophrenia. Forty stable outpatients with schizophrenia completed measures of shyness and QoL. Early visual ERP components (P1, N170) were recorded while participants viewed emotional faces. We observed a significant interaction between shyness and P1 and N170 amplitudes in response to fearful faces in predicting Intrapsychic Foundations QoL. Patients with reduced P1 and N170 amplitudes to fearful compared to neutral faces displayed the lowest QoL, but only if they were also high in shyness. We also found a significant interaction between shyness and ERP latency at the P1 and N170 in response to happy faces. Patients who displayed longer P1 and N170 latencies to happy faces compared to neutral faces and with higher shyness levels scored lower on Intrapsychic Foundations and Interpersonal Relations QoL, respectively. These findings suggest that the neural processing of emotional faces and shyness interact to predict aspects of QoL among outpatients with schizophrenia.

Key words: Schizophrenia; Shyness; Temperament; ERP; Emotion; Objective quality of life

Introduction

Schizophrenia is a debilitating neuropsychiatric disorder that can impact an individual's overall health, social and occupational functioning, social skills, cognition, and quality of life (QoL) (Frith & Corcoran, 1996; Jääskeläinen et al., 2012; Katschnig, 2000; Tolman & Kurtz, 2010). Although earlier outcome studies focused on treatment response and positive psychotic symptoms, recent work has focused on the QoL of patients with schizophrenia (Narvaez et al., 2008; Tolman & Kurtz, 2010; Yamauchi et al., 2008). Two facets of QoL have been identified: subjective and objective QoL. While subjective QoL refers to the individual's perceived life satisfaction and well-being, objective QoL focuses on the ability to perform activities and engage in relationships, is more indicative of overall functioning and participation in society, and is predictive of future relapse among adults with schizophrenia (Boyer et al., 2013). Given the importance of objective QoL in determining functional outcomes among individuals with schizophrenia, it is imperative to understand what factors may contribute to worsening QoL. Unlike subjective QoL which has been examined in relation to symptoms and external factors such as personality (Eklund et al., 2003; Hansson et al., 1999; Ritsner et al., 2003; Sevilla-Llewellyn-Jones et al., 2019), much of the literature on objective QoL has focused on how core symptoms of schizophrenia, such as neuropsychological functioning, and negative symptoms, influence objective QoL, and only a few studies have examined the relation between personality and objective QoL in this population (Goldberg & Schmidt, 2001; Sörgaard et al., 2001; Jetha et al., 2013a).

A personality trait that has been identified as a potential risk factor for psychopathology and has the potential to hinder QoL among healthy and psychiatric populations is shyness.

Shyness reflects a preoccupation with the self in social situations and/or in anticipation of those situations (Cheek & Melchior, 1990). A number of studies have shown that individuals with schizophrenia are more likely to report higher levels of shyness than healthy controls (Flanagan, 1992; Goldberg & Schmidt, 2001; Jetha et al., 2013a; Khalesi et al., 2021; Ritsner et al., 2003). This pattern is also seen with young adults at risk for schizophrenia, first episode psychosis patients, and in retrospective reports suggesting that these temperamental traits were present prodromal to the illness (Cuesta et al., 2002; Feola et al., 2019; Goldberg & Schmidt, 2001). Additionally, among adults with schizophrenia, higher shyness has been found to predict poorer subjective QoL, with estimates accounting for up to 16% of the variability (Ritsner et al., 2003; Ritsner et al., 2012). Research that has examined objective QoL in relation to shyness in adults with schizophrenia using the Quality of Life Scale (Heinrichs et al., 1984) has reported that patients with higher shyness demonstrate poorer functioning in the domains of *Interpersonal Relations* QoL (Goldberg & Schmidt, 2001; Jetha et al., 2013a) and to a lesser degree *IntraPsychic Foundations* QoL (a subscale which measures deficits in cognition, motivation and affect in relation to quality of life) (Jetha et al., 2013a). However, shyness was not found to predict activity levels in the community (*Instrumental Role*) or chores-like activities (*Objects and Activities*), which do not depend on abilities to form and maintain interpersonal relations. These findings suggest that shyness may influence outcomes in QoL that are more dependent on socio-emotional processing and affiliation.

Although increases in shyness have been associated with poor quality of life in schizophrenia, this relation is not a foregone conclusion. There is considerable heterogeneity in quality of life outcomes among people with schizophrenia suggesting possible moderating factors. For example, our group recently reported that salivary cortisol, a stress hormone,

moderated the relation between shyness and objective QoL in stable outpatients with schizophrenia (Khalesi et al., 2019), with reduced baseline cortisol and higher shyness predicting lower Intrapsychic Foundations QoL.

Another potential moderator that is more directly involved in socioemotional processing is the degree and nature of attentional processes that occur during the encoding of relevant social cues (e.g., Dodge, 1993). Importantly, studies using emotional faces (Beaton et al., 2009; Jetha et al., 2012), words (Helzer et al., 2009; Mauer & Borkenau, 2007), or complex emotional scenes (Pintzinger et al., 2017) have found that individual differences in temperament are related to the processing of emotional information in healthy adults, infants (Rajhans et al., 2015; Rennels et al., 2020) and children (Lonigan et al., 2004; Pérez-Edgar, & Fox, 2003).

Human faces are biologically relevant, conveying a variety of signals (e.g., emotion, identity, eye-gaze, intention) that are important for successful social interactions. Research strongly suggests that early aspects of face processing are automatic and occur prior to conscious awareness (Lamme & Roelfsema, 2000; Palermo & Rhodes, 2007; Whalen et al., 2004). The time course of the visual processing of emotional faces has been well-documented using event related potentials (ERPs), which are voltage fluctuations in the ongoing electroencephalogram (EEG) that are time-locked to an event, such as the onset of a stimulus (Sur & Sinha, 2009). The P1 and N170 are two well-studied ERP components that have been associated with the early perceptual processing of faces (see Rossion, 2014; Schindler & Bublatzky, 2020, for reviews). The P1 component is a positive peak (~100 ms post-stimulus onset) that is measured over posterior brain regions and is sourced to cortex involved in the early processing of visual input (extrastriatal cortex). The P1 has been shown to be sensitive to attention allocation as well as psychophysical properties of the stimulus (e.g., contrast and spatial frequency information)

(Nakashima et al., 2008). More fine-grained discrimination associated with structural encoding occurs after an additional 70 ms and is reflected in the N170, a negative peak that is measured over occipito-temporal regions (Bentin et al., 1996; Rossion & Jacques, 2011). The P1 and N170 components have been widely used to assess early and automatic stages of attentional processing (Gupta, Kujawa, & Vago, 2019). Among adults with schizophrenia, research has demonstrated lower ERP amplitude and longer response latencies at the P1 and N170 stage for faces, with a few studies showing deficits to specific emotional expressions (see Earls et al., 2015; McCleery et al., 2015; Murashko & Shmukler, 2019 for reviews). Deficits in these early components may suggest general impairments in perceptual processing (Johnston et al., 2006) or general reductions in visual attention to faces (Strauss et al., 2013). However, part of the variance in emotional face processing may also be due to individual differences in temperament.

Jetha and her colleagues have shown that healthy adults who scored high in shyness demonstrated reductions in the early electrocortical responses to emotional faces compared to neutral faces, such as the P1 response to fearful faces (Jetha et al., 2012). A similar pattern of reductions of electrocortical responses to emotional faces (angry, happy, and fearful faces) was also found in patients with schizophrenia who reported similar levels of shyness to controls. The reductions were interpreted to reflect the early and automatic suppression of attention to emotional faces, possibly conditioned avoidance strategies to stress-eliciting stimuli. In the same study, however, those patients who reported higher levels of shyness than controls (extreme shyness) showed enhanced electrocortical responses (hypervigilance) to emotional compared to neutral faces (Jetha et al., 2013b). These findings indicate that levels of shyness may influence the early perception of emotional faces in both healthy adults and patients with schizophrenia.

Given the recent interest in examining social cognition and external factors, such as personality, as related to community functioning (Vaskinn & Horan, 2020), we were interested in extending the findings reported by Jetha et al. (2013b) by re-examining whether the archival data which showed that the early processing of emotional faces interacted with shyness can also be shown to determine whether it predicts community adaptive functioning as measured by QoL in stable outpatients with schizophrenia. We examined the relations among individual differences in shyness, ERP responses to emotional faces, and objective QoL measures in stable outpatients with schizophrenia. Based on our previous research with this archival data set (Jetha et al., 2013b), we were interested in two facets of objective QoL that are known to be influenced by social and emotional processing: the intrapsychic foundations and interpersonal relations subscales.

We hypothesized that ERP responses would moderate the relation between shyness and QoL in stable outpatients with schizophrenia. Specifically, we predicted that individuals with schizophrenia who were high in shyness and exhibited reduced electrocortical responses to emotional faces would be at greatest risk for lower intrapsychic foundations, a subscale which is sensitive to motivation and emotion. We also predicted that individuals who were high in shyness and exhibited enhanced electrocortical responses (hypervigilance) to emotional faces would be more likely to avoid social interactions and at greatest risk for lower interpersonal relations.

Methods

Participants

Forty stable outpatients (28 males) with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder were included in the study. All patients attended the Hamilton Program for Schizophrenia (HPS, Hamilton, Ontario, Canada), a community-based treatment and rehabilitation program (Whelton et al., 1999). Diagnoses were determined by a psychiatrist upon entry to HPS and based on DSM-IV-TR criteria (American Psychiatric Association, 2000). Exclusion criteria included traumatic brain injury or concussions with loss of consciousness and neurological illness. All recruited participants were clinically stable at the time of testing, had been on a stable dose of antipsychotic medication for at least 1 month, and had normal or corrected-to-normal vision. Participants were primarily White (93%) and ranged in age from 27 to 56 years (M = 42 years, SD = 6.4 years). The characteristics of the sample can be found in Table 1.

Procedure

Upon arrival, participants were introduced to the laboratory, and given a chance to acclimate before any procedures commenced. Informed consent was obtained from all participants. Participants were then asked to complete questionnaires pertaining to temperament (Cheek & Buss, 1981). They also participated in a semi-structured interview to assess QoL (Heinrichs et al., 1984). Next, participants completed a passive emotion viewing task while electrocortical measures were collected. A trained clinician was present during all testing, and all procedures were approved by the McMaster Health Sciences Research Ethics Board.

Self-report and Clinical Interview Measures

Shyness. Shyness was self-reported using the five highest loaded items on the Cheek and Buss Shyness Scale (1981), for example, “I feel inhibited in social situations”. (See Bruch et al., 1989; Jetha et al., 2013b and Khalesi et al., 2021, for justification of the 5-items for this patient

population from the original Cheek and Buss (1981) Shyness Scale). Shyness scores ranged from 0 to 20, with higher scores reflecting more shyness. This measure demonstrated good internal reliability in our sample (Cronbach's alpha = 0.86).

Quality of Life. Quality of life was measured by a trained psychometrist using the Quality of Life Scale (Heinrichs et al., 1984). This instrument is a semi-structured interview consisting of 21-items providing information on functioning during the preceding four weeks. All items are based on a seven-point scale, with highest scores reflecting unimpaired functioning (Heinrichs et al., 1984). We were interested the *Intrapsychic Foundations* and *Interpersonal Relations* subscales due to their assessment of deficits in schizophrenia and social relationships, respectively. The *Intrapsychic Foundations* is a 7-item scale which examines deficits associated with negative symptoms, such as deficits in cognition, motivation, and affect in relation to QoL. A sample item from this subscale included "How have you been going about accomplishing your goals?". The *Interpersonal Relations* subscale contains 8-items relating to social experiences and aspects of avoidance and withdrawal tendencies. A sample item from this subscale included "Do you have friends with whom you are especially close other than your immediate family?". The interclass correlations for the subscales were as follows: Intrapsychic Foundations=.91 and Interpersonal Relations=.94.

Passive Emotion Viewing Task

As this is a re-examination of archival data, the details for this task has been described previously (see Jetha et al., 2013b). The participant was asked to view a series of emotional faces on a computer screen as they were presented individually and in a randomized order. The affective stimuli comprised grey-scaled Ekman faces (Ekman & Friesen, 1976) that varied in emotional expression (i.e., fear, happy, angry and neutral) and were chosen according to

reliability data (Ekman & Friesen, 1976). The stimuli were 20 x 13 cm in size and were presented on a computer monitor at a distance of 1 meter using E-Prime software (Psychological Software Tools, Pittsburgh, PA). The vertical length of the stimuli subtended 1.15 degrees and the horizontal length of the stimuli subtended .74 degrees at the 1 meter viewing distance. Trials comprised a fixation point presented for 500 ms, and then a 200 ms interval in which the screen was blank followed by target stimulus that was presented for 1000 ms. Inter-trial intervals were randomized and ranged from 1200 to1750 ms. Two blocks were presented, with each comprising 96 stimuli which were randomized and counterbalanced with no repetitions. Stimuli comprised 12 models (6 males and 6 females) expressing each of four conditions (fear, happy, angry, and neutral). Each condition was presented 48 times across the two blocks. Participants were monitored from a separate room by a closed-circuit video camera to ensure that they were attending to the computer screen during the task.

EEG Procedures, Reduction, and Measures

As this is a re-examination of archival data, the details for this task has been described previously (see Jetha et al., 2013b). Electroencephalogram (EEG) was recorded using the 128-channel Geodesic Sensor Net (Electrical Geodesics, Inc.) while participants completed the task. Data were analog filtered 0.1 to 100 Hz, digitized at 250 samples per second, and referenced to the vertex (Cz). Sensor impedances were kept below 50 k. EEG data were digitally filtered offline using a bandpass of 1 to 20 Hz, re-referenced to the common average of all scalp electrodes, segmented from 200 ms before to 1000 ms after stimulus onset, and baseline corrected using the 200 ms baseline prior to stimulus onset. Vertical and horizontal electrooculogram (EOG) activity were corrected (Gratton, Coles, & Donchin, 1983), and epochs with EEG greater than ±75 uV on any channel were excluded from further analysis. Artifact-free

trials were then averaged separately for each emotion type. For patients, the mean and standard deviation for the artifact-free trials by condition were M = 36.6, SD = 7.7 for the angry faces, M = 36.1, SD = 7.5 for happy faces, M = 37.4, SD = 7.8 for fearful faces, and M = 36.3, SD = 7.6 for neutral faces.

P1 was measured over left and right occipital regions and was scored as the largest of the positive deflections with latency between 80 and 130 ms post-stimulus at 7 sites in the regions of O1 (left) and O2 (right). See Figures 1 and 2 (adapted from Jetha, et al., 2013b) for topographies and waveforms, respectively.

N170 was measured over left and right lateral occipital–temporal regions and was scored as the largest of the negative deflections at 7 sites near PO7 (left) and PO8 (right) with latency between 130 and 200 ms post-stimulus. All waveforms had clear peaks within these ranges. See Figure 1 for topographies (adapted from Jetha, et al., 2013b) and Figure 2 for waveforms.

Component amplitude was scored blind to the temperament scores of the participants. The strategy of using the maximal score over a range of sites in the region of interest was adopted to account for variance due to individual differences in brain morphology of the P1 and N170 generators.

Difference scores were created for ERP amplitude and latency for each emotion condition (angry, happy, fear) minus the neutral condition and for each hemisphere (left/right) to examine emotion effects on the P1 and N170 components. Based on these calculations, higher amplitude scores reflect increased electrocortical activity for the emotion compared to the neutral condition, and higher latency scores reflect slower processing (longer time to reach peak amplitude) for the emotion compared to the neutral condition. These difference scores were used as predictor variables for the regression analyses.

Covariates

We adjusted for sex, age of schizophrenia onset, and positive and negative symptoms in our statistical analysis given their potential influence on QoL (Browne et al., 1996; Lehman et al., 1995) and ERP responses (Brennan et al., 2014; Pintzinger et al., 2017). Participant sex and age of onset were extracted from their medical chart, and symptoms were assessed using the *Positive and Negative Syndrome Scale* (PANSS; Kay et al., 1987). The PANSS was rated by a trained psychometrist and was conducted within 6 months of participation in the present study.

Data Analysis

To examine the moderating effects of ERP responses on the relation between shyness and QoL, we used separate multiple linear regressions with shyness, P1 and N170 components as the independent measures and *Intrapsychic Foundations* and *Interpersonal Relations* subscales as the dependent measures. We performed separate analyses for P1 and N170 difference scores for left and right hemispheres for amplitude and latency for each emotion (fear, angry, happy). In the first step, we entered our covariates (i.e., sex, age of onset, positive symptoms, negative symptoms) to allow these variables to account for as much variability as possible before entering the other predictors. On the second step, we entered shyness scores and ERP difference scores. Finally, on the third step we entered the interaction term between shyness and ERP difference scores.

All statistical analyses were performed using SPSS Version 21.0, with statistical significance levels set at $\alpha = 0.05$.

Results

Descriptive Statistics

Table 1 presents patient descriptive statistics.

Shyness, Processing of Emotional Faces, and Quality of Life

P1 amplitude (See Table 2, Model 1). In the first step, for the left hemisphere, we found that higher levels of positive symptoms were associated with decreases in scores on Intrapsychic Foundations (β = -.48; p = .01). On the second step, we found that higher shyness scores were associated with decreases in scores on Intrapsychic Foundations (β = -.53; p =.01). In step 3, we found a significant interaction between shyness and the processing of fear faces on the left hemisphere in predicting scores on Intrapsychic Foundations (β = -.31; p =.01). As illustrated in Figure 3a, individuals who scored relatively higher on shyness and displayed relatively lower P1 amplitude to fearful faces had relatively lower intrapsychic QoL scores.

There were no significant interactions for other emotions in the left hemisphere. There were no significant interactions with P1 amplitudes in the right hemisphere (all p's > 0.05).

N170 amplitude (See Table 2, Model 2). In the first step, for the left hemisphere, we found that higher levels of positive symptoms were associated with decreases in scores on Intrapsychic Foundations (β = -.48; p = .04). On the second step, we found that higher shyness scores were associated with decreases in scores on Intrapsychic Foundations (β = -.57; p =.01). In step 3, we found a significant interaction between shyness and the processing of fear faces in predicting scores on Intrapsychic Foundations (β = -.22; p =.01). As illustrated in Figure 3b, individuals who scored relatively higher on shyness and displayed relatively lower N170 amplitude to fearful faces had relatively lower intrapsychic QoL scores.

There were no significant interactions for other emotions in the left hemisphere. The were no significant interactions with N170 amplitudes in the right hemisphere (all p's > 0.05).

P1 latency (See Table 2, Model 3). In the first step, in the right hemisphere, we found that higher levels of positive symptoms were associated with decreases in scores on Intrapsychic Foundations QoL (β = -.48; p = .04). On the second step, we found that higher shyness scores were associated with decreases in scores on Intrapsychic Foundations (β = -.51; p =.01). In step 3, we found a significant interaction between shyness and the processing of happy faces in predicting the Intrapsychic Foundations scores (β = -.06; p =.04). As illustrated in Figure 3c, individuals who scored relatively higher on shyness and exhibited a longer latency to processing happy faces had relatively lower Intrapsychic Foundations QoL scores.

There were no significant interactions for other emotions in the left hemisphere. There were no significant interactions with P1 latencies in the right hemisphere (all p's > 0.05).

N170 latency (See Table 2, Model 4). In the first step, we found that higher levels of negative symptoms were associated with decreases in scores on interpersonal relations (β = -1.2; p < .01). On the second step, we found that higher shyness scores were associated with decreases in scores on interpersonal relations (β = -.90; p < .01). In step 3, we found a trend for an interaction between shyness and the processing to happy faces (β = .04; p =.07). As illustrated in Figure 3d, individuals who scored relatively lower on shyness and exhibited a longer latency to processing happy faces had relatively higher Interpersonal Relations QoL scores.

There were no significant interactions for other emotions in the left hemisphere. There were no significant interactions with N170 latencies in the right hemisphere (all p's > 0.05).

Discussion

The present study is the first known study to examine the interaction of temperamental shyness and neurophysiological processes underlying emotional face processing on QoL in

stable outpatients with schizophrenia and has implications for understanding the variability in functional outcome for patients who experience shyness. Our findings suggest that those patients who are high on shyness and demonstrate hyposensitivity in the early processing of emotional faces (i.e., reduced attention and slower processing at the P1 and N170 stage for emotional faces) are at higher risk for deficits in cognitive, affective, and motivational domains in relation to QoL. Although the findings were not robust for interpersonal relations at the P1 stage of processing, we found that the duration of time to process emotional faces at the N170 stage may play a role in interpersonal functioning, particularly for happy faces.

As hypothesized, we observed a statistically significant interaction between shyness and emotional face processing at both the P1 and N170 components in predicting intrapsychic foundations QoL, however, these relations were specific to the emotion of fear. Those individuals who demonstrated reduced attention for fearful faces (as evidenced by lower P1 and N170 amplitudes to fearful compared to neutral faces) and relatively higher levels of shyness displayed the lowest scores in intrapsychic foundations QoL. Those individuals who demonstrated higher amplitudes at the P1 and N170 (enhanced attention/emotion processing of fearful compared to neutral faces) showed similar levels of QoL across shyness levels.

The findings for component amplitude were specific to intrapsychic foundations QoL. The items on this subscale are potentially more sensitive to reduced levels of attention to emotional faces due to the subscale's specificity to emotional functions, including empathy, anhedonia, motivation, and emotional interaction (Heinrichs et al., 1984). We did not find similar predictions for interpersonal relations. While reductions in attention to emotion may hinder aspects of QoL that depend on emotional response, they may serve adaptive functions during social interactions. If we consider reductions in attention in the context of automatic and

conditioned avoidance strategies as proposed by Jetha et al., 2012, patients who automatically reduce attention to stress-eliciting stimuli (e.g., emotional faces) may subsequently experience lower arousal during social interactions, i.e., reductions in attention may feed forward to suppress later stages of emotion processing (Cisler & Koster, 2010; Gupta et al., 2019). Unfortunately, the suppression of attention to fearful faces (or ambiguous faces that are misinterpreted) may also serve to limit the amount of relevant social cues that are processed during social interactions.

Interestingly, hypersensitivity/hypervigilance to emotional faces, which was reported for patients with extreme shyness in Jetha and colleagues (2013b), did not interact with shyness to predict interpersonal relations QoL. It is possible that the impairments in social functioning due to fear and anxiety in social situations that would be most impacted by variance in hypervigilance to emotional stimuli have been largely accounted for by the shyness measure on the second step of the regression, which is particularly strong for interpersonal relations. Further information from the interaction of shyness and variance in attention to emotional faces does not appear to provide predictive value for QoL above and beyond the shyness measure.

The findings for amplitude were also specific to fearful expressions. The amplitudes of early face processing components have been shown to be more consistently modulated by fear and anger than by positive emotions (Schindler & Bublatzky, 2020). However, as discussed in Jetha and colleagues (2012), fear and anger differ in terms of information conveyed. Fearful expressions indicate indirect threat and danger from the environment, however, the source of the threat is ambiguous and uncertain, whereas angry expressions convey direct threat and hostility. Research suggests that these threat-related emotions may be processed differently with angry expressions holding/engaging attention and fearful expressions guiding attention (Fox et al.,

2007). Anger and fear have also been differentially associated with approach- and avoidance-related motivational systems, respectively. Shyness as a personality construct is thought to be subserved by avoidance-related motivation, which may also influence differential sensitivities to fearful and angry expressions.

When examining component latencies, we found that individual differences in ERPs to the processing of happy faces interacted with shyness to predict both intrapsychic foundations and interpersonal relations QoL. Importantly, the amplitude and latency of ERP components offer different information with respect to face processing. Component amplitude reflects the consistency of neuronal firing and the magnitude of the neural source activity (i.e., the strength of the signal). The latency of the component reflects the millisecond-level timing (i.e., when the neuronal firing reaches its peak).

Individuals who processed happy faces faster (i.e., shorter P1 latencies) had similar intrapsychic foundations QoL levels regardless of their shyness scores; conversely, those were slower to attend to happy faces (longer P1 latencies) and who scored relatively higher on shyness had relatively lower intrapsychic foundations QoL scores. When examining the N170 component, those who processed happy faces faster reported the highest QoL regardless of their shyness scores, while those who processed faces more slowly (i.e., longer N170 response latency) and who reported relatively higher shyness had relatively lower interpersonal relations QoL scores. The findings could be interpreted to mean that individuals who are faster to attend to positive or happy faces may be able to extract non-verbal social cues more readily and as such may not find social situations as anxiety-provoking or threatening. Conversely, those individuals who are shy and are also slower to discriminate and code for positive social cues, this

combination leads them to further withdraw from social interactions contributing to a relatively lower QoL.

The present findings re-examine and extend the work of Jetha and colleagues (2013b) who first reported relations among shyness levels and the processing of facial emotions in stable outpatients with schizophrenia. To our knowledge, the present study is the first to examine the interaction between shyness and emotional face processing to predict QoL in individuals with schizophrenia. Recent work from our laboratory has also demonstrated that endocrine variables such as salivary cortisol levels (i.e., a measure of stress reactivity) moderated the relation between temperamental shyness and QoL in stable out patients with schizophrenia (Khalesi et al., 2019). The findings from the present study extend this work to measures of central brain activity by demonstrating that early visual processing of emotions as indexed by ERP's can also modulate the relation between temperamental shyness and QoL in stable outpatients with schizophrenia.

Limitations

There were several limitations of the present study that warrant discussion. First, although our sample size was relatively large for a clinical study employing psychophysiological measures, the sample size could have hindered our ability to detect some relations due to being statistically underpowered. Secondly, our participants were not drug naïve, and all were on antipsychotics; this is important as antipsychotics can have side effects relating to altered cognition and potentially blunted affect (Keefe et al., 1999; Kirkpatrick, 2014), both of which could impact our outcome measures. Future studies can account for the antipsychotic medication using medication equivalencies or use drug naïve participants. Third, due to the correlational nature of the study, causation cannot be inferred so results about directionality must be

interpreted with caution. Future studies that incorporate the study measures during the prodromal stages may further our understanding of the development and maintenance of temperament-based affective processing and its potential influence on QoL.

Conclusion and Implications

QoL is often negatively impacted among individuals with schizophrenia (Ho et al., 2000), though not everyone with schizophrenia has a poor QoL, suggesting individual difference factors may contribute to this effect. Here we found that individual differences in shyness and neurophysiological correlates of emotional face processing were associated with differential QoL patterns in the intrapsychic foundations and interpersonal relations domains. These findings are of special clinical relevance since motivation and social relations are key remediation targets for this patient population in a clinical setting. By understanding which facets of personality and emotional processing differentially predict these two facets of QoL, we may be able to identify the mechanisms underlying some aspects of quality of life that can be targeted for intervention, among patients who are at risk for poor outcomes, focusing on improving attention to emotional faces and aspects of personality. For example, Sachs and colleagues (2012) demonstrated that training on affect recognition increased QoL in social relations for patients. Future work should further explore these types of training paradigms in conjunction with examining personality and emotional processing in order to improve the quality of life of people with schizophrenia.

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Figure 1. The topographic map illustrates the average positive and negative activity for the P100 and N170 occurring for all participants across the scalp. Adapted from Jetha et al. (2013b).

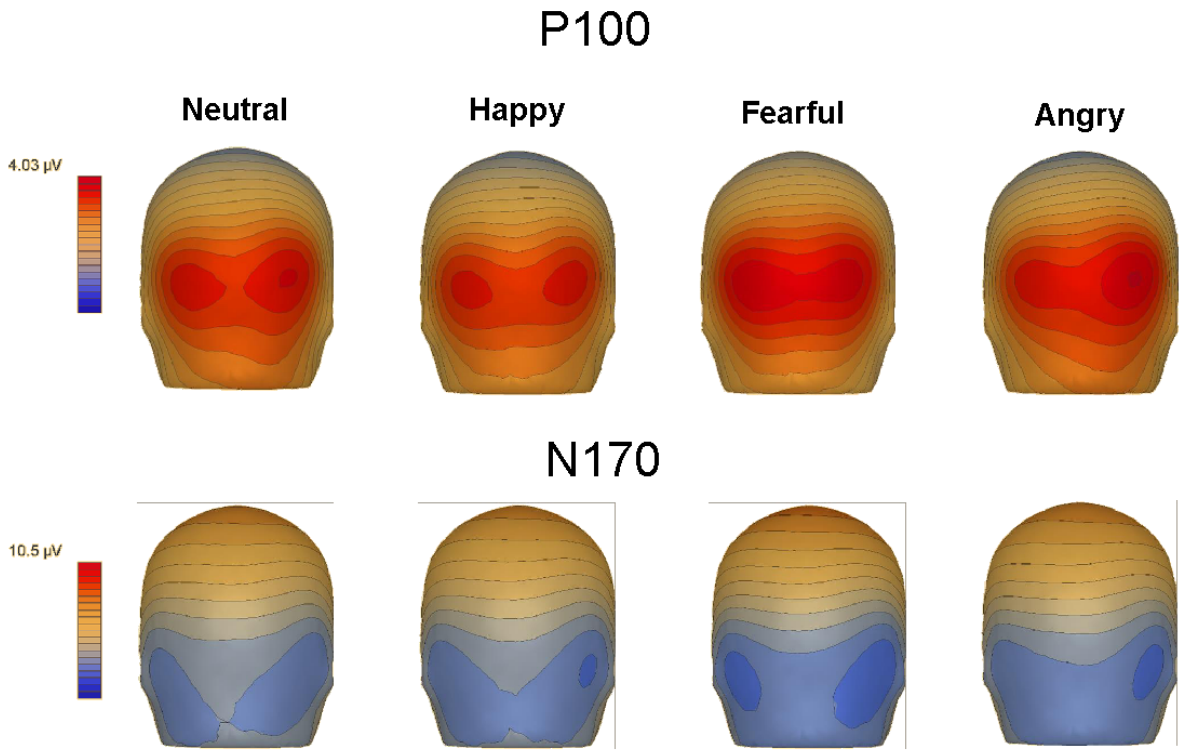


Figure 2. P100 and N170 wave form components at left and right electrode sites for emotional faces. Adapted from Jetha et al. (2013b).

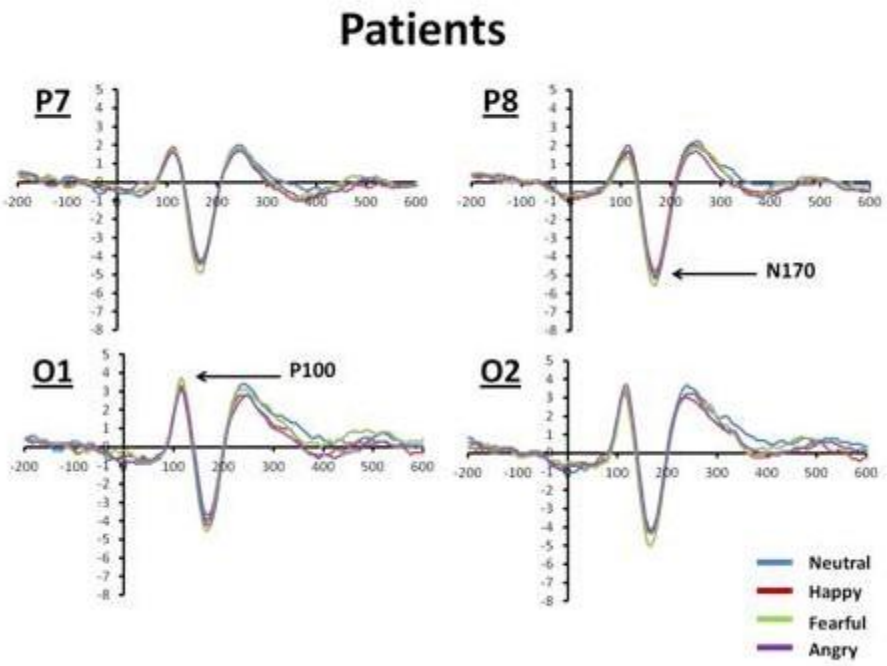
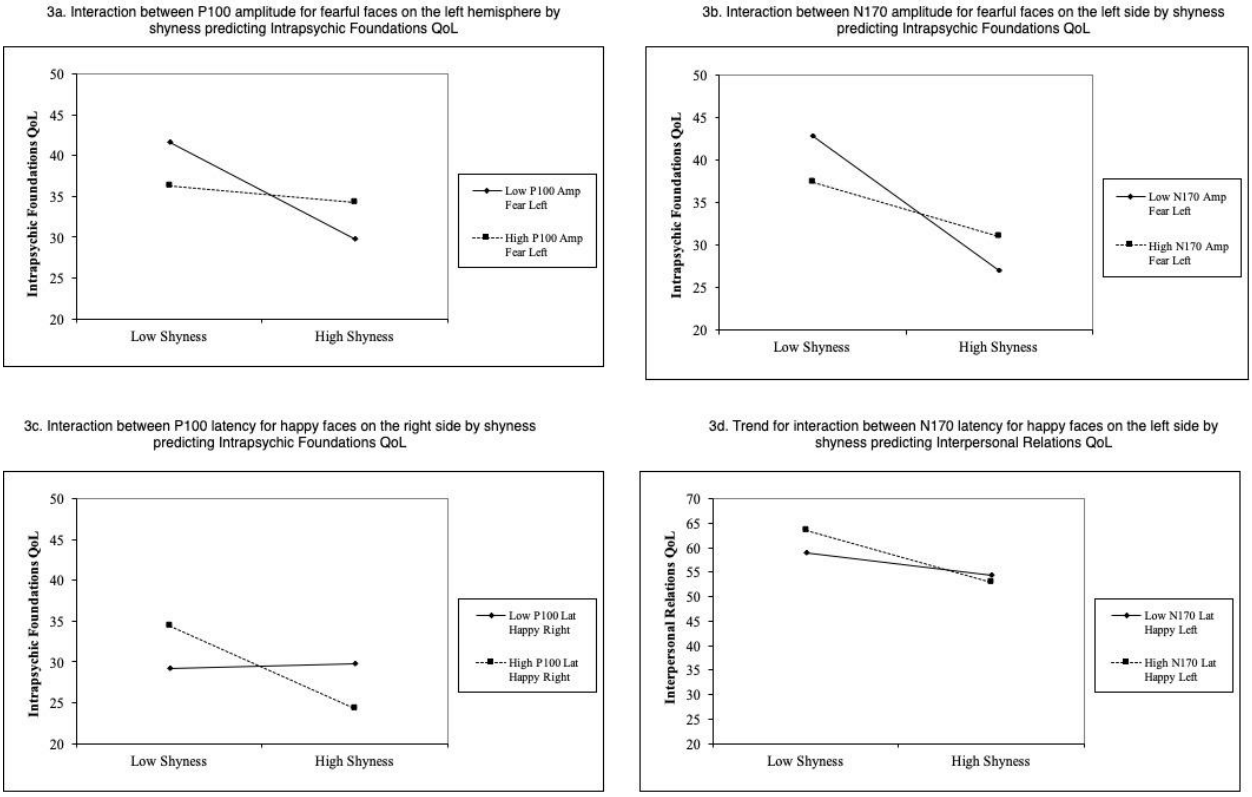


Figure 3. Interaction between shyness and ERP responses to emotional faces in predicting intrapsychic foundations and interpersonal relations quality of life in schizophrenia patients.



Note: Lat – Latency; Amp – Amplitude; plotted data are included for 1 SD above and below the mean of shyness.

Table 1. Sample characteristics

Characteristics	Participants ($N = 40$)
Sex	
Male	28
Female	12
Participant Age	
Mean, SD	42.1 (6.4)
Ethnicity	
Caucasian	37
Black or African American	1
Asian	2
Age of onset	
Mean, S.D.	19.6 (4.5)
Symptoms	
Positive	12.6 (4.4)
Negative	12.3 (3.7)
Measures	
Shyness	10.0 (4.8)
Interpersonal Relations QoL	25.9 (9.3)
Intrapsychic Foundations QoL	26.7 (6.3)

SD – standard deviation; age in years

Table 2. Summary of regression models for shyness and P100 models in predicting (A) intrapsychic foundations and (B) interpersonal relations.

Predictors	(A) Intrapsychic Foundations					(B) Interpersonal Relations				
	Zero-order r	Beta	S.E.	R^2	ΔR^2	Zero-order r	Beta	S.E.	R^2	ΔR^2
Model 1										
Step1				.31**	.31**				.51***	.51*
Sex	-.15	-1.5	2.0			-.29	-4.7*	2.5		
Age of Onset	-.05	.06	.15			-.38	-.33*	.19		
Positive Symptoms	-.46	-.48**	.23			-.33	-.29	.28		
Negative Symptoms	-.45	-.54*	.29			-.65	-1.2***	-.36		
Step 2				.46***	.15***				.69***	.18*
Shyness	-.42	-.53***	.17			-.55	-.86***	.19		
P100 Amp Left Fear	.00	-.05	.50			.02	-.05	.55		
Step 3				.54**	.08**				.70	.02
Shyness x P100 Amp Left Fear	.04	-.31***	.13			-.07	.07	.15		
Model 2										
Step1				.31**	.31**				.51***	.51*
Sex	-.15	-1.5	2.0			-.29	-4.7*	2.5		
Age of Onset	-.05	.06	.15			-.38	-.33*	.18		

	Positive Symptoms	-.46	-.48**	.23			-.32	-.29	.28		
	Negative Symptoms	-.45	-.54*	.29			-.65	-1.2***	.36		
Step 2					.48***	.17***				.70***	.19*
	Shyness	-.42	-.57***	.18			-.55	-.90***	.20		
	N170 Amp Left Fear	.07	.52	.45			.09	.53	.50		
Step 3					.63***	.15***				.72	.02
	Shyness x N170 Amp Left Fear	-.47	-.22***	.06			.18	-.11	.11		
					Model 3						
Step1					.31**	.31**				.51***	.51*
	Sex	-.15	-1.5	2.0			-.29	-4.7*	2.5		
	Age of Onset	-.05	.06	.15			-.38	-.33*	.19		
	Positive Symptoms	-.46	-.48**	.23			-.33	-.29	.28		
	Negative Symptoms	-.45	-.54*	.29			-.65	-1.2***	.36		
Step 2					.48**	.17**				.69***	.18*
	Shyness	-.42	-.51***	.17			-.55	-.86***	.20		
	P100 Lat Right Happy	-.13	-.10	.09			.00	-.01	.10		
Step 3					.54***	.07***				.72	.01

	Shyness x P100 Lat Right Happy	-.13	-.06**	.03			.02	-.03	.03	
						Model 4				
Step1					.31	.31			.51***	.51*
	Sex	-.15	-1.5	2.0			-.29	-4.7*	2.5	
	Age of Onset	-.05	.06	.15			-.38	-.33*	.19	
	Positive Symptoms	-.46	-.48**	.23			-.33	-.29	.14	
	Negative Symptoms	-.45	-.54*	.29			-.65	-1.2***	.34	
Step 2					.46***	.15***			.69***	.18*
	Shyness	-.42	-.57***	.19			-.55	-.89***	.21	
	N170 Lat Left Happy	.07	-.06	.11			.17	-.05	.12	
Step 3					.49	.03			.72	.02
	Shyness x N170 Lat Left Happy	.17	.02	.02			.22	.04*	.02	

Note: S.E. – standard error; $N = 40$; Lat – Latency; Amp – Amplitude; ***$p < .01$, **$p < .05$, *$p<.10$

CHAPTER 4:

SHYNESS, HORMONES, AND QUALITY OF LIFE AMONG ADULTS WITH SCHIZOPHRENIA

Chapter link: Khalesi, Z., Jetha, M. K., Poole, K. L., Goldberg, J. O., Van Lieshout, R. J., & Schmidt, L. A. (2019). Shyness, hormones, and quality of life among adults with schizophrenia. *International Journal of Neuroscience*, *129*(5), 470-480. https://doi.org/10.1080/00207454.2018.1543293

Shyness, Hormones, and Quality of Life Among Adults with Schizophrenia

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Abstract

Although individual differences in personality are known to influence quality of life in individuals with schizophrenia, relatively few studies have attempted to identify putative links underlying this relation. Here, we examined associations among temperamental shyness, hormones (i.e., baseline salivary cortisol and testosterone), and quality of life (QoL) measured in 42 stable outpatient adults with schizophrenia. We found that baseline cortisol, but not testosterone, moderated the relation between shyness and QoL ($\beta = 1.09$, $p = 0.004$). Among individuals with relatively low baseline cortisol, higher shyness was associated with lower Intrapsychic Foundations QoL. Individuals with relatively higher baseline cortisol reported similar QoL scores irrespective of level of shyness. These preliminary results suggest that relatively lower baseline cortisol may be helpful to understanding the relation between temperament and Intrapsychic Foundations QoL in schizophrenia. The present findings are consistent with previous studies implicating relatively lower baseline cortisol levels in nonclinical samples of people who are shy and the negative downstream effects resulting from HPA axis dysregulation and extends these prior findings to people with schizophrenia who are also shy.

Keywords: Temperament; Hormones; Quality of Life; Schizophrenia; Adults

Introduction

Schizophrenia is among the most debilitating mental illnesses and is associated with reduced cognitive function, positive symptoms such as hallucinations and delusions, and negative symptoms, including social withdrawal and anhedonia (Andreasen et al., 1995). Individuals with schizophrenia are also known to experience poorer quality of life (QoL) than those without (Ritsner, 2007; Ruhrmann et al., 2008). However, the degree to which QoL is affected in those with schizophrenia varies, suggesting that certain factors may moderate these relations. Indeed, several studies have examined psychosocial variables that could account for these variations (Eklund, Bäckström & Hansson, 2003; Suttajit & Pilakanta, 2015). For example, anxiety, depression, social support, level of functioning, impaired social interactions, and lack of motivation and core symptoms of schizophrenia such as negative symptoms, have been directly linked to decreased QoL (Chan & Yu, 2004; Corrigan & Buican, 1995; Hansson, 2006; Suttajit & Pilakanta, 2015; Sullivan, Wells & Leake, 1992). Individual characteristics such as temperament are also associated with QoL in both healthy individuals (Rubin, Burgess & Coplan, 2002) and those with schizophrenia (Ritsner, Farkas & Gibel, 2003).

Temperament is a characteristic way of thinking, feeling, and acting, and individual differences in temperament appear early in life and are presumed to be stable across time and context (Mathewson et al., 2017). Adults with schizophrenia who have a temperament characterized by withdrawal-related behaviors, such as shyness or harm avoidance, tend to experience poorer QoL than those who are more approach-related in their behaviors, e.g., relatively less shy or more sociable (Goldberg & Schmidt, 2001; Hansson, Eklund & Bengtsson-Tops, 2001; Jetha, Goldberg & Schmidt, 2012; Kurs, Farkas & Ritsner, 2005; Margetić et al., 2011; Muller et al., 2004; Ritsner, Farkas & Gibel, 2003; Smith et al., 2008). Eklund and

colleagues (2003) have also shown that personality characteristics such as relatively lower self-directedness, higher harm avoidance, and lower stress-regulation are significant predictors of several domains of impaired QoL, including social relations, health, leisure, and work and finances in adults with schizophrenia.

In addition to temperamental factors, it is also possible that neuroendocrine processes underlying approach-avoidance related behaviors may play a moderating role in the relation between temperament and QoL. Hormones, specifically cortisol and testosterone, have been linked to social interactions and social behaviors (Eisenegger, Haushofer & Fehr, 2011; Seeman et al., 2022). Cortisol is the primary signalling molecule of the HPA axis and a stress hormone that has been associated with aspects of temperament and psychopathology (e.g., anxiety-related disorders, schizophrenia) (Corcoran et al., 2003; Thompson et al., 2007). Relatively higher cortisol levels are commonly seen in psychopathology and individuals experiencing elevated levels of stress. Indeed, some samples of shy children and adolescents exhibit high levels of cortisol (e.g. Altamura, Boin & Maes, 1999; Schmidt & Schulkin, 1999; Thompson et al., 2007); however, other studies have also shown that relatively *lower* cortisol levels can be associated with stress and shyness in nonclinical samples (Badanes, Watamura & Hankin, 2011; Beaton et al., 2006; Beaton et al., 2013).

It has been hypothesized that relatively low baseline cortisol is preceded by excessive overactivation of the HPA axis occurring in response to high stress (and elevated cortisol). One study that illustrates this relation followed females between the ages of 6 and 16 with documented sexual abuse and matched controls. Initially, those who previously experienced trauma had higher cortisol levels than matched controls, however, when followed into adulthood, they showed relative lower baseline cortisol than control participants (Badanes, Watamura &

Hankin, 2011). Further support comes from studies that have demonstrated lower baseline cortisol levels in individuals with PTSD compared with healthy controls (Badanes, Watamura & Hankin, 2011; Morris, Compas & Garber, 2012) suggesting that repeated stressors could initially lead to higher levels of cortisol but ultimately result in cortisol downregulation. These findings raise the possibility that some temperaments that are more susceptible to stress and negative outcomes may be associated with cortisol dysregulation. Cortisol dysregulation appears to play a role in the degree to which an individual experiences negative outcomes such as stress or psychopathology.

In those with schizophrenia, evidence points to elevated levels of cortisol at baseline and blunted cortisol responses to stressors (Brenner et al., 2011; Ritsner et al., 2004; Thompson et al., 2007). In first episode psychosis patients, psychotropic medication, such as risperidone or olanzapine, have shown to dampen baseline plasma cortisol levels (Ryan et al., 2004; Serwinski, 2017; Tanaka et al., 2008). Further, there exists individual variation in baseline cortisol levels in adults, with some shy, healthy adults showing relatively lower baseline cortisol (Badanes et al., 2011; Beaton et al., 2006, 2013), and non-shy adults with schizophrenia showing higher baseline cortisol (Corcoran et al., 2003; Thompson et al., 2007). Cortisol dysregulation can be indicative of perceived stress and occurrence of psychopathology (Badanes et al., 2011; Beaton et al., 2006, 2013). These negative outcomes (shyness, stress, and psychopathology) are often associated with poorer perceived QoL, hence suggesting that cortisol dysregulation may also be related to poorer perceived QoL.

Cortisol also has been associated with life satisfaction among introverted individuals within a general population—those with relatively higher baseline cortisol and who are also introverted reported poorer well-being than those who are extraverted or social (Oishi et al.,

2012). Unfortunately, no study has examined whether cortisol plays a role in understanding the relation between individual differences in temperament and QoL in those with schizophrenia. One study reported that blunted cortisol response levels to a stressful task were associated with better QoL in adults with schizophrenia (Brenner et al., 2011; Corcoran et al., 2003; Tanaka et al., 2008). The few studies available support the notion that cortisol, baseline or reactive, influences aspects of QoL (Brenner et al., 2011; Tanaka et al., 2008), though more research is needed to determine the extent to which cortisol impacts QoL in schizophrenia and what role individual differences in temperament play.

Testosterone is another hormone that has been studied in relation to temperament (Määttänen et al., 2013) and schizophrenia (Goyal et al., 2004; Ko et al., 2007). In contrast to cortisol, which is viewed as a stress hormone, testosterone has an anxiolytic effect as shown in male rats (Frye & Seliga, 2001) and lowered fear responses in adult humans (Hermans et al., 2006; van Honk, Peper, & Schutter, 2005). Testosterone also has been associated with approach-related behaviors and social interactions, such as trust and decreased facial mimicry (see Eisenegger et al., 2011). Relatively higher levels of testosterone also have been linked to temperamental traits such as novelty seeking and reward dependence (Määttänen et al., 2013). Although novelty seeking and reward dependence are measures of sociability (Jetha, Goldberg & Schmidt, 2012), to our knowledge, no study has examined the relation between testosterone and shyness in healthy or in clinical populations. Moreover, testosterone is inversely correlated with negative symptoms of schizophrenia, which may contribute to or be reflective of social withdrawal (Goyal et al., 2004; Ko et al., 2007).

Although no significant associations have been reported between testosterone and QoL, individual difference factors such as novelty seeking behaviors and less shyness (i.e.,

characteristics that are indirectly related to testosterone) have been associated with better QoL in healthy individuals, as well as those with schizophrenia (Ritsner et al., 2003; Smith et al., 2008). It is, therefore, possible that the association between such personality traits and QoL might be partially due to testosterone levels.

To our knowledge, no study has examined relations among temperament, cortisol, testosterone, and QoL in adults with schizophrenia. The present study attempted to fill gaps in the existing literature by examining these associations in a sample of stable outpatient adults with schizophrenia. We were interested in examining baseline salivary cortisol and testosterone levels moderated the relation between temperamental shyness and specific subscales of the Quality of Life Instrument (Heinrichs, Hanlon & Carpenter, 1984) that measure aspects of current interpersonal relations and subjective assessments of motivation, goals, and sense of purpose that would indirectly be related to social engagement or withdrawal. Since previous research has found that relatively lower baseline cortisol or shyness has been linked with QoL (Badanes et al., 2011; Beaton et al., 2006, 2013), we predicted that adults with schizophrenia who were relatively higher on shyness and who also had relatively lower baseline cortisol would report the lowest QoL. Secondly, due to the inverse relation between negative symptoms (which, among other things, reflect hindered social interactions) and testosterone (Goyal et al., 2004; Ko et al., 2007), we predicted that relatively lower baseline testosterone and relatively higher shyness would predict the lowest QoL.

Method

Participants

Forty-two stable, outpatients (29 males) with a DSM-IV diagnosis of schizophrenia participated in this study. Participants were primarily Caucasian (92.9%) and ranged in age from 27 to 56 years (M = 42.1 years, SD = 6.4 years). All patients attended the Hamilton Program for Schizophrenia (Hamilton, Ontario, Canada), a community-based treatment and rehabilitation program (Whelton, Pawlick & Cook, 1999). All recruited participants were psychiatrically stable at the time of testing and were receiving antipsychotic medication. No other exclusion criteria were used. The characteristics of the sample can be found in Table 1.

Procedure

Upon arrival, participants were introduced to the Child Emotion Laboratory at McMaster University and given a chance to acclimate before any procedures commenced. They were then briefed about the study's procedures and informed consent was obtained. Upon acclimation to the laboratory, participants provided their first saliva sample (i.e., baseline). Participants then completed a self-report questionnaire pertaining to temperament (Cheek & Buss, 1981), and a trained researcher administered the Quality of Life Scale (Heinrichs et al., 1984) through an interview. Participants then provided their second saliva sample. Participants then completed several computerized face processing tasks while ERP and heart rate measures were collected. These measures were collected as part of the larger study, and the findings from those measures are presented elsewhere (Jetha et al., 2013). Finally, participants provided their third saliva sample prior to leaving the laboratory. A trained clinician was present during all testing, and all procedures were approved by the McMaster Health Sciences Research Ethics Board.

Self-report and Interview Measures

Shyness. Shyness was self-reported using the five highest loaded items (Bruch et al., 1989) from the original Cheek and Buss Shyness Scale (Cheek & Buss, 1981). An example of an item from the scale is: "I feel inhibited in social situations". Items were scored on a 5-point scale ranging from 0 (''not at all characteristic'') to 4 (''extremely characteristic''), and thus the shyness scores can range from 0 to 20, with higher scores reflecting a temperament characterized by more shyness. This measure of shyness has been validated for use in individuals with schizophrenia (Jetha, Goldberg & Schmidt, 2012). The measure also demonstrated good internal reliability in our sample (Cronbach's alpha = 0.86).

Positive and Negative Syndrome Scale (PANSS). Psychiatric status was measured by a trained psychometrist using the positive (e.g., delusions, hallucinations, disorganized behavior; $M = 13.00$, $SD = 4.7$) and negative (e.g., behavioral deficits; $M = 13.86$, $SD = 5.3$) syndrome scale (PANSS) (Kay, Fiszbein & Opfer, 1987). Each scale comprises seven symptoms that are rated on a 1(Absent) to 7(Extreme) metric. The mean symptom scores experienced in this sample were similar to those of stable community outpatients with schizophrenia. The PANSS was rated by a trained psychometrist and was conducted within 6 months of participation in the present study (see Table 1 for patient demographics).

It is important to point out that shyness reflects a temperament that is thought to be stable across time and is an antecedent to psychopathology in some individuals. Accordingly, our shyness measure is distinct from the negative symptoms experienced in schizophrenia and measured by the PANSS (Kay et al., 1987). The items on the shyness scale identify how individuals specifically respond to social situations, for example "When I'm in a group of people, I have trouble thinking of the right things to talk about."; and "It takes me long to overcome my shyness in new situations." Conversely, the items on the PANSS relating to

negative symptoms reflect the individual's blunted affect, emotional withdrawal, or social withdrawal some sample items include: "Diminished interest and initiative in social interactions due to passivity, apathy, energy or avolition. This leads to reduced interpersonal involvements and neglect of activities of daily living." and "Reduction in the normal flow of communication associated with apathy, avolition, defensiveness or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal interactional process." To further highlight this differentiation, the shyness and negative symptoms measures utilized in this study were not correlated ($r = .14$, $p = 0.4$).

Quality of Life. Quality of life was measured by a trained psychometrist using the Quality of Life Scale (Heinrichs et al., 1984). This instrument is a 21-item scale that rates quality of life using a semi-structured interview providing information on functioning during the preceding four weeks. The instrument contains four subscales: Intrapsychic Foundations, Interpersonal Relations, Instrumental Role Category, and Common Objects and Activities. The psychometrist was blind to the results of all non-clinical assessments, such as the participant's temperament. All items are based on a seven-point scale, with the high end of the scale reflecting unimpaired functioning, and low levels reflecting severe impairment (Heinrichs et al., 1984). Given the social-cognitive basis of the main objective of our study, we focused on the *Intrapsychic Foundations* and *Interpersonal Relations* subscales. The *Intrapsychic Foundations* is a 7-item scale tapping the dimensions of core symptoms, cognition, motivation, and affect in the participant. The *Interpersonal Relations* subscale contains 8-items and assesses social experiences and aspects of avoidance and withdrawal tendencies. The Cronbach's alpha for the subscales we used are as follows: Intrapsychic Foundations = .91 and Interpersonal Relations = .94 (Heinrichs, Hanlon & Carpenter, 1984).

Neuroendocrine Measures: Salivary Cortisol and Testosterone

Data collection. Each participant was asked to refrain from eating or drinking 1 hour prior to coming to the laboratory and to report any atypical recent life events (e.g., atypical stressful events), as these factors are known to influence cortisol and testosterone levels. No participants reported daily life stressors during laboratory testing. Each participant was asked to donate three individual saliva samples during the laboratory visit. Passive saliva was collected by having each participant expectorate into a 50-ll cryogenic tube. Approximately 50-ll of saliva were collected at each sample. We were interested in the first saliva sample collected as this was presumed to reflect a baseline state where the participant had acclimated to the laboratory setting, while the other saliva samples were collected after an approximately 20-25 minute interval and then again after completion of several computerized tasks. The median time of day for the three saliva collections were 1:48 pm (*SD* = 1 hour 31 minutes), 2:15 pm (*SD* = 1 hour 23 minutes), and 3:17 pm (*SD* = 1 hour 30 minutes), respectively. The time of day that the saliva samples were collected did not systematically vary with any of the other study measures.

Assay Determinations. The following standard procedures have been previously described in Giannopoulou, 2015. All saliva samples were transported on ice and stored at -80 °C prior to assays. Saliva was centrifuged at 3000xg for 15 minutes and only the supernatant was assayed in the Neuroendocriniology Laboratory at Brock University (St. Catharines, ON, Canada). All enzyme immunoassays were carried out on NUNC Maxisorb plates. Cortisol (R4866) and testosterone (R156/7) antibodies and corresponding horseradish peroxidase conjugates were obtained from C. Munro of the Clinical Endocrinology Laboratory, University of California, Davis. Steroid standards were obtained from Steraloids, Inc. Newport, Rhode Island.

Plates were first coated with 50 µl of antibody stock diluted at 1:10,000 in a coating buffer (50 mmol/L bicarbonate buffer pH 9.6) for the testosterone assay while cortisol antiserum was diluted at 1:8000 for the cortisol assay. Plates were stored for 12–14 h at 4 °C. 50 µl wash solution (0.15 mol/L NaCl solution containing 0.5 ml/L of Tween 20) were added to each well to rinse away any unbound antibody, then 50 µl phosphate buffer per well was added. The plates were incubated at room temperature for 30 min for testosterone, and 2 hours for cortisol before adding standards, samples, or controls.

For each hormone, two quality control samples at 30% and 70% binding (the low and high ends of the sensitive range of the standard curve) were prepared. For all assays, 50 µl testosterone, or cortisol horseradish peroxidase conjugate were added to each well, with 50 µl of standard, sample, or control for testosterone or cortisol. Testosterone plates remained incubated for 2 h at room temperature while cortisol plates remained incubated for 1 h. Next, the plates were washed with 50 µl wash solution and 100 µl of a substrate solution of citrate buffer, H2O2 and 2,2′-azino-bis [3-ethylbenzthiazoline-6-sulfonic acid] was added to each well and the plates were covered and incubated while shaking at room temperature for 30–60 min.

Plates were then read with a single filter at 405nm on the microplate reader (Titertek multiskan MCC/340). Blank absorbances were obtained, standard curves generated, a regression line was fit to the sensitive range of the standard curve (typically 40 – 60 % binding) and samples were interpolated into the equation to give values in pg or ng per well. All samples were assayed in duplicate and ran in the same batch. The testosterone assay has been previously validated by Carre and his colleagues (Carré et al., 2006). The intra- and inter- assay CVs were 6.5% and 6.8% for salivary testosterone and 7.8% and 6.5% for salivary cortisol. The cortisol and testosterone levels were natural log transformed to reduce skewness.

Covariates

Given their potential influence on quality of life among patients with schizophrenia, we adjusted for sex, age of onset of schizophrenia, positive symptoms, and negative symptoms in our statistical analyses (Browne et al., 1996; Lehman et al., 1995). We also adjusted for the time of the baseline saliva collection due to its possible influence on cortisol levels (Dickstein et al., 1991). Participant sex and age of onset were extracted from the participant's medical chart, and symptoms were assessed using the PANSS (Kay et al., 1987). Although previous studies have shown a positive relation between cortisol and symptom severity (Coulon et al., 2016), the PANSS did not correlate with cortisol or the other study measures in our sample. Lastly, we did not include medication in our covariates because all participants were taking medications, and thus we opted to retain statistical power by not co-varying medication type or dosage but have noted this as a limitation.

Statistical Analysis

We were interested in examining the influence of shyness, neuroendocrine hormones, and the interaction between these variables on quality of life in individuals with schizophrenia. Four regression analyses were performed in total. We ran separate regression analyses for baseline cortisol and testosterone as moderators. We used multiple linear regression separately for Intrapsychic Foundations and Interpersonal Relations as dependent measures. On the first step, we entered continuous scores of shyness and baseline cortisol or testosterone. On the second step, we entered the interaction term between shyness and baseline cortisol or shyness and baseline testosterone. On the third step, we entered participant sex, age of schizophrenia onset, positive symptoms, negative symptoms, and time of saliva collection to provide adjusted estimates. The data were transformed so that it met the requirements for parametric testing. All

statistical analyses were performed using SPSS Version 21.0, with statistical significance levels set at $\alpha = 0.05$.

Results

Descriptive Statistics

Table 2 displays the descriptive statistics and Pearson's correlations for the measures used in the present study. As predicted, shyness was negatively correlated with the Quality of Life Interpersonal Relations subscale (r = -.56; p = .01) and the Intrapsychic Foundations subscale (r = -.39; p = .01). However, shyness was not correlated with baseline cortisol (r = .02; p > .05) or baseline testosterone (r = .22; p > .05). Further, contrary to other published work (Frye & Seliga, 2001; Hermans et al., 2006), we did not find a significant correlation between testosterone and negative symptoms. As well, the Interpersonal Relations subscale did not correlate with either baseline cortisol (r = .02; p > .05) or baseline testosterone (r = .10; p > .05). The Intrapsychic Foundations subscale also did not correlate with baseline cortisol (r = .12; p > .05) or baseline testosterone (r = .11; p > .05). The Interpersonal Relations subscale was correlated with the Intrapsychic Foundations subscale (r = 0.67; p < .01). Baseline cortisol and testosterone were also positively correlated (r = .35, p < .05).

Shyness, Baseline Salivary Cortisol, and Quality of Life

Table 3 displays the results for the regression analyses in which shyness and baseline cortisol were predictors of Intrapsychic and Interpersonal quality of life measures.

Intrapsychic Foundations. On the first step, we found that relatively higher levels of shyness, but not baseline cortisol, was associated with decreased Intrapsychic Foundations QoL (β = -.52; p = .01). On the second step, we found a significant shyness by baseline cortisol interaction predicting the Intrapsychic Foundations subscale (β = .15; p = .03). The interaction

between shyness and baseline cortisol remained statistically significant after controlling for the covariates (β = .15; p = .02). As illustrated in Figure 1, individuals who scored relatively higher on shyness and who had relatively lower baseline cortisol reported the lowest Intrapsychic Foundations QoL.

Interpersonal Relations. On the first step, we found that relatively higher levels of shyness, but not baseline cortisol, was associated with decreased Interpersonal Relations QoL scores (β = -1.1; p < .01). On the second step, the shyness by baseline cortisol interaction did not predict the Interpersonal Relations subscale in the unadjusted (β = -.00; p = .99) or adjusted models (β = .02; p = .81).

Shyness, Baseline Salivary Testosterone, and Quality of Life

Table 4 depicts the results for the regression analyses in which shyness and baseline testosterone were the predictors of intrapsychic and interpersonal quality of life measures.

Intrapsychic Foundations. On the first step, we found that relatively higher levels of shyness, but not baseline testosterone, was associated with decreased Intrapsychic Functioning (β = -.43, p = .03). On the second step, the interaction between shyness and baseline testosterone was not statistically significant in the unadjusted (β = .002, p = .99) or adjusted models (β = .03, p = .86).

Interpersonal Relations. In the first step, we found that relatively higher levels of shyness, but not baseline testosterone, was associated with decreased Interpersonal Relations QoL scores (β = -1.2, p < .01). In the second step, the interaction between shyness and baseline testosterone was not statistically significant (β = .00, p = .99). The interaction remained not significant after adjusting for covariates (β = .01, p = .94).

Discussion

We examined whether baseline salivary cortisol and testosterone, separately, moderated the relation between shyness and QoL in adults with schizophrenia. We examined two facets of QoL, Intrapsychic Foundations, which is related to core negative symptoms of schizophrenia, and Interpersonal Relations, which is related to the individual's companionships. We found that baseline salivary cortisol, but not baseline testosterone, was a significant moderator on the relation between shyness and intrapsychic functioning QoL. Individuals with relatively lower baseline cortisol and relatively higher shyness displayed the lowest QoL; individuals with relatively higher baseline cortisol reported similar QoL scores irrespective of level of shyness.

The present study appears to be the first to examine whether individual differences in personality and hormones interact to confer different facets of QoL in adults with schizophrenia. Our findings suggest that baseline salivary cortisol may influence how the core symptoms of schizophrenia, such as avolition and cognitive deficits, affect an individual's satisfaction depending on temperamental shyness. This is reflected by the Intrapsychic Foundations QoL subscale where a subgroup of individuals with relatively lower baseline salivary cortisol and higher shyness had the lowest QoL. To our knowledge, although no other study has assessed the interaction among personality, cortisol, and QoL, one study has shown that coping styles and cortisol predicted QoL in people with schizophrenia (Brenner et al., 2011). Brenner and colleagues (2011) used a QoL measure that assessed overall life satisfaction and found that blunted cortisol responses moderated the relation between coping styles and QoL in adults with schizophrenia. This result suggests that individual level neuroendocrine factors interact with individual personality characteristics or behaviors to influence QoL. Previous literature has also found that relatively lower baseline cortisol levels are associated with documented exposure to

trauma and is thought to reflect an eventual downregulation of the HPA axis after its prolonged overactivation (which leads to high cortisol levels) (Badanes et al., 2011; Morris, Compas & Garber, 2012). The impact and presence of relatively low baseline cortisol in our sample could be explained in at least two ways. First, it is possible that individuals who are shy and have schizophrenia tend to perceive or experience more events as adverse, which eventually leads to the HPA dysregulation seen in our sample. A second possibility is that shy individuals with schizophrenia may be more reactive to the world around them and have ongoing stressors throughout their life, which leads to unsustainable overregulation of the HPA axis and eventually a downregulation of the HPA axis. Consistent with this latter idea, Beaton et al. (2006, 2013) have reported relatively lower baseline salivary cortisol levels in a nonclinical sample of adults who are shy. Here we extended these previous finding by showing that baseline cortisol also moderated the link between shyness and intrapsychic foundations QoL in stable outpatients with schizophrenia.

Contrary to our hypothesis, we found that cortisol did not influence the relation between shyness and Interpersonal Relations QoL. This was unexpected since the links between shyness and social relations, cortisol and QoL, shyness and QoL have been independently supported in those with schizophrenia (Rubin et al., 2022; Goldberg & Schmidt, 2001; Hansson et al., 2001; Jetha, Goldberg & Schmidt, 2012; Brenner et al., 2011). Since cortisol might influence how shy individuals respond to social situations (Cooper, Bloom & Roth, 1991), we thought that it might ultimately impact their satisfaction with Interpersonal Relationships. However, our findings suggest that cortisol levels, despite previously being shown to be related to social characteristics (Thompson et al., 2007; Schmidt & Schulkin, 1999), may not be contributing to how satisfied an individual is with his/her overall interpersonal relations in schizophrenia populations. This could

be due to the fact the individuals with schizophrenia often experience poor social cognition and have hindered social relations (Penn et al., 1997). With already poor social relationships, the impact of cortisol may be too small to make a significant difference in their interactions. Further, the items that are used to assess interpersonal relations QoL ask about current relationships and whether the individual feels comfortable discussing things with their friends. These kinds of items are inherently different and are more functional and objective assessments than are those used to assess intrapsychic foundations QoL, which are focused more on internal and subjective feelings, such as the individual's motivation, goals, and sense of purpose. These subjective feelings measured by the intrapsychic foundations subscale, such as motivation, also could be more susceptible to factors such as stressors, medication, or cognition (Suttajit & Pilakanta, 2015).

We also did not find a significant correlation between baseline cortisol and shyness within our sample. This could be due to two different reasons. First, it could be that due to the relatively small sample size that we were unable to detect a relation between the two variables. Secondly, shyness has been associated with cortisol in nonclinical adult samples (Beaton et al., 2013). It could be that there is a mechanism related to the pathology that masks this relation in individuals with schizophrenia. Further studies are needed to assess the relation between shyness and baseline cortisol in individuals with schizophrenia.

We also found that testosterone and cortisol were positively correlated. Although cortisol and testosterone have similar site of origin mechanistically, their concentrations in relation to each other vary across the lifetime (Kamin & Kertes, 2017). Further, they are thought to mediate opposing biologic and neurologic functions. That said, both cortisol and testosterone levels increase in response to stress, which suggests a positive relation between the levels of baseline

cortisol and testosterone. This is consistent with literature examining the relation between these two hormones in aggressive adolescents (Popma et al., 2007). To our knowledge, this is the first study to demonstrate the relation between cortisol and testosterone in adults with schizophrenia. Moreover, we found that baseline testosterone did not moderate the relation between shyness and either measure of QoL. To our knowledge, no study has examined the association between baseline testosterone and QoL in adults with schizophrenia. That said, previous studies have examined the relation between testosterone and stress levels (Hermans et al., 2006; van Honk, Peper, & Schutter, 2005). A reduction in stress levels could ultimately lead to better QoL, however, we did not find any links between baseline testosterone, shyness and QoL. Although previous research has found a relation between heightened testosterone and anxiolytic effects (Frye & Seliga, 2001), this effect may not be strong enough to impact their QoL. Moreover, because previous literature has shown that cortisol levels moderate QoL outcomes in individuals with schizophrenia (Brenner et al., 2011), this suggests that there is either specificity within the neuroendocrine markers where baseline cortisol, but not testosterone, can predict QoL (intrapsychic at least) in those with schizophrenia, or the effect that baseline testosterone has may not have been strong enough to find with our relatively small sample size.

Limitations

There were several limitations of this study that should be noted. First, our relatively small sample size may limit the reliability of the findings, and also may have also reduced statistical power and our ability to detect a statistically significant interaction for our *Interpersonal Relations* outcome. Second, the sample was not drug naïve, making it difficult to discern whether the results observed are due to the qualities measured or whether medication had an effect on them. Some antipsychotic medications can affect cortisol levels (Oishi et al., 2012;

Määttänen et al., 2013; Goyal et al., 2004) and cognitive functioning (Keefe et al., 1999), which is related to the intrapsychic quality of life subscale used. Medication may also affect HPA axis functioning (Mondelli et al., 2010; Ho et al., 2000). We were also unable to assess whether overall levels of cortisol were elevated in our group. Due to the lack of a control group, we were not able to determine whether cortisol levels were elevated in our sample of people with schizophrenia. Further, we could not reliably compare our sample to published samples since factors that influence cortisol levels (e.g., the methods, time of day, and patient population) could be different (Määttänen et al., 2013), and no normative data regarding cortisol levels in general are available to make a comparison. Lastly, the cross-sectional design of this study poses a limitation to the developmental framework suggested herein as well as limiting any causal relations. Future studies need to replicate the current findings using a larger sample, a longitudinal study design, and controlling for type and dosage of medication and possibly drug naïve patients prior to first episode and/or at risk for schizophrenia in order to ensure the reliability and generalizability of the current findings.

Conclusion and Implications

Quality of life is generally reduced in those with schizophrenia (Mondelli et al., 2010). Here we report preliminary findings relating temperamental shyness and baseline salivary cortisol to the intrapsychic and interpersonal domains of QoL, as they measure the core deficits of schizophrenia, including avolition and cognition (Heinrichs, Hanlon & Carpenter, 1984). We found that individual differences in temperamental shyness and baseline salivary cortisol, but not baseline testosterone levels were associated with different QoL outcomes in the intrapsychic functioning domain. Our preliminary results suggest that the interpersonal relations domain may be relatively unaffected by neuroendocrine functioning. More research is required to better

describe the relative influences on all of the domains of QoL in individuals with schizophrenia, and the mechanisms through which relatively lower baseline salivary cortisol appears to place shy adults with schizophrenia at greatest risk for impaired QoL.

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Tables

Table 1. Sample characteristics

Characteristics	Participants (N = 42)
Sex	
Male	29
Female	13
Participant Age (in years)	
Mean, S.D.	42.1 (6.4)
Ethnicity	
Caucasian	39
Asian	1
Hispanic	1
Black	1
Age of onset (in years)	
Mean, S.D.	19.5 (4.4)
Symptoms (PANSS)	
Positive	12.6 (4.4)
Negative	12.2 (3.7)
General	26.1 (5.6)
Total	50.8 (11.4)
Average number of Antipsychotic Medications	2 (1)

S.D. – standard deviation

Table 2. Summary of Pearson's correlations among shyness, baseline salivary cortisol, baseline testosterone, and the quality of life subscales

	1	2	3	4	5	*M*	*SD*
1. Shyness	--	.02	.22	-.56**	-.39*	10.0	4.8
2. Baseline Cortisol		--	.35*	.016	.12	-.12	2.4
3. Baseline Testosterone			--	.10	.11	4.7	1.2
4. Quality of life Interpersonal Relations				--	.67**	26.1	9.2
5. Quality of life Intrapsychic Foundations					--	26.6	6.2

Note: *M* = mean; *SD* = standard deviation; *N* = 34; **$p < .01$, *$p < .05$

Table 3. Summary of shyness and baseline salivary cortisol regression models predicting (A) intrapsychic foundations and (B) interpersonal relations

	Predictors	(A) Intrapsychic Foundations				(B) Interpersonal Relations			
		Beta	S.E.	R^2	ΔR^2	Beta	S.E	R^2	ΔR^2
Step 1				.18**	.18**			.33***	.33**
	Shyness	-.52***	.19			-1.1***	.25		
	Cortisol	.32	.38			.10	.51		
Step 2				.28**	.10**			.33	.00
	Shyness x Cortisol	-.15**	.06			-.001	.09		
Step 3				.52**	.24**			.72***	.39**
	Shyness	-.32*	.18			-.89***	.20		
	Cortisol	-1.1	.72			.15	.81		
	Shyness x Cortisol	.15**	.06			.02	.07		
	Sex	-.87	1.7			-1.7	2.0		
	Age of Onset	-.26	.21			-.01	.21		
	Positive symptoms	-.43**	.21			-.22	.23		
	Negative Symptoms	-.43*	.25			-1.3***	.28		
	Time	-.00	.00			-.00	.02		

Note: S.E. – standard error; $N = 40$; ***$p < .01$, **$p < .05$, *$p < .10$

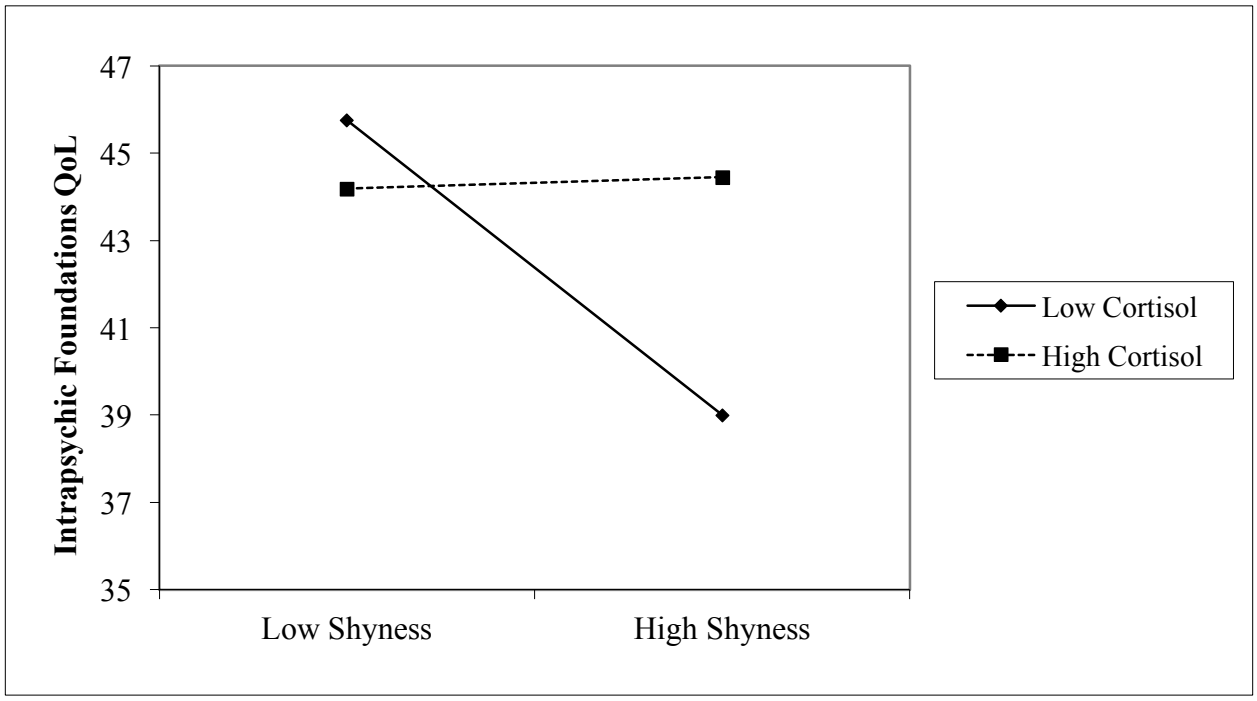
Table 4. Summary of shyness and baseline salivary testosterone regression models predicting (A) intrapsychic foundations and (B) interpersonal relations

	Predictors	(A) Intrapsychic Foundations				(B) Interpersonal Relations			
		Beta	S.E.	R^2	ΔR^2	Beta	S.E	R^2	ΔR^2
Step 1				.13*	.13*			.41***	.41**
	Shyness	-.43**	.20			-1.3***	.26		
	Testosterone	.85	.74			1.8*	.99		
Step 2				.13	.00			.42	.00
	Shyness x Testosterone	.002	.18			.001	.24		
Step 3				.43	.31**			.73***	.32**
	Shyness	-.44	.18			-1.1	.87		
	Testosterone	-03	1.6			.80	.10		
	Shyness x Testosterone	.03	.16			.01	.18		
	Sex	.84	1.8			-2.1	2.0		
	Age of Onset	-.13	.19			-.02	.21		
	Positive symptoms	-.45**	.20			-.21	.23		
	Negative Symptoms	-.47*	.26			-1.2***	.29		
	Time	-.00	.00			-.00	.01		

Note: S.E. – standard error; $N = 40$; ***$p < .01$, **$p < .05$, *$p < .10$

Figure

Figure 1. Interaction between shyness and baseline salivary cortisol in predicting intrapsychic quality of life in schizophrenia patients



Note: Plotted data are included for 1 SD above and below the mean shyness scores and baseline salivary cortisol levels.

CHAPTER 5:

GENERAL DISCUSSION

Schizophrenia is a widely heterogeneous disorder where individual presentations, prognosis, and recovery vary to great extents (Buchanan & Carpenter, 1994; Case et al., 2011; Tsuang, Lyons & Faraone, 1990). Several studies have attempted to explain this heterogeneity by determining whether subtypes of schizophrenia exist based on neurocognitive differences or other presenting factors (Buchanan & Carpenter, 1994; Tsuang et al., 1990; Seaton, Goldstein & Allen, 2001). Personality and temperament types have been examined to understand the heterogeneity of observed phenotypes of many disorders, including, but not limited to, anxiety disorders, depression, and substance use disorder (Kagan, 2022; Lemyre, Gauthier-Légaré & Bélanger, 2019; Rubin, Coplan & Bowker, 2009; Tsui, Lahat, & Schmidt, 2017) that may contribute to different outcomes. Extant literature has also shown this relation among individuals with schizophrenia.

For example, individuals at risk for, and with schizophrenia, are more likely to report higher levels of shyness than healthy controls (Beaucham et al., 2006; Cuesta et al., 2002; Feola et al., 2019; Goldberg & Schmidt, 2001; Jetha, Goldberg, & Schmidt, 2013a). Shyness has been correlated with different outcomes, such as hindered objective quality of life (QoL) (Jetha et al., 2013a) and subjective QoL (Ritsner et al., 2003; Ritsner et al., 2012) among adults with schizophrenia. Although temperament traits are important for further understanding the heterogeneity observed among individuals with schizophrenia, there remains a large gap in understanding how they impact the QoL among individuals with schizophrenia.

The aim of three empirical studies in this dissertation was to address three major gaps in the field examining the intersection of schizophrenia and personality in relation to QoL outcomes. The overarching goal in addressing these questions was to shed light on the importance of considering individual differences in temperament, alongside stress-related variables, when evaluating the QoL among individuals with schizophrenia. For example, shyness has been associated with heightened stress responses such as increased cortisol levels and right frontal brain asymmetry in nonclinical, healthy samples (Poole & Schmidt., 2020), but we know relatively little about how temperament and stress-related physiology and their roles predict different outcomes in people with schizophrenia. I discuss below these three questions and respective studies designed to address them are discussed below in turn.

Study 1: Do individuals with schizophrenia respond to items on self-report measures of shyness and sociability in the same way as healthy controls?

In Study 1, I first sought to determine whether widely-used measures of shyness and sociability were empirically reliable to use with people with schizophrenia before making comparisons with nonclinical populations by examining the measurement invariance structure of these two measures. Such personality measures are often used across many populations, though relatively few studies have examined whether individuals in different populations, particularly clinical populations, understand and respond to the questionnaire items in the same way as healthy controls. The results of Study 1 supported the notion that adults with schizophrenia were indeed responding to items on the questionnaires in the same way as age and sex matched controls. These results suggest that researchers using the Cheek and Buss Shyness and Sociability questionnaires with adults with schizophrenia can be confident when interpreting

responses from this self-report measure and trustworthy comparisons can be made using these measures between people with schizophrenia and healthy controls. The establishment of measurement invariance on the shyness measure was also critical for the next two studies in my dissertation in which the very same shyness measure was used to understand the role of temperament and stress-related physiology in predicting different outcomes in QoL among adults with schizophrenia.

Study 2: Does the central nervous system's response to stressful and non-stressful social stimuli (i.e., fearful faces and happy faces, respectively) moderate the relation between shyness and quality of life?

In Study 2, I examined central nervous system responses to facial emotional stimuli as a moderating variable for understanding the relation between shyness and QoL. Prior evidence has shown that the processing of emotional faces occurs very quickly, prior to conscious awareness and (Lamme & Roelfsema, 2000; Palermo & Rhodes, 2007; Whalen et al., 2004) and is influenced by temperament factors among healthy adults, children, and infants (Jetha et al., 2012; Lonigan et al., 2004; Pérez-Edgar & Fox, 2003; Rajhans et al., 2015; Rennels et al., 2020).

In the present study, two facets of objective QoL were examined as they had previously been implicated in studies examining the relation between shyness and QoL in schizophrenia (Jetha et al., 2013a): IntraPsychic Foundations QoL (i.e., a subscale which measures deficits in cognition, motivation and affect in relation to QoL) and Interpersonal relations QoL (i.e., a subscale which measures deficits observed in social functioning) (Heinrichs et al., 1984).

I found that that those patients with schizophrenia who scored relatively higher on shyness and demonstrated hyposensitivity to the early processing of fearful emotional faces (i.e.,

reduced attention and slower processing at the P1 and N170 stage for emotional faces) were at higher risk for deficits in cognitive, affective, and motivational domains in relation to QoL. However, I did not find the same robust findings for intrapersonal QoL outcomes. I also found a significant interaction between shyness and ERP latency at the P1 and N170 in response to happy faces. Patients who displayed longer P1 and N170 latencies to happy faces compared to neutral faces and with higher shyness levels scored lower on Intrapsychic Foundations and Interpersonal Relations QoL, respectively. These results provide support that early visual processing of emotions can also modulate the relation between temperamental shyness and QoL in stable outpatients with schizophrenia. The processing of stressful stimuli (i.e., fearful faces) is an important moderating variable to examine when investigating the relation between shyness and intrapsychic foundations, while the processing of non-stressful stimuli (i.e., happy faces) is an important moderating variable to examine when investigating the relation between shyness and intrapsychic foundations and interpersonal relations.

Study 3: Does the peripheral nervous system's response to stress moderate the relation between shyness and quality of life?

Having found distinct central nervous system responses to stressful stimuli moderated the relation between shyness and QoL among adults with schizophrenia, I was interested in extending the findings from Study 2 by examining whether there were distinct peripheral nervous system responses to stress that also moderated this relation. Here I examined whether neuroendocrine hormones (i.e., baseline salivary testosterone and cortisol) underlying stress-related approach-avoidance related behaviors, respectively, moderated the relation between shyness and QoL among a sample of stable adults with schizophrenia.

While cortisol has been implicated as a stress-related hormone associated with avoidance-related behaviors (Altamura, Boin & Maes., 1999; Badanes, Watamura & Hankin., 2011; Beaton, Schmidt, Schulkin & Hall., 2013; Schmidt & Schulkin, 1999; Thompson et al., 2007), testosterone has been viewed as an anxiolytic hormone associated with approach-related behaviors (Eisenegger, Haushofer & Fehr, 2011; Hermans et al., 2006; van Honk, Peper & Schutter, 2005). Understanding how these hormones differentially interact to predict IntraPsychic Foundations QoL (assessing cognitive, affective, and motivational domains of QoL) can help further understand the nuances of the relation between shyness and QoL.

I found that baseline salivary cortisol, but not baseline salivary testosterone, moderated the relation between shyness and IntraPsychic Foundations QoL. Individuals with relatively lower cortisol levels and higher shyness levels were more likely to have hindered IntraPsychic Foundations QoL. Conversely, those with relatively lower cortisol levels and lower shyness had relatively higher Intrapsychic Foundations QoL. The specificity of these results to baseline cortisol, but not baseline testosterone, levels suggests that these responses are related to stress-related processes linked to the HPA axis and potential dysregulation of this system that occurs among individuals with schizophrenia who are also shy.

Theoretical, Methodological, and Practical Implications

The findings of this dissertation have important theoretical, methodological, and practical implications related to understanding the heterogeneity observed among individuals with schizophrenia. Study 1 demonstrated that the use of self-report measures targeting temperament traits of shyness and sociability can reliably provide meaningful interpretations among this population (Khalesi et al., 2021). This is especially important as the reliability of an instrument can vary across populations (Murray et al., 2014). By establishing measurement invariance of the

Cheek and Buss Shyness and Sociability Scales (Bruch et al., 1989; Cheek & Buss, 1981), results of Study 1 may allow researchers to be confident that individuals with schizophrenia are responding to items on these scales in a reliable and trustworthy manner and as intended and thus meaningful generalizations and confidence in conclusions drawn can be made. It also helps reliably support previous research which demonstrated associations between shyness and schizophrenia outcomes using these same personality measures (e.g., Jetha et al., 2013a,b).

As discussed earlier in the dissertation, shyness can be understood within a three-component model: somatic-emotional, behavioral, and cognitive (Cheek & Watson., 1989). This suggests that shyness can interact within the individual on many different levels, which are then observed to be expressions and experiences of shyness. As we are working within a complicated system where a psychopathology is introduced, it is possible to assume that the characteristics of shyness may interact with the characteristics of the psychopathology. Studies 2 and 3 demonstrated that the relation between shyness and QoL was moderated by idiosyncratic physiological correlates. The results of Study 2 underscored the importance of examining neural correlates of attention to emotional social stimuli (faces) when examining the relation between shyness and QoL. Although attention to emotional faces is automatic, it is also shaped by prior experiences and internal factors (Bar-Haim et al., 2007; Fox, 2002; Palermo & Rhodes 2007). For example, patients with schizophrenia who are relatively higher on shyness demonstrate markers of higher vigilance towards emotional faces than those who are relatively lower on shyness (Jetha et al., 2013b), demonstrating that prior experiences of avoiding social stimuli can result in heightened reactions and salience towards emotional faces.

Study 2 demonstrated that individuals with a relatively lower amplitude of neural response to fearful faces were more likely to experience hindered QoL if they were also

relatively higher in shyness. Moreover, this finding was specific to the QoL subscale measuring cognitive, affective, and motivational QoL. This suggests that incremental differences in neurophysiological responses to stressful social stimuli can have adverse effects when assessing higher order QoL functioning. It is possible that prior experiences with shyness leads to avoidance of fearful faces. It is also possible that this attentional avoidance towards negative emotions may lead to negative interpretations about the social stimuli being communicated. This potential misinterpretation could be leading to the affective and motivational deficits observed by the intrapsychic foundations QoL outcome measure.

Study 3 found that examining peripheral nervous system responses to stress (i.e., through baseline cortisol) is also important in further delineating the relation between shyness and QoL. Here, I found that individuals with *lower* cortisol levels and higher shyness, were more at risk of reduced QoL. Although this appears counterintuitive at first, it supports the notion that individuals who are highly vulnerable to stressful life events, as is common among individuals with schizophrenia (Norman & Malla 1993; Read et al., 2001; Tandon, Keshavan, & Nasrallah 2008), may experience a disruption in their HPA axis leading to lower overall cortisol levels (Badanes, Watamura & Hankin, 2011). That being said, the literature is inconclusive with findings relating to cortisol levels, with some studies demonstrating heightened cortisol levels in individuals with schizophrenia who were exposed to stressful life events (Mondelli et al., 2010) and others demonstrating no significant difference or a lower response (Mayo et al., 2017). These findings suggest that understanding the underlying stress response along with the temperament of patients with schizophrenia is a complicated endeavor and important in predicting QoL outcomes.

In summary, the current findings have notable theoretical, methodological, and clinical implications. Upon replication of the present findings, researchers and clinicians working with this population should consider screening for individual differences temperament when trying to understand the nuances of QoL outcomes among this population and ensure these measures are equivalent before comparisons between people with schizophrenia and nonclinical samples are made. Further understanding of stress-related physiological responses can also help delineate individuals with schizophrenia who demonstrate hindered QoL. Given that these physiological systems appeared to serve as moderators of the relation between shyness and QoL, and are more likely to be open to change than one's temperament, these systems may provide opportunities for targeting interventions (i.e., biofeedback, cognitive therapy etc.) directed at specific physiological systems. Such interventions could potentially positively influence and improve QoL outcomes among some people with schizophrenia with temperaments known to predict risk.

Limitations and future directions

There are several broad limitations to consider within the studies provided throughout this body of work. The first applies across all of three of the studies and is related to sample size. Although the three studies used a moderate- to-large sample size in comparison to other work with this special population and biological measures, they are still relatively small when compared to sample sizes used in personality research. Accordingly, future studies are needed to replicate these findings with larger sample sizes. Second, given the studies were cross-sectional in design, causality among variables cannot be established, so we do not know whether shyness is causing differences in QoL or vice versa. Moreover, the choice to examine physiology as the moderating factor was determined from theoretical reasons, but it is also plausible that shyness

could moderate the relation between physiology and QoL, and QoL could moderate the relation between shyness and physiology.

A final point is also important to mention here. Although our studies built upon extant literature, there remains a considerable gap in the breadth of studies examining the relation between shyness and QoL among adults with psychosis and schizophrenia. That is, we cannot be completely confident of making generalizations prior to exploring more studies with different methodologies in understanding the phenotypes of schizophrenia and QoL outcomes. Similarly, although this work is foundational in providing evidence that temperament traits can influence outcomes observed with schizophrenia, it also underscores the necessity to investigate how other features of temperament and various personality traits may influence outcomes with schizophrenia. By understanding the confluences of different internal factors and how they integrate with the psychopathology, we may further be able to delineate "subtypes" of schizophrenia and potentially predict outcome differentials. In addition, although the current studies provided important theoretical understandings of the moderating influences between shyness and QoL, it is necessary to also examine whether these moderating factors are amenable to interventions. For example, future studies can examine whether facial emotion recognition training (Russell et al., 2008), with specific exposures to fearful faces, can influence neurophysiological responses to fearful faces. This may be especially impactful within the subtype of individuals with schizophrenia who are also shy as they may be more likely to avoid looking at faces in general. Due to the potentially limited experience of looking and discerning faces, individuals with schizophrenia who are shy may experience an altered neurophysiological response to threat stimuli compared to healthy controls. As such, future studies can aim to investigate this neural response and determine if it is amenable to change through training.

The three empirical studies within the dissertation were apparently some of the first to examine the moderating influences of the central and peripheral nervous system on the relation between shyness and QoL among adults with schizophrenia. In order to make accurate generalizations, other markers of these systems can be investigated to determine whether they also moderate the relation between shyness and QoL. For example, as discussed earlier, shy individuals have also been shown to have right frontal brain asymmetry (Poole & Schmidt, 2020). Future studies can examine whether this is also the case with individuals with schizophrenia who are shy and whether that serves as a potential moderating variable of QoL. Lastly, these relations can be extended to other variables of outcome among individuals with schizophrenia, such as determining whether they predict treatment response, symptom improvement, or functional recovery.

General conclusions

The series of three studies in this dissertation support the notion that moderating variables exist in influencing the relation between shyness and QoL among individuals with schizophrenia. Specifically, the results from this body of work elucidate the role of central and peripheral nervous system responses in exploring the complex relation between shyness and QoL while contributing to important theoretical and clinical implications. Shyness has been conceptualized as a risk factor for hindered QoL due to the general association found in the population. This body of work has elucidated that although shyness is generally associated with QoL, that is not always the case and idiosyncratic factors can moderate this relation. Despite the information gathered from these set of studies, the limitations described warrants further research in this area to generate more confident conclusions on understanding the factors that contribute to the heterogeneity of observed schizophrenia presentations and prognoses. Further replication

of these studies with larger sample sizes and different populations of psychosis (i.e., first episode psychosis) will provide us with a more thorough understanding of the factors influencing the heterogeneity observed within this population.

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