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Social cognition in early schizophrenia: exploratory factor analysis and subcortical biomarkers

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Thesis

**SOCIAL COGNITION IN EARLY SCHIZOPHRENIA: EXPLORATORY
FACTOR ANALYSIS AND SUBCORTICAL BIOMARKERS**

By

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LUKE T. MIKE

ABSTRACT

Background: One of the central determinants of functional outcome in schizophrenia is social cognition (SC). With the wide array of SC domains, factor-analysis provides a powerful tool to identify commonalities amongst their underlying dysfunctions and its neural underpinnings.

Methods: The present study performed exploratory factor analysis (EFA) on 93 patients with early course schizophrenia using eight validated SC subtests. Factors derived from this analysis were then used to investigate their relationships with neurocognitive performance, clinical symptoms, and functional outcome. Moreover, subsequent shape analysis of the amygdala and hippocampus was performed using the MAGeT Brain pipeline to investigate their relationship to the composite scores of SC factors.

Results: EFA revealed a 3-factor solution, representing the domains of emotion management, emotion recognition, and theory of mind-social contextual appraisal, together accounting for 63.58% of the variance. Interestingly, only the theory of mind-social context appraisal factor correlated with measures of functional outcome. Addition analysis revealed that higher score on the theory of mind factor is significantly related with higher functional outcome measures and verbal learning performance, as well as

with lower negative symptoms. Both emotion management and emotion perception factors indicated significant positive correlations with attention-vigilance while only emotion perception significantly correlated with visual learning and memory. Outward convexity of the right amygdala was identified to be positively correlated with the theory of mind-social context appraisal factor ($p < 0.05$, FDR corrected), while the left and right hippocampus, specifically greater surface area of the dorsal-medial and ventral-lateral aspect of the hippocampus respectively, were positively correlated with higher composite score on theory of mind factor ($p < 0.05$, FDR corrected).

Conclusion: Our EFA indicates overlap amongst SC subtests which represent three different SC subdomains. Furthermore, shape analysis reveals that displacement and surface area of the amygdala and hippocampus respectively play a role in theory of mind. In the future, the SC factors that we identified, along with their neural correlates, could provide essential diagnostic tools to assess SC functioning in early schizophrenia patients, as well as identify strategies for potential improvement following cognitive remediation therapy.

TABLE OF CONTENTS

TITLE.....	i
COPYRIGHT PAGE.....	ii
READER APPROVAL PAGE.....	iii
ACKNOWLEDGMENTS	iv
ABSTRACT.....	v
TABLE OF CONTENTS.....	vii
LIST OF TABLES	xi
LIST OF FIGURES	xii
LIST OF ABBREVIATIONS.....	xiii
INTRODUCTION	1
Functional Outcome in Schizophrenia	2
Clinical Symptomology in Schizophrenia	3
Neurocognition	5
Social Cognition	5

Social Cognition and its Relation to Neurocognition and Functional Outcome in Schizophrenia	6
Social Cognition in Schizophrenia	9
Social Cognition: Theory of Mind and Social Context Appraisal	9
Social Cognition: Emotion Perception	11
Social Cognition: Emotion Regulation and Management	12
Exploratory Factor Analysis	15
Social Cognitive Endophenotype Markers in Schizophrenia	17
Specific Aim	21
METHODS	23
Subjects & Demographics	23
Social Cognition Measures	23
Neurocognitive Measures	26
Functional Measures	26
Clinical Measures	28
Statistical Analysis Factor Correlates: Neurocognition, Clinical, Functional Outcome	28

RESULTS	33
Demographics results of EFA Analysis	33
Exploratory Factor Analysis	33
Social Cognition Factor Correlates: Neurocognition, Clinical, Functional Outcome	35
Social Cognition Factor Performance Comparisons	38
DISCUSSION	44
Social Cognition in Schizophrenia: EFA, Neurocognition, Clinical, Functional Outcome Correlates, & SC Performance Comparisons	44
Social Cognition Factor Correlates: Hippocampus & Amygdala	47
Limitations and Conclusions	51
APPENDIX	54
Appendix 1. Definitions of Terms	54
Appendix 2. Definitions of Positive Symptoms & Negative Symptoms	54
Appendix 3. Functional Outcome Measures/Functional outcome measures can be split into two domains (social or non-social) for which there are a number of subdomains.	55
REFERENCES	57

CURRICULUM VITAE..... 80

LIST OF TABLES

Table	Title	Page
1	Demographic Characteristics: Exploratory Factor Analysis	33
2	Social Cognition Exploratory Factor Analysis	34
3	Two-tailed Partial Pearson Correlations between Neurocognition and SC EFA	36
4	Demographics: Shape Analysis	40

LIST OF FIGURES

Figure	Title	Page
1	Two-tailed Partial Pearson Correlations between Social Adjustment Scale and Factor 3-Theory of Mind	37
2	Two-tailed Partial Pearson Correlations between Scale for the Assessment of Negative Symptoms without attention and Factor 3-Theory of Mind	38
3	Male versus Female Factor Score Comparisons	39
4	Right Amygdala Displacement Versus Factor 3-Theory of Mind	40
5	Right Hippocampus Surface Area Versus Factor 3-Theory of Mind	42
6	Left Hippocampus Surface Area Versus Factor 3-Theory of Mind	43

LIST OF ABBREVIATIONS

BU.....	Boston University
DSM.....	Diagnostic and Statistical Manual of Mental Disorders
EFA.....	Exploratory Factor Analysis
FDR.....	False Discovery Rate
MAGeT.....	Multiple Automatically Generated Templates
MATRICES.....	NIMH- Measurement and Treatment Research to Improve Cognition in Schizophrenia
MRI.....	Magnetic Resonance Imaging
SC.....	Social Cognition
ToM.....	Theory of Mind
QOL.....	Quality of Life

INTRODUCTION

Diagnosis of schizophrenia has often carried with it a grave prognosis (Grohol & Psy.D., n.d.). Daily living and health standards amongst patients with schizophrenia are poor; the illness positions itself amongst the world's top ten causes of disability (Mathers, Fat, & Boerma, 2008). Patients oftentimes find themselves struggling to maintain good physical health, social lives, jobs, and obtain the same achievements as those of healthy individuals (Messias, Chen, & Eaton, 2007).

Overall, disability associated with schizophrenia strongly parallels lower socioeconomic status (Dohrenwend, 1990). A retrospective study found poorer outcome in the areas of work history, marital status, and residential status (Jobe & Harrow, 2005). In terms of personal relationships, lower rates of marriage and higher rates of divorce are commonly found (Thara & Srinivasan, 1997; Hutchinson et al., 1999). Furthermore, as nearly 15 percent of patients are homeless here in the U.S., residential status is unstable and thus is likely to deter acquisition of strong social relationships (Folsom et al., 2005). Although patient residence is often outside of institutional settings, independent living is still reliant on financial and other forms of support from others (Bowie & Harvey, 2006). These financial challenges are commonplace as one study reported that 72.9 percent of schizophrenic patients are unemployed here in the U.S. (Rosenheck et al., 2006). Employment status is likely to be partially related to lower than average educational achievement with patients obtaining nearly two years less education than their healthy counterparts (Goldberg et al., 1990).

Severity of disease is often stated in terms of translation to mortality rates; in the acute state, one study found schizophrenia to be the most severe out of 220 disorders (Salomon et al., 2013). Overall, these patients often have a dramatic decrease in life expectancy, nearly 10% being due to the high rate of suicide (De Hert, McKenzie, & Peuskens, 2001). High comorbidity also accompanies the causative agents for increased mortality rates (Laursen, Munk-Olsen, & Gasse, 2011). Commonly associated illnesses include cardiovascular, gastrointestinal, respiratory, urogenital, infectious, metabolic and malignant conditions (Schultz, North, Shields, & others, 2007).

Disease etiology still remains elusive and therapeutic intervention is far from a cure (Grohol & Psy.D., n.d.). However, meta-analysis of cognitive remediation therapy revealed its effectiveness in improving psychosocial functioning in patients with schizophrenia (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007). These findings are encouraging in that improved competence in psychosocial functioning is related to better socioeconomic outcome (Perlick, Stastny, Mattis, & Teresi, 1992). Even still, significant opportunities still remain for researchers and physicians to enhance the lives of these patients in terms of outcomes and daily functioning. In an effort to improve the prognosis of schizophrenia, the current project investigated potential measures, on both psychological and neurobiological levels, that could be predictive of outcome and patient wellbeing. In addition, this project looked to identify therapeutic targets for the improvement of functioning and outcome in society.

Functional Outcome in Schizophrenia

Functional competence in the areas of social (e.g., eye gaze, meshing (smoothness of turn taking and conversational pauses), latency and duration of verbal responses,) and nonsocial skills (e.g., personal hygiene, appearance and care of clothing, care of personal possessions, food preparation/storage, health maintenance), can be translated into higher achievement in quality of life and socioeconomic status in patients with schizophrenia (Penn, Corrigan, Bentall, Racenstein, & Newman, 1997; Perlick, Stastny, Mattis, & Teresi, 1992). As patients are likely to experience difficulties of finances, it is beneficial if they have the knowledge and skills to balance a checkbook, pay utility bills, make change for an item purchased at a store, etc. (Mausbach et al., 2011). Similarly, if patients are to maintain employment at a job, interpersonal skills such as eye contact, voice volume, meshing, etc. is all vital (Couture, Penn, & Roberts, 2006). Methodology for assessing these features are diverse, some are self-report, others are observer rated, and a few are performance-based. Even amongst the broad range of measures and methods, there is a general consensus that patients with schizophrenia have poorer performance amongst social and nonsocial categories of functional outcome (Refer to appendix 3 for examples of social and nonsocial measures of functional outcome)(Bowie et al., 2008; Couture et al., 2006; Harvey, Green, Keefe, & Velligan, 2004; Bellack, Sayers, Mueser, & Bennett, 1994; Perivoliotis, Granholm, & Patterson, 2004; Mausbach et al., 2011).

Clinical Symptomology in Schizophrenia

Schizophrenia is commonly regarded in terms of its clinical symptoms, classified by the DSM-5 as positive and negative symptoms (Association & others, 2013). Positive

symptoms include delusions, hallucinations, disorganized thinking, and abnormal motor behavior, while negative symptoms consist of diminished emotional expression, avolition, alogia, and anhedonia (refer to appendix 2 for definitions of negative symptoms)(Association & others, 2013). Onset, duration, degree of symptoms, and symptom presentation is varied, with no single sign or symptom can be used by itself to make a definitive diagnosis (refer to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition for current criteria for diagnosis)(Schultz et al., 2007). Criteria for such a diagnosis includes a duration of one month or longer of delusions, hallucinations, and grossly disorganized behavior along with a significant portion of time since onset in level of functioning in areas of interpersonal relations and work (Association & others, 2013). In terms of onset, symptoms are often gradual with patients initially going through a prodromal phase first (Schultz et al., 2007). Similarly, duration of symptoms may be just as varied (Schultz et al., 2007). These fluid features of symptomology often results in fluctuating diagnosis as indicated by 21.9 percent of those diagnosed with schizophrenia will be diagnosed with a different psychiatric disease on recurrent hospitalizations (Schultz et al., 2007). Furthermore, early diagnosis may result in a more favorable long-term outcome (Wyatt, Green, & Tuma, 1997). Reliable neurobiological and neuropsychological measures which are present even before first-episode of psychosis are an important area of research for both predictive and diagnostic purposes. Additionally, while antipsychotics are effective at treating positive and negative symptoms, patients still experience significant social and neurocognitive impairments affecting their daily functioning and outcomes (Sergi et al., 2007; Michael F. Green, Horan, & Lee, 2015;

Bellack, Morrison, Wixted, & Mueser, 1990) which places increased interest in these areas as potential therapeutic targets (Gold, 2004).

Neurocognition

According to the National Institute of Mental Health (NIMH)-Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus, there are eight separate subdomains of neurocognition relevant to schizophrenia research (Michael F. Green et al., 2004). These domains include verbal learning and memory, visual learning and memory, attention/vigilance, working memory, speed of processing, reasoning and problem solving. These dimensions of cognitive performance are dependent on discrete and identifiable neurobiological pathways in the brain (Michael F. Green et al., 2004). While neurocognition is readily described and understood, social cognition is a newer area of study and thus provides more of a challenge for defining as well as delineating specific subdomains.

Social Cognition

Humans are generally defined as social beings, with this characteristic being evolutionarily derived from the species need for collaboration and reproduction (Penn et al., 1997) . Even more crucial is its function in today's society where complex social situations are at the forefront of everyday life (Gallese, Keysers, & Rizzolatti, 2004). Although there is large variability in definitions for social cognition (SC), to be most inclusive of its vastness, it is defined as the capability of reciprocal interactions between

the self and others, holding the ability to recognize, manipulate, and behave in a socially appropriate manner (Adolphs, 2001). Within this stepwise process, in order to respond in a socially appropriate manner, an individual will need to recognize social and emotional cues, analyze the social context of the situation, mentalize the thoughts and intentions of the other, and regulate/manage their own emotional experience all to make a socially appropriate response (Adolphs, 2001). Individually, these are categorized into subprocesses such as theory of mind and emotion perception. Theory of mind is defined as the ability to infer mental states, intentions, or beliefs of another individual while emotion perception is defined as the capacity to recognize emotional expression of another person (Michael F. Green et al., 2015).

Social Cognition and its Relation to Neurocognition and Functional Outcome in Schizophrenia

A number of social cognitive subprocesses such as ToM and emotion perception indicate an overlap with specific neurocognitive processes in schizophrenia (Lam, Raine, & Lee, 2014). For example, in schizophrenia, one study showed correlations between inferring the intentions of another and executive functioning (see appendix 1 for definition of executive functioning)(Lam et al., 2014). Another study found that better emotion recognition ability of faces positively correlated with attention and verbal/spatial memory in patients with schizophrenia (Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000). However, taken as a whole, social cognition and neurocognition are thought to represent

two distinct domains and dependent, at least in part, on different neurobiological structures.

Moreover, there has been a number of studies which indicate the distinctiveness of SC from neurocognition in schizophrenia (Buchanan et al., 2005; Allen, Strauss, Donohue, & van Kammen, 2007; Pinkham, Penn, Perkins, & Lieberman, 2003; Sergi et al., 2007; Van Hooren et al., 2008). To aid in our understanding of why this may be the case, Penn et. al. (1997) outlined a number of distinctions made between the two domains (Penn et al., 1997). The first included the fact that the stimuli of neurocognition are affectively neutral and unchanging while SC stimuli involve emotions that are dynamic and constantly in a flux, and emotionally related situations are less concrete (Penn et al., 1997). The second is that neurocognition involves stimuli that are unidirectional, meaning they cannot gather information, act on, or perceive our intentions whereas SC is bidirectional (Penn et al., 1997). Further evidence of the distinction comes from psychological studies in which compared social intelligence to verbal and performance intelligence finding the two are separate (Sternberg, Wagner, Williams, & Horvath, 1995). Another type of evidence comes from neurological studies, which looked at individuals with prefrontal cortex and left amygdala damage. These studies found that despite impaired social behavior and functioning, cognitive skills such as memory recall and language were retained (Fine, Lumsden, & Blair, 2001; Anderson, Bechara, Damasio, Tranel, & Damasio, 1999). While SC and neurocognition are different domains impaired in schizophrenia, the question remains as to which provides a greater

contribution to functional outcome (refer to appendix 2 for definition, categories, and subdivisions of functional outcome). Clarifying such information would help to establish a therapeutic target for improving functional outcome in patients.

One supported hypothesis is that SC plays an intermediary role between neurocognition and functional outcome (Vauth, Rüsçh, Wirtz, & Corrigan, 2004; Brekke, Kay, Lee, & Green, 2005; Lam et al., 2014). Furthermore, a number of studies have examined the relationship between neurocognition and functional outcome, identifying the relationship as modest, with only 20-40 percent contribution from neurocognition leaving 60 to 80 percent to other contributing factors such as SC (Couture et al., 2006; Michael Foster Green, Kern, Braff, & Mintz, 2000). In terms of vocational functioning, SC was shown to have a larger impact than neurocognition (Vauth et al., 2004). Associations were also found between quality of life scales and facial affect recognition (Addington, Saeedi, & Addington, 2006). Overall, meta-analysis comparing the contribution of SC and neurocognition to functional outcome found a stronger association with SC (Fett et al., 2011). Thus, it is plausible that SC provides a greater degree of latitude as a therapeutic target for the mediation of long term outcomes (Pinkham et al., 2003). Furthermore, with its close association to functional outcome measures, SC could provide a predictive role in diagnostics. Interestingly, social dysfunctions are apparent as early as preschool in high-risk children (see appendix 1 for definition for “high-risk”)(Tarbox & Pogue-Geile, 2008; Davidson et al., 1999; Dworkin et al., 1993). Both of these applications, as a target and a predictor, would thus require measurements for the

assessment of social cognitive functioning. Before delving into the various methods for creating SC measures, a closer look at SC in schizophrenia is necessary.

Social Cognition in Schizophrenia

As part of the discussion at the National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia New Approaches Conference, a number of SC subdomains were highlighted to be the focus of continued research in schizophrenia; subdomains included emotion processing (which includes emotion perception and emotion regulation), theory of mind, social perception/context processing, social knowledge, and attributions (Michael F. Green, Olivier, Crawley, Penn, & Silverstein, 2005a). The first three will be reviewed in this study. However, we will look at Theory of Mind and social context appraisal together, and emotion perception and emotion regulation separately due to their relevance to the tasks assessed. It is important to keep in mind that these subdomains are dynamic and can also to some extent overlap.

Social Cognition: Theory of Mind and Social Context Appraisal

Theory of Mind (ToM) refers to the ability to make inferences about another's thoughts, beliefs, or intentions based on social and emotion cues, as well as social context. This ability has also been referred to as mentalizing and mental state inference at times. There is a large variation in terms of how ToM ability is assessed (ie. stimulus modality can be verbal or visual); they can be simple written stories about people

interacting, cartoon panels depicting people interacting, or people showing eye region of face, and then asking participants to infer beliefs, intentions or emotions. However, even with this variability, there is a consensus that patients with schizophrenia perform poorer in comparison to healthy controls (Penn et al., 1997). Meta-analysis indicates that both state of mind (ie. active symptoms or not) and task, lead to slight variation in performance (Bora, Yucel, & Pantelis, 2009; Sprong, Schothorst, Vos, Hox, & Van Engeland, 2007). However, performance in first-episode and high-risk patients show that deficits exist in comparison to healthy controls (Chung, Kang, Shin, Yoo, & Kwon, 2008; Koelkebeck et al., 2010). The current study was unable to identify any literature sources that investigated ToM performance in early schizophrenia patients.

Impaired emotion and social contextual information is theorized to play a mediating factor of theory of mind ability in schizophrenia (Champagne-Lavau, Charest, Anselmo, Rodriguez, & Blouin, 2012). Studies have identified deficiencies in integrating auditory and visual information to make conclusions about facial emotion expression (Jayne Green, Waldron, & Coltheart, 2007). Others have looked at the use of concurrent visual contexts to make judgements on the mental state of the individual (Jayne Green et al., 2007). Overall, social context seem to be closely associated with ToM ability (Champagne-Lavau et al., 2012; Uhlhaas, Phillips, Schenkel, & Silverstein, 2006; Simpson & Max Coltheart PhD, 2008; McCabe, Leudar, & Antaki, 2004).

Social Cognition: Emotion Perception

Emotion perception refers to an individual's ability to perceive the emotional state of another through verbal communication, body language, and/or face expression. As was the case with ToM tasks, there is considerable variation in emotion perception tasks that have been used to assess this ability in schizophrenia. Some important differentiating features of tasks relate to different modalities such as visual (facial or body language) or auditory. Emotion recognition of faces is one of the more studied areas in schizophrenia. Researchers have shown that patients have difficulties in terms of face emotion recognition (Borod, Martin, Alpert, Brozgold, & Welkowitz, 1993; Kohler et al., 2000). Patient ability to identify the intensity at which a given emotion is being portrayed in has been implicated as well (Gur et al., 2006; Kohler et al., 2003; Addington & Addington, 1998). Although these studies have varied in terms of task instructions, there appears to be a consistent deficit when it comes to detecting the emotion of faces (Penn et al., 1997) as patients have no trouble with non-affective (sex and age) face perception (Darke, Peterman, Park, Sundram, & Carter, 2013; Bortolon, Capdevielle, & Raffard, 2015).

Although longitudinal and sex differences studies in emotion perception have been less common, a few studies indicate a pattern. Deficits have been identified in individuals high-risk (see appendix 1 for high-risk definition) for schizophrenia, thus suggesting a genetic component to dysfunction (Eack, Mermon, et al., 2010).

Furthermore, impairments occur early on, research showing identifying face emotion recognition deficits after first-episode (Edwards, Pattison, Jackson, & Wales, 2001). In

terms of sex differences, male patients performed worse than females in facial emotion identification tasks (Scholten, Aleman, Montagne, & Kahn, 2005).

Social Cognition: Emotion Regulation and Management

The inherent complexity of emotion regulation and its management leads to definitional challenges. Humans are able to reach specific goals and complete tasks by being able to maintain attention toward that goal and ignore distractions presented by external and/or internal stimuli (Gazzaniga, G. R Mangun, Blakemore, & MIT CogNet\$epvider, 2014). Maintaining this attention can be defined as regulation, which is particularly important when emotional events arise. According to the “Influential model”, this control over emotion involves an interplay between emotion generation and emotion regulation (Gross, 2013). Emotion generation, consisting of coordinated behavioral, experiential, and physiological, is triggered unconsciously (Gross, 2002). Regulation can involve the increase or maintenance of positive emotions or the decrease of negative emotions through the manipulation of the rise time, magnitude, or duration of behavioral, experiential, or physiological domains (Thompson, 1991). This control can be conscious or unconscious (Boden & Baumeister, 1997; Cole, 1986). In terms of conscious control, a number of techniques can be employed; they differ based on where in the emotional timeline they are used. Strategies can either be antecedent-focused which precede the emotional response or response-focused, which take place after the emotion has already been initiated (Gross, 2002).

Response-focused techniques commonly used include cognitive reappraisal, in which an individual attaches a more favorable meaning to a situation in order to regulate the imminent emotional experience. In contrast, suppression refers to the reduction of emotion-expressive behavior once emotionally aroused. Generally, suppression has been suggested to be less effective, as it fails to regulate the experiential component of the emotion (Perry, Henry, & Grisham, 2011) whereas cognitive appraisal is associated with more favorable set of cognitive, affective, and social outcomes (M. J. Green & Malhi, 2006).

A decrease in emotion expression is also related to the negative symptoms commonly found in patients with schizophrenia (O'Driscoll, Laing, & Mason, 2014). Despite a blunted affect, patients indicate a normal emotional experience (Berenbaum & Oltmanns, 1992). The question thus becomes of whether this is the result of a deficiency in up-regulating emotion expression or overuse of certain emotion regulating techniques (Henry, Rendell, Green, McDonald, & O'donnell, 2008). While two studies have found that, relative to controls, participants with schizophrenia do not differ in their self-reported habitual use of either strategy (Henry, Rendell, Green, McDonald, & O'Donnell, 2008; Badcock, Paulik, & Maybery, 2010), greater use of suppression and lower use of reappraisal has also been reported (van der Meer, van't Wout, & Aleman, 2009). Another study found between-group differences in reappraisal, but not suppression (Livingstone, Harper, & Gillanders, 2009; Henry et al., 2008; van der Meer, van't Wout, & Aleman, 2009). In addition to inconsistent findings, neither strategy was found to be associated

with clinical ratings of blunted affect (Henry et al., 2008). Researchers have also looked toward emotional intelligence in the form of emotion management to elucidate the mechanism behind reduced emotional expression. Compared to healthy controls, schizophrenic patients had a poorer performance during an emotion management task (Kimhy et al., 2012). In addition, these findings were associated with more severe negative symptoms (Kee et al., 2009).

Interestingly, the implications of emotion regulation strategies and management abilities are relevant to social functioning. Findings in one study indicated that lower use of reappraisal was associated with greater social function impairments (Henry et al., 2008). Likewise, other studies found associations between greater use of reappraisal, less use of suppression, and better emotion management ability with better social functioning (Kimhy et al., 2012; Kee et al., 2009).

Overall, the review of SC dysfunction in schizophrenia point out that multiple subdomains seem impaired in the illness. With the understanding that SC is related to functional outcome, SC subdomains could not only be used as therapeutic targets but also, as potential measures to predict functional outcome. Creating SC measures can be done through a number of ways. One way is through exploratory factor analysis, which could indicate overlap and/or separation amongst subdomains and then identify more specific variables otherwise difficult to assess. A second method is to determine neurobiological correlates of the various social cognitive abilities. Both of these measures could also be beneficial for understanding disease etiology.

Exploratory Factor Analysis

The use of factor analysis is commonly applied to psychological sciences, which use a vast array of multivariate data in a given population. The technique is used to categorize correlated tasks and/or scores on psychological assessments into groupings. The overlap in a given grouping then reveals a codependence on a single psychological construct thus giving order and structure to the dataset. Indeed, factor analysis is a useful tool to study an array of variables or tasks in a given domain such as SC, in which unobservable characteristics may be defined in order to determine underlying deficits (Tucker & MacCallum, 1997). When structure is applied to an array of variables, relationships between them are identified which are accounted for by groupings or factors. A secondary function of this statistical technique is to use the factor scores to create measures for the unobservable constructs (Tucker & MacCallum, 1997). In addition, it is useful as a data reduction technique when researchers have large datasets. Factor analytical techniques have been previously applied to the study of SC in schizophrenia patients but due to discrepancies in factor solution, variability between the measures, and inclusion of non-validated tests, a single unifying structure for SC in schizophrenia has yet to be discovered.

A number of studies attempting to define the latent structure of SC in schizophrenia have conducted cross-sectional analyses to determine its relationship with neurocognitive ability, and suggest that the two are distinct domains in schizophrenia (Williams et al., 2008; Williams et al., 2008; Mehta et al., 2013). When looking solely at SC measures,

previous studies have found results such as 2-factor solution (1) Theory of Mind and Problem Solving/Reasoning (2) Emotional Intelligence and understanding of irony (Ziv, Leiser, & Levine, 2011), 3-factor solution (1) Interpersonal Discomfort (2) Basic Social Cognition, (3) Empathy (Corbera, Wexler, Ikezawa, & Bell, 2013), and a 2-component solution (1) Social Cognition (2) Metacognitive Awareness (Mehta et al., 2013). The lack of consistency observed in the factors could potentially be explained by the variability in the different tests used. Moreover, some subdomains (irony understanding, empathy, metacognition) included in these studies were outside the recommendations made by the MATRICS conference (Michael F. Green, Olivier, Crawley, Penn, & Silverstein, 2005b). This conference was constructed with the goal of improving the lives of individuals with schizophrenia through establishing the relative importance of SC and creating more coherent definitional terms of social cognitive subprocesses for research purposes (Michael F. Green et al., 2005a). To the best of our knowledge, only one study has followed these recommendations which uncovered a 3-factor solution (1) Hostile attributional style, (2) Lower-level social cue detection, (3) Higher-level inferential and regulatory processing solutions using tasks of Facial Emotion Identification Test, The Half-Profile of Nonverbal Sensitivity, the MSCEIT management subscale, The Ambiguous Intentions Hostility Questionnaire (an emotion attribution task), and The Awareness of Social Inference Test (a social context inference task)(Mancuso, Horan, Kern, & Green, 2011) however the first two are not validated tasks. Herein lies an opportunity to define a social cognitive structure in patients with early stage schizophrenia using only validated measures and SC domains relevant to this population.

Social Cognitive Endophenotype Markers in Schizophrenia

While the etiology of schizophrenia involves neurodevelopmental, genetic, environmental and psychosocial factors, its pathological traits are associated with abnormalities in specific brain regions. In this context, it is important to search for genetic predispositions underlying neurobiological anomalies. One promising avenue is the identification of endophenotypes. The term endophenotype has been widely adopted in psychiatric research to distinguish phenotypes that are unobservable to the unaided eye (Gottesman & Gould, 2003). The criteria to identify a useful endophenotype is that it needs to have an association with illness, be heritable, be primarily state-independent, and be found within families, which indicate inheritance patterns (Gottesman & Gould, 2003). Because social cognitive deficits precede the diagnosis of schizophrenia and are present in individuals with familial high risk for schizophrenia, SC subdomains could be particularly good endophenotypic markers for the condition (Eack, Mermon, et al., 2010; Gottesman & Gould, 2003; Michael F. Green et al., 2015).

The hippocampus and amygdala are the major subcortical structures associated with social cognitive ability (Adolphs, 2010; Rubin, Watson, Duff, & Cohen, 2014). Based on the general hypothesis that successful social behavior is dependent on memory and application of social norms, the hippocampus must play a key role in SC (Rubin et al., 2014). In mice, lesions in the hippocampus induce alterations of social behavior, which provides supportive evidence that the hippocampus is necessary to identify and remember members of a social group (Kogan, Frankland, & Silva, 2000). Furthermore,

memory functions are suggested to play a supportive role in cognitive flexibility which are quintessential to elicit a proper response in social situations (Rubin et al., 2014).

Research on the amygdala has documented its role in social behavior, emotion, and reward learning, which all belong to various domains of social cognition (Adolphs, 2010). For example, fearful and happy but not neutral faces elicit increase of activation in the amygdala (Phillips et al., 1997). A number of studies have shown that activation of the amygdala is positively correlated with the intensity of emotional facial expressions (Zald, 2003). Moreover, experimental activation of the amygdala has been shown to enhance memory of emotional stimuli (Babinsky et al., 1993). Interestingly, researchers have identified that amygdala and hippocampus activation may be involved with the encoding of emotionally charged experiences (Richardson, Strange, & Dolan, 2004).

In schizophrenia, structural abnormalities of both the amygdala and hippocampus have been found (Lawrie & Abukmeil, 1998; Levitt, Bobrow, Lucia, & Srinivasan, 2010; Shepherd, Laurens, Matheson, Carr, & Green, 2012), but the findings were variable (Shepherd et al., 2012). Specifically, structural MRI documented a reduction in hippocampal size in schizophrenia (Lawrie & Abukmeil, 1998). Other studies indicate a reduction in bilateral hippocampal and amygdala volume in patients with chronic schizophrenia (Lawrie & Abukmeil, 1998). Another group discovered smaller left hippocampal volumes in patients with chronic schizophrenia and first-episode psychosis in comparison to healthy controls (Velakoulis et al., 1999). Studies show that abnormalities are present prior to chronic status (see Appendix 1 for definition of chronic

status), thus implying a genetic and/or developmental link. In unaffected young offspring's of schizophrenic patients, the volume of the left amygdala-hippocampus complex was found to have lateralization alterations (Keshavan et al., 2002). Similarly, volume reductions in first-episode patients were found in the left amygdala in comparison to that of healthy controls (Witthaus, Mendes, Bohner, Msc, & Kalus, 2010).

Interestingly, a number of functional MRI studies have indicated alterations of hippocampus and amygdala activation in schizophrenia during social cognitive tasks. Abnormal activation of the parahippocampal gyrus, hippocampus, and amygdala have been shown to parallel deficits in the perception of facial emotions in schizophrenia compared to healthy controls (H. Li, Chan, McAlonan, & Gong, 2009; Habel et al., 2010; Gur et al., 2002; Gur et al., 2007; Holt et al., 2006). In emotion regulation tasks, the amygdala was activated while viewing emotionally negative images (ex. individuals suffering) in healthy controls but not in schizophrenia patients (Morris, Sparks, Mitchell, Weickert, & Green, 2012). To date, only one study has identified that the hippocampus is dysfunctional in schizophrenia patients during ToM tasks (Andreasen, Calage, & O'leary, 2008). This study found that compared to healthy controls, medication-free patients had lower blood flow in the posterior hippocampus during ToM tasks (Andreasen et al., 2008). Furthermore, studies have found associations between performance on ToM tasks and the amygdala, as well as the hippocampus, in patient populations with autism and with congenital left amygdala damage (Baron-Cohen et al., 1999; Howard et al., 2000; Fine et al., 2001). Furthermore, in healthy subjects, increase of activity in the

hippocampus have been shown during ToM eliciting tasks (Rilling, Sanfey, Aronson, Nystrom, & Cohen, 2004).

With the goal of determining neuroanatomical aberrations dependent on genetic predispositions, a growing number of studies have proposed that shape deformations are tied to developmental anomalies (Shenton, Gerig, McCarley, Szekely, & Kikinis, 2002; D. C. Van Essen & Drury, 1997). Morphometric scales, which are commonly utilized, are those of surface area and displacement (e.g. concavity or convexity). One study found abnormalities of hippocampus displacement in schizophrenia patients (Csernansky et al., 2002). Displacement abnormalities of the hippocampus were also found in subregions that send projections to the prefrontal cortex (Csernansky et al., 1998). In schizophrenia, inward shape deformities of the anterior hippocampus have also been associated with cortical thinning in regions responsible for visual-spatial and verbal memory pathways (Qiu et al., 2010). For both the amygdala and hippocampus, larger shape asymmetries were found to be significantly different from that of healthy controls (Shenton et al., 2002). Furthermore, a study looking at surface area of the amygdala revealed a greater amount of atrophy in multiple subregions in schizophrenia patients in comparison to psychotic bipolar patients (Mahon et al., 2015). These findings suggest that amygdala and hippocampal deformations could be the result of developmental anomalies. To the best of our knowledge, no study has investigated the link between shape patterns of subcortical structures and function in SC subdomains in schizophrenia.

In the current study, we used state-of-the-art segmentation techniques such as those of Multiple Automatically Generated Templates for different Brains (MAGeT Brain). The MAGeT algorithm, although similar to traditional techniques in its use of multiple atlases, holds a significant advantage in its ability to create template libraries using the inherent variability of the given dataset (Pipitone et al., 2014). This provides a more reliable segmentation of target brain structures (Voineskos et al., 2015). Together, investigation of the link between shape and SC subdomains using the MAGeT Brain tool, provides a novel opportunity to examine shape of the amygdala and hippocampus in schizophrenia.

Specific Aim

The current thesis had two aims. The first was to determine the SC structure of patients with early schizophrenia and to investigate its relationship with neurocognition, clinical symptoms, and functional outcome. We first performed EFA on 93 patients using only validated measures of SC and those that are relevant to the specific social cognitive deficits in schizophrenia patients. We included tasks relevant to the theory of mind, emotion perception, and emotion management. We predicted derived factors to represent these three distinct areas of SC. Furthermore, we investigated the relationships between social cognition and clinical symptoms, neurocognitive performance, and functional outcome. We hypothesized that higher scores on the different domains will correlate with a better functional outcome and neurocognitive ability, as well as lower symptomatology.

The second aim was to identify subcortical endophenotypes of SC in schizophrenia patients. Through the use of state-of-the-art segmentation instruments such as the segmenting tool MAGeT Brain, we investigated the relationship between amygdala and hippocampal shape using derived EFA factors in patients with early schizophrenia. We hypothesized a positive correlation between shape measures (ie. smaller surface area and concavity) of the hippocampus/amygdala and various social cognitive deficits.

Together, findings provided additional knowledge of the social cognitive deficits in schizophrenia. In addition, findings suggest whether various measures (both psychological and biological) of SC are appropriate to predict functional outcome.

METHODS

Subjects & Demographics

Subjects were recruited through a National Institute of Mental Health (NIMH) funded study (#MH 92440): Brain Imaging, Cognitive Enhancement and Early Schizophrenia (BICEPS). The total number of subjects recruited was 126. Subjects were recruited from well-established early course treatment programs and referral sources in Boston and Pittsburgh. Patients with either schizophrenia and schizoaffective, as verified by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders SCID, were included in the study. Aiming to access specifically those patients in the early course of the illness, only individuals aged 18-45 with a duration of less than 5 years from time of first psychotic symptom were included. A medication compliance of greater than 50% was also necessary for inclusion. Subjects with court ordered guardianship were not included in the study.

Social Cognition Measures

Based upon the conclusion of the MATRICS consortium (Michael F. Green et al., 2004) and Phase 3 of the Social Cognition Psychometric Evaluation (SCOPE) study, all social cognitive measures utilized in the present study are valid and reliable psychometric measures used for analyzing social cognition (Pinkham, Penn, Green, & Harvey, 2015). Furthermore, these tests measure social cognitive subprocesses that were identified to be impaired in patients with schizophrenia (Michael F. Green et al., 2005b).

Theory of Mind/Social Context Appraisal

Hinting Task (Corcoran, Mercer, & Frith, 1995). The Hinting Task accesses the participant's ability to decipher the true meaning and intent behind indirect speech. For this task, the participant read a passage presenting a social situation between two characters. There are ten passages total. The participant is then asked what is the true meaning behind one of the character's statements or actions. If on the first attempt the participant fails to provide the correct answer, a second hint is provided allowing the participant to earn partial credit. Scoring is based on number of correct answers provide, scores range from 0 to 20.

The Awareness of Social Inferences Test, Part III (TASIT)(McDonald, Flanagan, Rollins, & Kinch, 2003). The TASIT examines the participant's ability to detect lies and sarcasm, through the recognition of a visual cues. There are 16 video scenes total, each lasting from 15-60 seconds, in which actors act out an everyday social situation. After viewing each scene, the participant is asked four separate questions which deal with the thoughts, intentions, and feelings of one of the actors. Responses can be "yes", "no", or "don't know". Scoring is based on total number of correct answers provide, scores range from 0 to 64.

Face Emotion Perception.

Recognition Task (Kohler et al., 2003): Penn Emotion Recognition consisted of displaying 40 color photographs of faces depicting a given emotion (ie. happiness,

sadness, anger, or fear) or a neutral expression. In the recognition task, the participant is required to identify the correct emotion for the face presented. Scoring is based on total number of correct answers provided; scores range from 0 to 40.

Acuity Task (Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004): Penn Emotion Acuity task consisted of displaying 40 color photographs of faces depicting a given emotion (ie. happiness, sadness, anger, or fear) or a neutral expression.

Specifically, the participant is required to rate the faces on the intensity of the specified emotion. Scores are based on total correct. Scoring is based on total number of correct answers provided; scores range from 0 to 40.

Emotion Management.

Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (Mayer & Salovey, 2007).

This test, which is part of the larger MATRICS battery. The entire test consists of multiple-choice questions which access the participant's competence in a number of areas of emotional intelligence. In the test, subdomains are examined separately and have their own branch scores from which a standard score is created. The standard score was utilized which is not corrected for age or sex. While the MSCEIT tasks assess four domains of emotional intelligence only Managing emotion (Branch 4) and Using emotions (Branch 2) subtasks scores were used for the current EFA. Branch 1 was left out due a ceiling effect observed in its distribution. Branch 3 was excluded due to its inability to load onto a single factor. Managing emotions (Branch 4, tasks D and H) consists of identifying an effective emotional strategy for accomplishing a desired goal or

asks how to obtain a desired emotional outcome out of a given social situation. On the other hand, using emotions (Branch 2, tasks B and F) consists of determining how different moods impact thinking and decisions-making.

Neurocognitive Measures.

MATRICES (Nuechterlein et al., 2008). The MATRICS battery was used to assess neurocognitive function in the areas of speed of processing (Composite of Trail Making Test, Brief assessment of cognition in Schizophrenia, Category Fluency), attention/vigilance (Continuous Performance Test- Identical Pairs), working memory (Composite of Wechsler Memory Scale-III Spatial Span, Letter-Number Span), verbal learning (Hopkins Verbal Learning Test), visual learning (Brief Visuospatial Memory Test), and reasoning and problem solving (Neuropsychological Assessment Battery Mazes). First individual scores of tests were standardized, then global composite scores were derived for each of the areas. Higher scores indicate higher functioning.

Functional Measures.

Global Assessment of Functioning (GAF) (Aas, 2011). The GAF allows for assessment of an individual's overall functioning levels. Areas include psychological, social, and occupational functioning. Scale range from 0 to 100, lower values indicate lower/indicate functioning. Values are designated by clinicians.

Social Adjustment Scale (SAS)(Gameroff, Wickramaratne, & Weissman, 2012). This is a self-report scale which assesses the subject's satisfaction with their social situation.

Includes 44 items rated on a scale of 0 (good adjustment) to 5 (poor adjustment).

Domains include work, social and leisure activities, relationships with extended family, role as marital partner, parental role, and role within the family unit and global scores of work (Area 1), household (area 2), external family (area 3), social leisure (area 4), and general adjustment. Global scores are rated by a trained expert, rating the individual from 0 (excellent adjustment) to 6 (severe maladjustment). Only global scores were used for correlation analysis.

Major Role Adjustment Inventory (MRAI)(Eack et al., 2009). This is a 32-item measurement of global functioning in the areas of vocational, social, and household role. Assessment is conducted by a trained professional. Multiple scale ranges exist for this tool however, lower numbers indicate better adjustment and functioning.

UCSD Performance Based Skills Assessment (UPSA-B)(Mausbach et al., 2011).

Contrary to the other functional assessment tools, the UPSA tests actual performance.

The brief version of this task contains finance (e.g. counting change and writing checks to pay bills) and communication (e.g. using a telephone for emergency and non-emergency purposes) subscales which spans 10 to 15 minutes. The two domain raw scores are converted to a standardized score ranging from 0-50 with higher scores equating to better functioning.

Clinical Measures

Scale for Assessment of Positive Symptoms (SAPS)(Andreasen, 1984). This scale is used to assess positive symptoms of psychiatric patients, specifically designed for schizophrenia patients. Higher scores indicate a greater number of symptoms and more severe.

Scale for Assessment of Negative Symptoms (SANS)(Lyne et al., 2013; Andreasen, 1989). The SANS on the other hand, is used to assess negative symptoms of psychiatric patients. Higher scores indicate a greater number of symptoms and more severe. Only the total score without attention was used.

Brief Psychiatric Rating Scale (BPRS)(Overall & Gorham, 1962). The Brief Psychiatric Rating Scale is a 24-item clinical rating scale used to assess positive and negative symptoms of psychopathology. The scale allows for quantitative values to symptoms. Subscales include positive, negative, depression-anxiety, and agitation. Higher scores indicate a greater number of symptoms and more severe.

Statistical Analysis Factor Correlates: Neurocognition, Clinical, Functional

Outcome

All statistical analyses were conducted using IBM Statistical Package for Social Scientists (SPSS), Version 24. Data analyses were performed in four steps.

Sample Characteristics. Chi-squared and Independent T-tests were performed to examine distribution amongst demographic information between recruitment sites (Pittsburgh and Boston) in regards to age and sex.

Exploratory Factor Analysis.

Of 126 subjects recruited, 93 had completed all relevant SC tasks and were then kept from further analysis. Before Exploratory Factor analysis was conducted, each participant social cognitive task scores were also inspected for normalized distribution by looking at skewness and kurtosis. Outliers with a score more than three standard deviations from the mean have been excluded, this included only 3 subjects; a total of 93 subjects were utilized for the EFA. SC scores were then converted into Z-Scores using the mean for each site separately to control for potential site differences. For factor extraction, we used the maximum likelihood method since the primary aim was to develop factors that could reflect the structure of the larger early schizophrenia population. An orthogonal rotation (varimax) was utilized since distinct social cognitive sub-processes were reflected by the tasks thus making correlated factors unlikely. To select an appropriate number of reliable factors, the Eigenvalue greater-than-1-rule was applied as well as the examination of the scree plot. To further determine whether the correct number of factors was selected, a chi-squared test was performed to determine the difference between different levels of factor solution. Individual tasks were included on a given factor if the factor loading number was greater than 0.4.

Neurocognitive, Functional, and Clinical Factor Correlates.

Factor scores were derived by averaging z-scores of each test relevant to each factor. The composite score for each factor were then used to perform two-tailed partial pearson correlations with neurocognitive, functional, and clinical outcome data using raw or standardized scores. Site was used as a covariate for all correlations. Bonferroni correction for multiple comparisons were applied for each factor separately to keep the type I error rate below an alpha level of 0.05 for correlation analysis with neurocognition scores, functional outcome, and clinical.

Exploratory Factor Sex Comparisons.

Comparisons involving social cognitive performances, utilized independent t-tests to compare male versus female patients on each factor score.

MRI Data Acquisition

MRI study was performed on a 3.0T Siemens Trio Imaging Systems at the University of Pittsburgh, PA and Athinoula M. Martinos Center at Massachusetts General Hospital in Boston, MA. A T1-weighted 3D MPRAGE sequence was collected (voxel size of 1.0x1.0x1.2mm, TR 2300ms, TI = 900ms, TE = 2.89ms, flip angle = 90°, FOV = 256 mm, 256x256 matrix, 160 slices, slice thickness = 1.2mm). Site acquisition parameters are identical. Each brain was visually inspected for quality control of artifact and motion. From the 93 subjects included in the EFA, MRI brain scans were acquired on 74 subjects, and 44 brains were deemed fit for shape and surface area analysis after quality control process.

Hippocampal and Amygdala Segmentation

Hippocampal and amygdala segmentation was performed using MAGeT (Multiple Automatically Generated Templates) Brain, a multi-atlas technique that uses minimizes the number of atlas needed thus decreasing time and the need for expertise in manual segmentation of structures (Pipitone et al., 2014). Atlas segmentations are matched to a subset of target images to create a template library (Pipitone et al., 2014). The resulting library segmentations are then warped to target images and used using a label fusion technique (Treadway et al., 2015). Individual segmentations are then visually verified for quality control. Segmentation of 44 brains were successful and included for subsequent analysis. Outcome measures included vertex-wise measures of concavity and surface area, which define the shape of the subcortical structures (Payer et al., 2015).

Statistical Analysis: Hippocampus and Amygdala

Morphometry Correlations. Vertices-wise correlation between each factor derived from the EFA and surface area measures and convexity measures, for both the amygdala and the hippocampus, were performed using SurfStat (<http://www.math.mcgill.ca/keith/surfstat>), a statistical tool for analyzing surface-based data, implemented in MATLAB (<http://www.mathworks.com>). Each analysis used age, sex, and site as covariates, and results were FDR corrected for multiple vertices comparisons for each structure and hemisphere separately. For surface areas analysis only, total surface of the structure was also entered as covariate (Sussman, Leung,

Chakravarty, Lerch, & Taylor, 2016). Images were then visualized through the employment of Brain View2.

RESULTS

Demographics results of EFA Analysis

Results of Table 1 indicate that no significant differences exist between sites in terms of sex or age.

Table 1. Demographic Characteristics: EFA / SZ=Schizophrenia; M=Male; F=Female;

SD=Standard Deviation.

	SZ: Boston Site N=42	SZ: Pittsburgh Site N=46	P-Value
Sex			0.26
M	32	30	
F	10	16	
Age	23.93/4.436 (Mean/SD)	25.8/6.445 (Mean/SD)	0.119

Exploratory Factor Analysis

Using the Eigenvalue-greater-than-one rule and assessment of the scree plot, a three-factor solution was identified that accounted for 63.5% of the total variance. Additional analysis have been done to validate the 3-factor solution, comparing 2-factor to the 3-factor ($\Delta\chi^2=15.157$, $df=6$, $p=0.02$) and to the 4-factor ($\Delta\chi^2=6.678$, $df=5$, $p=0.25$), which shows a significant improvement from the 3-factor solution over the 2-factor, but no significant improvement from the 4-factor solution over the 3-factor. Factor loadings are

presented in Table 2 and resulted in three distinct factors, which accounted for 30.4%, 17.5%, and 15.6% of the variance respectively. Subdomains included, an emotion management factor (Factor 1) consisting of MSCEIT tasks B, D, F, and H; an emotion perception factor consisting of Penn Emotion Recognition and Acuity tasks (Factor 2); and a Theory of Mind factor consisting of the Hinting Task and the TASIT (Factor 3).

Table 2. Social Cognition Exploratory Factor Analysis / MSCEIT-B2-B=Mayer-Salovey-Caruso Emotional Intelligence Test-Emotion Facilitation (Branch)-Facilitating Thought (Task); MSCEIT-B2-F=Mayer-Salovey-Caruso Emotional Intelligence Test-Facilitating Thought (Task); MSCEIT-B4-D=Mayer-Salovey-Caruso Emotional Intelligence Test-Managing Emotions (Branch-Emotion Management (Task); MSCEIT-B4-H=Mayer-Salovey-Caruso Emotional Intelligence Test-Emotion Management (Branch)-Emotion Relations (Task); ERF-40=Penn Face Emotion Discrimination; ER-40=Penn Face Emotion Recognition; PEAT-40= Penn Face Emotion Acuity; Bolded numbers correspond to variables included in designated factor. N=93.

	Factor 1- Emotion Management	Factor 2- Emotion Perception	Factor 3- ToM
Hinting Task	-0.016	-0.025	0.683
TASIT	0.107	0.065	0.413
MSCEIT-B2-B	0.486	0.078	-0.265
MSCEIT-B2-F	0.444	0.227	-0.004
MSCEIT-B4-D	0.746	0.085	0.252
MSCEIT-B4-H	0.756	0.089	0.23
ER-40	0.047	0.853	0.081
PEAT-40	0.221	0.55	-0.008

Social Cognition Factor Correlates: Neurocognition, Clinical, Functional Outcome

Neurocognition: Through the use of two-tailed partial Pearson correlations, a number of relationships were identified between neurocognition subdomains and SC EFA factors. Each factor significantly positively correlated with MATRICS overall composite score (OCS) ($r=0.524$, $p=0.000$; $r=0.371$, $p=0.001$; $r=0.405$; $p=0.000$). Post hoc correlation analysis was then performed to examine the relationship between each factor score and individual MATRICS Composite scores for Speed of Processing (SOP), Attention/Vigilance (AV), Working Memory (WM), Verbal Learning and Memory (VLHVL), Visual Learning (VLBVM), and Reasoning/problem solving (RPS). Results are presented in Table 3. After Bonferroni correction for multiple comparisons ($p<0.008$), Factor 1-emotion management was significantly positively correlated with AV ($r=0.419$; $p=0.000$), Factor 2-emotion perception was significantly positively correlated with AV ($r=0.354$; $p=0.001$) and VLBVM ($r=0.381$; $p=0.000$), and Factor 3-Theory of Mind was significantly positively correlated with VLHVL ($r=0.491$; $p=0.000$).

Table 3. Two-tailed Partial Pearson Correlations between Neurocognition and SC

EFA/ MATRICS=Measurement and Treatment Research to Improve Cognition in Schizophrenia; SOP=speed of processing (Composite of Trail Making Test, Brief assessment of cognition in Schizophrenia, Category Fluency); AV=attention/vigilance (Continuous Performance Test- Identical Pairs); WM=working memory (Composite of Wechsler Memory Scale-III Spatial Span, Letter-Number Span); VLHVL=Verbal learning (Hopkins Verbal Learning Test); VLBVM=visual learning (Brief Visuospatial Memory Test); RPS=reasoning

and problem solving (Neuropsychological Assessment Battery Mazes); Bonferroni correction for multiple comparisons (*= $p < .05$ corrected). **Bolded**=Trending Significance ($p < .05$ uncorrected)

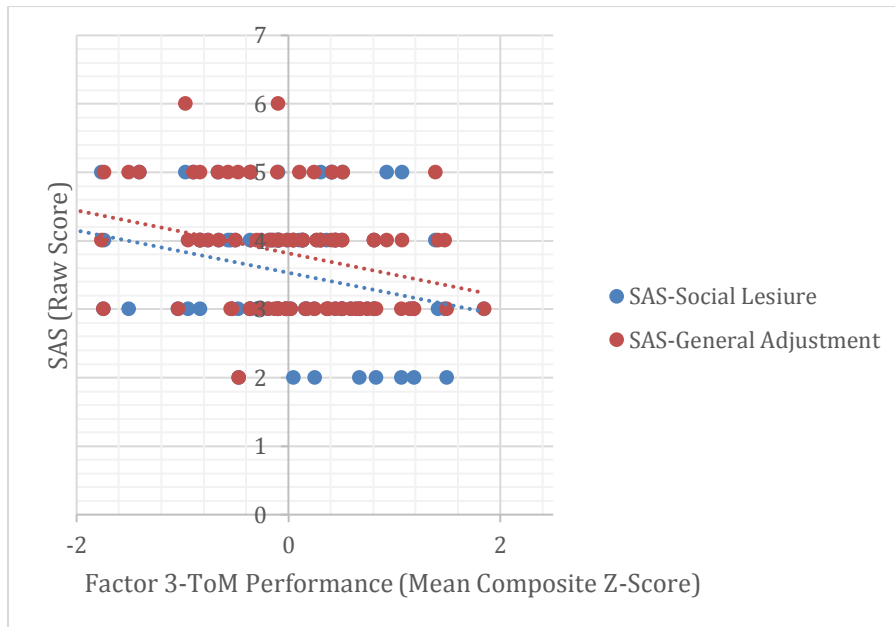
		Factor 1- Emotion Management	Factor 2- Emotion Perception	Factor 3- ToM
NeuroCognition (MATRICS)	SOP	0.135	0.144	0.194
	AV	0.419*	0.354*	0.127
	WM	0.196	0.168	0.234
	VLHVL	0.112	0.143	0.491*
	VLBVM	0.254	0.381*	0.26
	RPS	0.217	0.119	0.146
	OCS	0.524*	0.371*	0.405*

Functional outcome: Only one of the factors, Factor 3-theory of mind, was found to be correlated with functional outcome measures through the use of two-tailed partial pearson correlations: SAS-household ($r = -0.256$; $p = 0.017$), SAS-external family ($r = -0.235$; $p = 0.03$), SAS-social leisure ($r = -0.311$; $p = 0.003$), SAS-general adjustment ($r = -0.344$; $p = 0.001$), MRAI ($r = 0.246$; $p = 0.022$), and UPSA-B ($r = 0.213$; $p = 0.045$), however only SAS-general adjustment and SAS-social leisure survived Bonferroni correction ($p < 0.007$, see Figure 1). No significant or trending correlations was observed with the other two factors.

Figure 1. Two-tailed Partial Pearson Correlations between SAS and Factor 3-ToM /

ToM=Theory of Mind; SAS=Social Adjustment Scale. Linear=Line of Best Fit for the data. SAS-Social Leisure

correlation with Factor 3-ToM was significant ($r=-0.311$; $p=0.003$), SAS-General Adjustment correlation with Factor 3-ToM was significant ($r=-0.344$; $p=0.001$). Bonferroni corrected for multiple comparisons ($p<0.007$). Location was used as a covariate. SAS raw scores=higher the number, the poorer the adjustment.

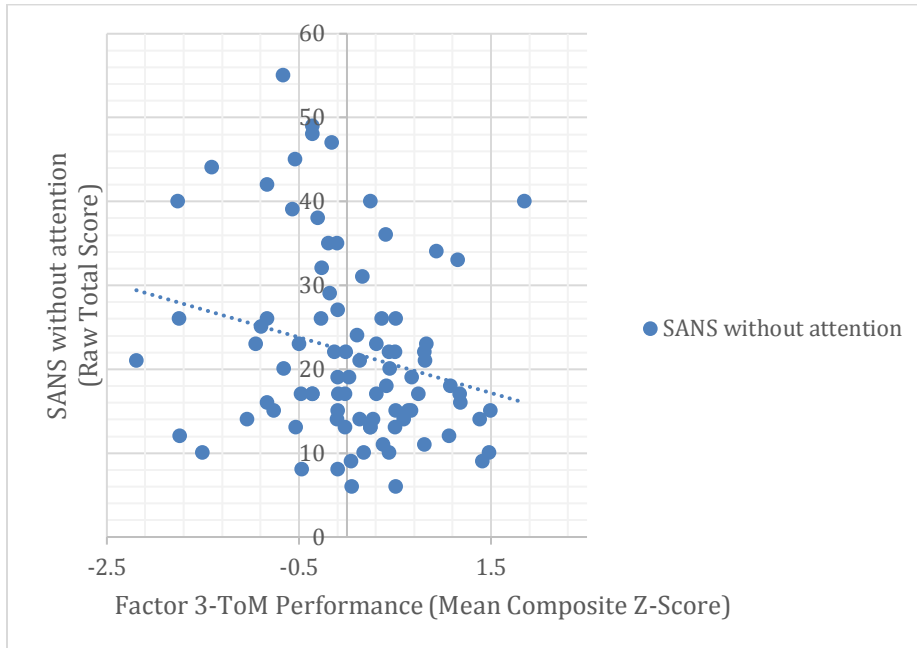


Clinical: Of all three of our factors, Factor 3-theory of mind was shown to have an inverse relationship with SANS without attention ($p=0.03$; $r=-0.233$, see Figure 2) meaning the lower the theory of mind factor composite score the more severe the negative symptoms. No significant or trending correlations were observed between any of the other two factors and SANS without attention, SAPS, or BPRS scores.

Figure 2. Two-tailed Partial Pearson Correlations between SANS without attention

and Factor 3-ToM / ToM=Theory of Mind; SANS=Scale for the Assessment of Negative Symptoms.

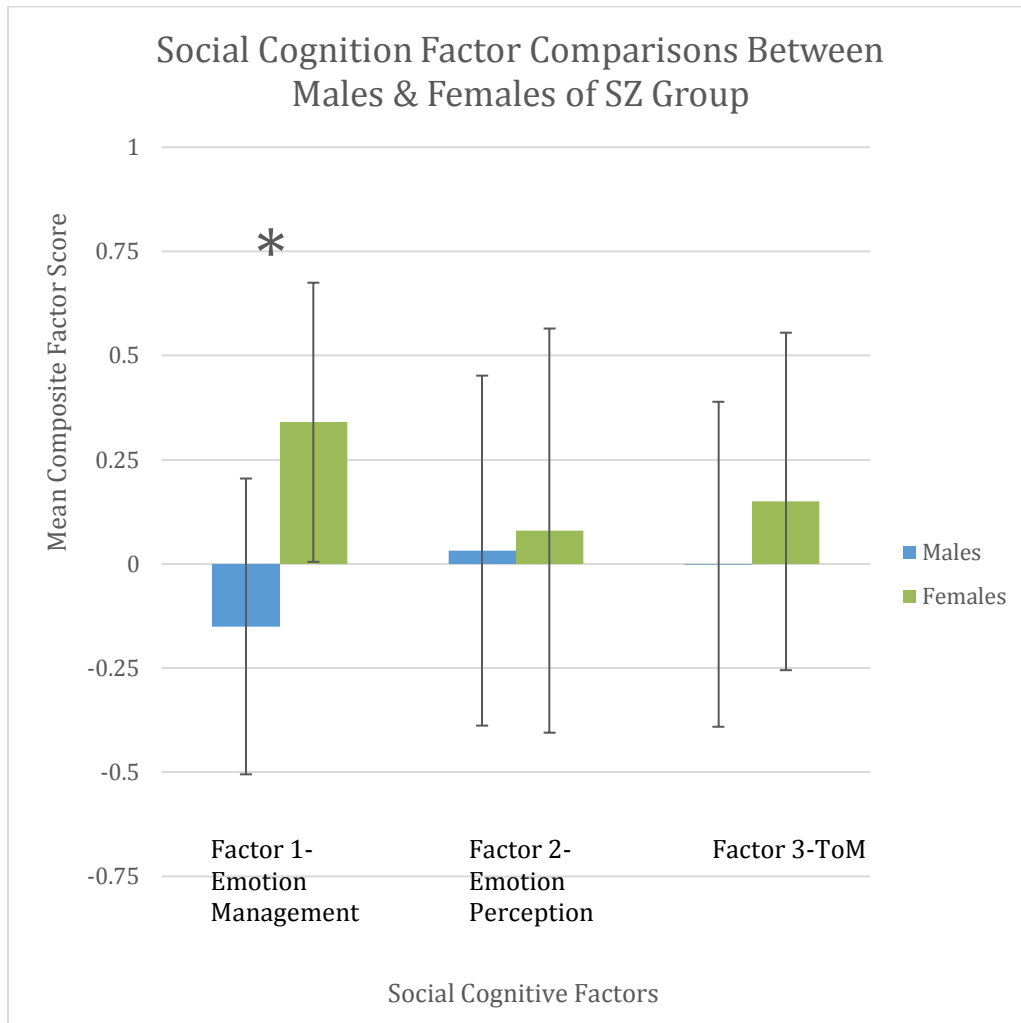
Linear=Line of Best Fit for the data. SANS without attention correlation with Factor 3-ToM was significant ($p=0.03$; $r=-0.233$). Covaried for site location. SAS raw scores=higher the number, the greater the severity of symptoms.



Social Cognition Factor Performance Comparisons

Gender comparisons indicated that only for Factor 1 was there a difference in performance ($p=0.003$); specifically, females performed better than males. Results are presented in Figure 3.

Figure 3. Male versus Female Factor Score Comparisons / Figure depicts the difference in performance between males (blue) and females (gray) on SC factor mean composite scores. Negative mean composite scores indicate poorer performance while positive indicate better performance. Significant differences existed on Factor 1-Emotion Management ($p=0.004$) but not with Factor 2-Emotion Perception or Factor 3-ToM ($p=0.714$; $p=0.43$ respectively).



Demographics: Hippocampus & Amygdala Shape Analysis

Results of Table 4 indicate that no significant differences exist between sites in the demographic domains of sex or age.

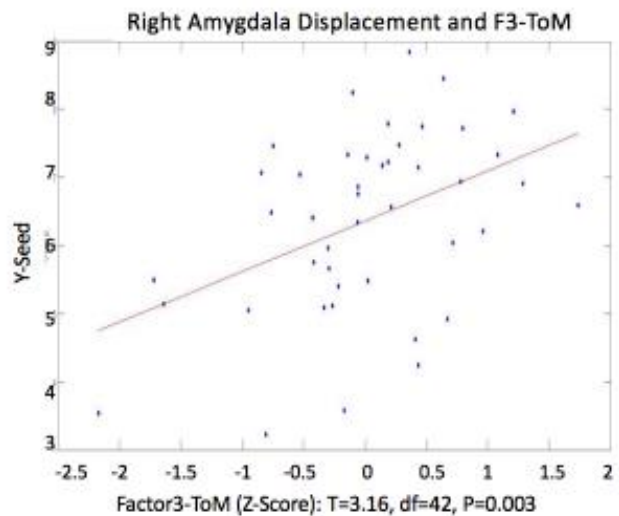
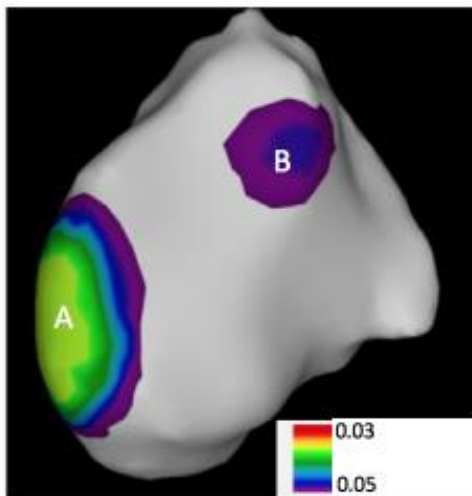
Table 4. Subjects & Demographics: Shape Analysis / M=Male; F=Female; SD=Standard Deviation.

Boston Location	Pittsburgh Site
-----------------	-----------------

	N=27	N=17	p-value
Sex			
M	19	13	0.658
F	8	4	
Age	23.22/4.1 (Mean/SD)	27.35/8.3 (Mean/SD)	0.07

Amygdala: Shape Analysis

Figure 4: Right Amygdala Displacement related to Factor 3-Theory of Mind / Image is the right amygdala shown from its medial side. Color scheme represents p-values spanning from 0.03 (red) to 0.05 (purple) FDR corrected. Colored regions are those in which there is a significant relationship between the right amygdala displacement and Factor 3-ToM. Graph indicates the relationship between performance on Factor 3-ToM (x-axis) and peak vertex, Yseed (y-axis), within the highlighted region in the image (A). X-axis values represent z-scores of the Factor 3-ToM in which higher values indicate better performance. Y-axis values represent degree of displacement in which higher values represent a greater degree of convexity. Each point on the graph represents a patient from either Boston or Pittsburgh sites.



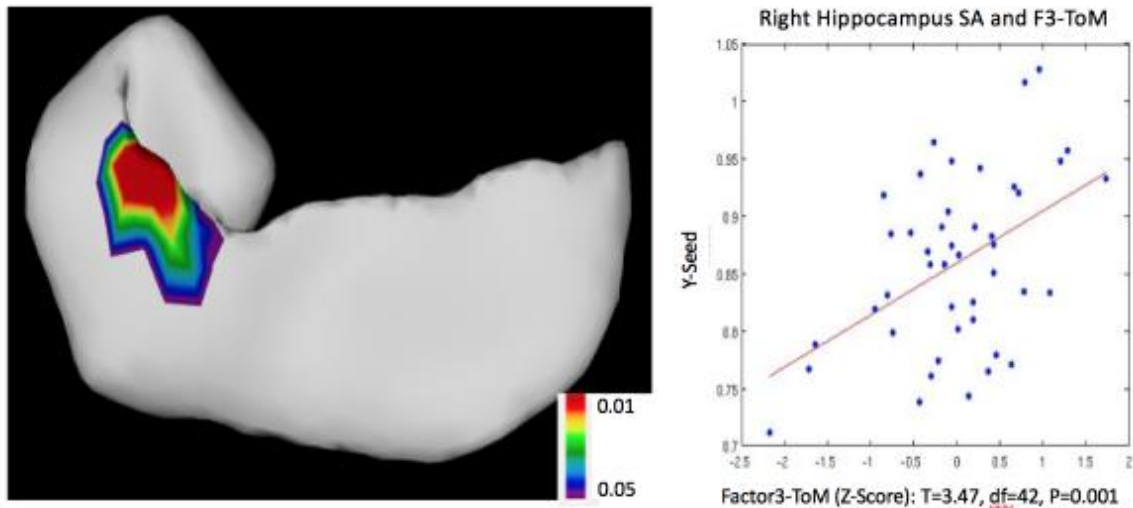
Results of right amygdala displacement indicate a significant positive correlation between the right amygdala convexity and patient performance on Factor 3-ToM ($T = -2.98$, $p = 0.005$), that is, with greater convexity of the amygdala the greater the performance in ToM. This relationship exists in two regions of the medial amygdala (Region A (more posterior) and B (more dorsal)). Results are indicated in Figure 4, and are FDR corrected for multiple comparisons using age, sex, and site as covariates.

No other significant social cognitive factor (Factor 1-Emotion Management, Factor 2-Emotion Perception, Factor 3-ToM) correlations were identified for the right or left amygdala for either displacement or surface area.

Hippocampus: Shape Analysis

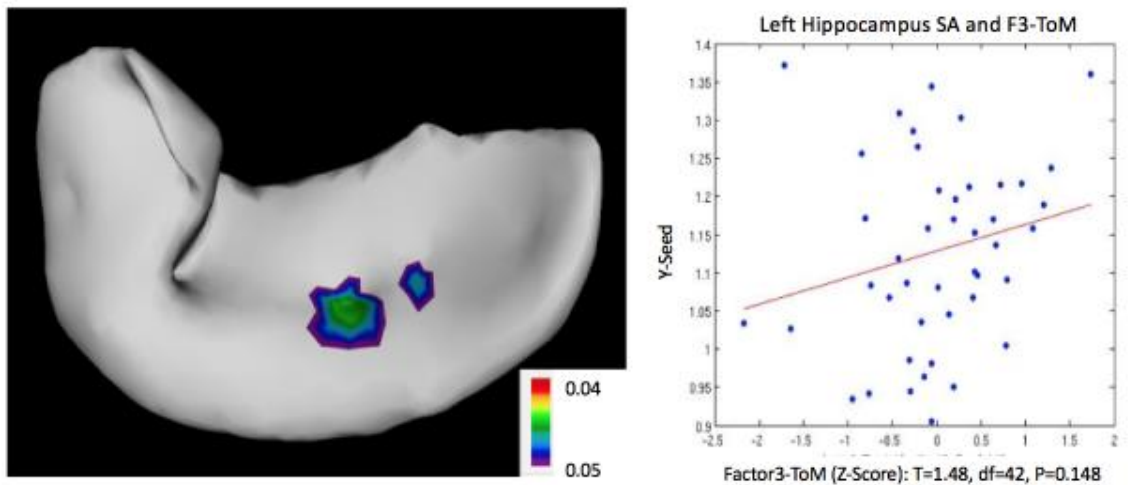
Figure 5: Right Hippocampus Surface Area related to Factor 3-Theory of Mind /

Image is the right hippocampus shown from its lateral side. Color scheme represents p-values spanning from 0.01 (red) to 0.05 (purple). Colored regions are those in which there is a significant relationship between the right hippocampus surface area and Factor 3-ToM. Graph indicates the relationship between performance on Factor 3-ToM (x-axis) and an arbitrarily picked vertex (y-axis), Yseed, within the highlighted region in the image. X-axis values represent z-scores of the Factor 3-ToM in which higher values indicate better performance. Y-axis values represent size of surface area in which higher values indicate a larger surface area. Each point on the graph represents a patient from either Boston or Pittsburgh sites.



Results of right hippocampus surface area indicate a significant positive correlation between the right hippocampus surface area and patient performance on Factor 3-ToM ($T= 3.47, p=0.001$), that is, with greater surface area the greater the performance in ToM. This relationship exists in one region of the right hippocampus, that being, dorsal-lateral surface. Results are indicated in Figure 5. This was FDR corrected for multiple comparisons using age, sex, and site location as covariates.

Figure 6: Left Hippocampus Surface Area versus Factor 3-Theory of Mind / Image is the left hippocampus shown from its medial side. Color scheme represents p-values spanning from 0.01 (red) to 0.05 (purple). Colored regions are those in which there is a significant relationship between the left hippocampus surface area and Factor 3-ToM. Graph indicates the relationship between performance on Factor 3-ToM (x-axis) and an arbitrarily picked vertex (y-axis), Yseed, within the highlighted region in the image. X-axis values represent z-scores of the Factor 3-ToM in which higher values indicate better performance. Y-axis values represent size of surface area in which higher values indicate a larger surface area. Each point on the graph represents a patient from either Boston or Pittsburgh sites.



Results indicate a positive correlation between the left hippocampus surface area and patient performance on Factor 3-ToM ($T= 1.48$, $p=0.148$), that is, with greater surface area the greater the performance in ToM (see figure 6). This relationship exists in one region of the hippocampus, that being, medial surface. This was FDR corrected for multiple comparisons using age, sex, and site location as covariates.

No other significant social cognitive factor (Factor 1-Emotion Management, Factor 2-Emotion Perception, Factor 3-ToM) correlations were identified for the right or left hippocampus for either displacement or surface area.

DISCUSSION

Social Cognition in Schizophrenia: EFA, Neurocognition, Clinical, Functional Outcome Correlates, & SC Performance Comparisons

Results in this study indicate a 3-factor structure of SC in early course schizophrenia. The factors represent three SC domains that are commonly impaired in schizophrenia, namely emotion perception, emotion management and ToM (Michael F. Green et al., 2005b). Interestingly, previous EFA studies in the SC domain of schizophrenia patients have found similar SC derived factors that we did (Eack, Greeno, et al., 2010; P. H. Lysaker et al., 2013; Ziv et al., 2011). However, these studies were limited in their ability to explain the latent structure of SC in schizophrenia patients because they included external psychological domain tasks to their factor analysis or used only a limited number of relevant SC domains. Our current results indicate more confidently that emotion perception, emotion management and ToM seem distinct SC subdomains in schizophrenia. This suggests that impairments in each of these subdomains can be due to different underlying neurological anomalies. Therefore, if SC needs to be improved, our results suggest that therapeutic approaches could gain to assess and treat subdomains accordingly rather than using broad scale methods.

An important finding from this study is that theory of mind factor demonstrates a particular relationship with functional and clinical outcome (negative symptoms). Although previous studies have identified ToM to correlate with neurocognitive and clinical symptomatology, less is known about its importance in predicting functional

outcome (Harrington, Siegert, & McClure, 2005; Pickup & Frith, 2001). Only a few studies have been conducted which indicate a potential relationship between social functioning and ToM ability (Pickup & Frith, 2001; Bora, Eryavuz, Kayahan, Sungu, & Veznedaroglu, 2006). Our results bring support to ToM being a potential moderator of functional outcome in schizophrenia patients, and thus treatment improving ToM in early schizophrenia should be encouraged.

Moreover, the present findings also improve our understanding of the dynamic interplay between neurocognitive and social cognitive deficits in early schizophrenia. Indeed, our findings suggest that SC subdomains are linked to various domains of neurocognition which coincides with previous research (Addington & Addington, 1998; Greig, Bryson, & Bell, 2004). Specifically, the emotion perception factor and emotion management factor, show a positive relationship with neurocognitive scores of attention-vigilance. As previous literature suggests, our results indicate that impaired emotion perception and management could be related to an inability to bring attention to environmental and internal emotional cues (Vuilleumier, 2005). Emotion perception factor also indicated a significant positive relationship with visual learning and memory. Although previous studies have found similar relationships between emotion perception and visual memory, they also found significant relationships with verbal memory and language abilities (Kohler et al., 2000). Further research is needed to confirm the relationships between emotion perception and neurocognitive subdomains. In terms of ToM, although there is a general consensus about impaired ToM ability in patients with

schizophrenia, it remains uncertain what aspect of cognition is responsible for the deficit. The present factor grouping of hinting task and TASIT is consistent with previous studies which hypothesized ToM deficits in Hinting task to be related to deficits in context processing (Schenkel, Spaulding, & Silverstein, 2005). Other studies have indicated patients ToM ability is dependent on processing contextual information, and suggested that this is due to an inability to integrate contextual information to form judgements about mental states (Champagne-Lavau et al., 2012). Furthermore, contextual information must be integrated with pre-existing representations based on past experiences if informed judgements about novel situations are to take place (Rubin et al., 2014). Interestingly, theory of mind factor demonstrates a specific relationship with verbal learning and memory. Our results support previous claims that verbal learning and memory is implicated as potential reasoning for impaired ToM ability in schizophrenia as well (Paulsen et al., 1995). The overlap between the hinting task and the TASIT, which is a contextual processing task that utilizes learning and memory, thus presents a greater impetus for the impairment of ToM in schizophrenia being due to contextual processing deficit.

Finally, Emotion Management factor indicated significant sex differences with females performing better than males. Sex differences in schizophrenia patient's emotion management ability reflect general findings within healthy populations, that being, women use more emotion regulation techniques (Nolen-Hoeksema, 2012). Furthermore, previous research on emotion regulation in schizophrenia has resulted in a vast amount of

variability in terms of which conscious regulation technique (reappraisal or suppression) is used to a greater extent (Henry et al., 2008; van der Meer et al., 2009). As it has already been suggested by O’Driscoll, Laing, & Mason (2014), our finding indicates that sex differences in these previous studies could be a potential cause of this disparity. Studies in the future investigating differences in regulation techniques between sexes could help explain these indiscriminant findings.

Social Cognition Factor Correlates: Hippocampus & Amygdala

Out of our three SC factors, ToM was the only one to show significant correlations with amygdala and hippocampus shape. Deficits in both ToM ability (Penn et al., 1997) and abnormalities in shape of the amygdala and hippocampus have both been identified in schizophrenia (Shenton et al., 2002; Qiu et al., 2010; Csernansky et al., 1998; Csernansky et al., 2002). Although there are a number of studies that have identified a relationship between ToM ability and the amygdala and hippocampus, few have examined this relationship in schizophrenia (Baron-Cohen et al., 1999; Howard et al., 2000; Fine et al., 2001). Furthermore, only one study was found that looked at ToM ability and shape of the structures (Andreasen et al., 2008).

It is widely known that the amygdala responds to emotionally eliciting cues in the environment (Hermans et al., 2014). However, this study did not identify a significant relationship to exist between shape measures of the amygdala and emotion perception while it did with ToM. It could be that ToM is a more cognitively taxing task requiring the integration of emotional cue recognition, memory, and context, while emotion

perception requires recognition of visual cues and thus subtle amygdala shape abnormalities are less likely to implicate emotional perception. In relation to ToM, Gerald (1961) posed a *modulation hypothesis* of the amygdala which asserted that the emotional response of the amygdala enhances the consolidation and storage of memory, and thus providing the necessary emphasis for remembering the stimulus (Gerard, 1961)(Hermans et al., 2014). This hypothesis has been supported by a number of studies since then (Hermans et al., 2014). This function of the amygdala is thought to play a role in the development of ToM ability (Gallagher & Frith, 2003). Specifically, the amygdala aids in the ability to make associations in the social world which the aids in ability to make similar associations which are necessary for mental state inference (Zald, 2003). This idea is characterized by the example of a child that recognizes of the emotion of fear in a parent during a given event, thus learning to associate that emotion with the event (Gallagher & Frith, 2003). Support for this comes from the fact that ToM acquisition partially depends on social environment; children of parents who frequently use expressions referring to mental states will develop the ability earlier, a similar relationship is observed with the presence of older siblings (Carpendale & Lewis, 2004). Other supporting evidence comes from studies indicating that patients with congenital left amygdala damage have later impaired performance on ToM tasks (Fine et al., 2001). Evidence for such a relationship existing in schizophrenia patients comes from studies which identified both amygdala abnormalities (Shenton et al., 2002) and ToM disabilities in high-risk individuals (Chung et al., 2008). The present study supports the idea that amygdala deformations are developmental in origin, in that shape of neurobiological

structures is the outcome of neurodevelopment (David C. Van Essen, 1997; Shenton et al., 2002). Thus, it may be that ToM deficits in schizophrenia stem from developmental deformations in the amygdala, which impedes acquisition of semantic material necessary for proficiency in later ToM performance. Future research should focus on longitudinal studies to determine the development of the relationship between amygdala shape and ToM ability over time in high risk individuals.

Recently, long-term, declarative, and episodic memory functions of the hippocampus have been expanded to include cognitive flexibility; a function in which previous representations are adaptively applied to current environmental context (Rubin et al., 2014). Rubin et. al (2014) recognize that although flexible cognition is typically related to executive function, decision making is also dependent on the ability to apply previously learned information to new situations to make informed judgements (Rubin et al., 2014). Cognitive flexibility relates to ToM in that the ability to perceive mental states is dependent on the ability to identify contextual cues and then integrate this information into previous representations about attitudes, knowledge, and experiences (Sabbagh, 2004). Recent research identified that impaired ToM ability was associated with cognitive flexibility in patients with schizophrenia (Champagne-Lavau et al., 2012). In addition, through its extensive network of connections with the prefrontal cortex, the hippocampus works in concert with executive functions (Simons & Spiers, 2003). Correlations between ToM ability and shape of the hippocampus in the present research suggests that impaired ToM ability in schizophrenia may reflect abnormal shape of the

hippocampus and its supportive role in cognitive flexibility. Future research should look to uncover functional relationships between prefrontal cortex areas and the hippocampus during ToM and cognitive flexibility tasks in schizophrenia.

Associations between ToM ability and functional outcome measures identified in this study and others, posits neurobiological ToM biomarkers (see Appendix 1 for definition of biomarkers), such as the shape of the hippocampus and amygdala, as promising measures for the assessment of functional outcome and the effectiveness of cognitive enhancement therapy (refer to the following link for a description of cognitive enhancement therapy (CET)(<http://www.cognitiveenhancementtherapy.com>)). Longitudinal studies aimed at investigating the effectiveness of CET could benefit from the discovery of quantitative biological markers that shows discrete changes as functional outcome improves. Shape provides a significant advantage to other measures, such as volume, in that shape provides a greater acuity to detect discrete difference, thus allowing for greater discrimination (S. Li et al., 2012). This is due to the fact that while most volumetric analyses of subcortical structures look at the entire structure, shape provides an advantage in its vertex-wise approach (Voineskos et al., 2015). Comparison studies of methodologies support this having found that while volume measures indicated no differences between populations, shape metrics did (Tamburo et al., 2009; Posener et al., 2003).

Limitations and Conclusions

Interpretation of EFA results should be made with the acknowledgement of several limitations. First, patients were all medicated and in early phase schizophrenia thus limiting inferences that could be drawn about whether or not a consistent pattern would be observed in patients who are not being medicated or chronic patients. Second, in terms of EFA, our sample size was relatively small thus bringing to question the stability of our factor structure. Next, without a SC EFA of the normal population to compare with, it is unknown of whether or not our EFA is representative of pathology or a general pattern; for future studies, it would be beneficial to make this comparison. Moreover, while the analysis of eight social cognitive tasks representing three of the subdomains for EFA is beneficial, it is not exhaustive as additional measures of SC are implicated in schizophrenia such as attribution bias and social knowledge. Future EFA should try to include all of these relevant measures.

In addition, since shape analysis measures were recommended for use as biomarkers for functional outcome, the results are limited in their ability to be used as such a measure since identified regions were not correlated with functional outcome scales. Furthermore, it remains unknown whether these relationships between ToM and subcortical structures were specific to schizophrenia or if similar associations are present in healthy populations since comparisons healthy controls were not included in this study. Lastly, it is unknown whether association between the shape of subcortical structures and ToM are unique to

early schizophrenia or whether they exist at different time points during disease progression.

Nonetheless, to the best of our knowledge, the present study was the first to investigate the social cognitive factor structure in patients with early course schizophrenia and to relate shape of the hippocampus and amygdala to SC, providing the added benefit to determining predictive markers of functional outcome. EFA results indicate that social cognitive subdomains of emotion management, emotion perception, and theory of mind are distinct in schizophrenia. Correlation analyses between these subdomains and neurocognitive, clinical, and functional measures help us better understand the relationship between these features in schizophrenia. Specifically, results suggest there is a unique relationship between ToM ability, in comparison to other SC subdomains, to functional outcome. Nonetheless, to the best of our knowledge, this was the first study to relate shape of the hippocampus and amygdala to SC. Specifically, significant correlations were also found between ToM ability and shape of the amygdala and hippocampus. These findings suggest that perhaps patients are limited in their ability to acquire relevant information necessary later ToM use. Additionally, deficits in ToM ability may be due to inadequate cognitive flexibility in early schizophrenia patients. Lastly, these results present potential measures to be used to assess functional outcome. Future research should investigate these relationships in other chronic, high-risk populations, and healthy populations as well as determine if shape correlations are related to functional outcome. Furthermore, these results establish potential SC therapeutic

targets aimed at early intervention. Future research should be in the realms of cognitive enhancement therapy, attempting to assess the factor structure over the course of treatment.

APPENDIX

Appendix 1. Definitions of Terms

- *Executive function*: refers to a set of cognitive processes to successfully perform behaviors that facilitate the attainment of chosen goals; it is also referred to as neurocognition (Diamond, 2013)
- *High-Risk*: individuals that have a first degree or second degree relative with schizophrenia
- *Chronic Status*: Individuals that been diagnosed with schizophrenia for a duration longer than 8 years.
- *Early Schizophrenia*: individuals that have been diagnosed with schizophrenia for a duration of any amount of time up until 8 years.
- *Emotion management*: the ability to utilize emotion to aid in the achievement of effectively the desired outcome in oneself (Brackett & Salovey, 2006)
- *Biomarkers*- is a biological substance which is an indication of medical state that can be measured accurately and reproducibly (Strimbu & Tavel, 2010)

Appendix 2. Definitions of Positive Symptoms & Negative Symptoms

1. Positive Symptoms

- 1.1. Delusions-fixed beliefs that are not amenable to change in light of conflicting evidence.

1.2. Hallucinations-perception-like experiences that occur without an external stimulus.

2. Negative Symptoms

2.1. Avolition- decrease in motivated self-initiated purposeful activities.

2.2. Alogia-diminished speech output.

2.3. Anhedonia-decreased ability to experience pleasure from positive stimuli.

NOTE: All definitions were taken from the DSM-V.

Appendix 3. Functional Outcome Measures/Functional outcome measures can be split into two domains (social or non-social) for which there are a number of subdomains.

Definition: all social and nonsocial skills relevant and essential to the achievement of a higher quality of life.

Social	Interpersonal skills	-eye gaze, meshing (smoothness of turn taking and conversational pauses), latency and duration of verbal responses, use of illustrative gestures and social reinforcers (Bellack et al., 1994) -fluency, interest/disinterest, clarity, focus, affect, social appropriateness (Patterson, Moscona, McKibbin, Davidson, & Jeste, 2001)
	Communication	-how to use a telephone for emergency services, call a number to acquire information, call physician to reschedule a medical appointment (Mausbach et al., 2011) -Ability to generate effective verbal content in conversation and conflict situations (Bellack et al., 1994)
	Social problem solving	-defining the goals of the individual and determining alternate solutions to hypothetical social problems. Answers rated on relevance and how likely they are to work (Bellack et al., 1994)
Non-Social	Work Skills	-work skill acquisition via index card filing and toilet tank assembly (Sergi, Kern, Mintz, & Green, 2005) -task orientation (works steadily during work period), work motivation (works at routine jobs without resistance), work conformance (conforms to rules and regulations), personal presentation (arrives appropriately dressed) (P. Lysaker & Bell, 1995)

	Basic Living Skills	<p>-count and make change for an item purchased at a store, write a check for a utility bill (Mausbach et al., 2011)</p> <p>-money management, medication management (Patterson et al., 2001)</p>
	Self-care	<p>-personal hygiene, appearance and care of clothing, care of personal possessions, food preparation/storage, health maintenance (Perivoliotis et al., 2004)</p>

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