Social deficits in schizophrenia: Pinpointing illness-and task-related factors linked to impairments

Thèse

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Résumé

La schizophrénie est une maladie invalidante caractérisée par d'importants déficits sociaux qui affecte la capacité de comprendre et d'interagir avec autrui. Plus précisément, des déficits de théorie de l'esprit, c'est-à-dire la capacité de déduire les états mentaux d'autres personnes, sont un facteur prédictif important du niveau de fonctionnement au sein de la communauté en schizophrénie. La délimitation des facteurs sous-jacents aux déficits sociaux dans la schizophrénie est donc cruciale pour améliorer les interventions. L'hétérogénéité de la présentation clinique de la schizophrénie peut influencer les habiletés sociales. Par exemple, plusieurs patients démontrent de l'anxiété sociale, et la présence de cette comorbidité peut influencer davantage leur intégration sociale. De plus, l'hétérogénéité des types de tâches utilisées pour mesurer les déficits sociaux, et notamment le degré de dépendance de ces tâches au contexte, peut affecter les déficits observés dans la schizophrénie. La présente thèse décrit trois études visant à cerner si ces composantes reliées à la pathologie et aux tâches jouent un rôle dans les déficits sociaux en schizophrénie. Cette souligne particulièrement le rôle de la théorie de l'esprit (l'habilité à inférer l'état mental d'autrui), puisque cette habilité a un lien important avec le fonctionnement en schizophrénie.

Cette thèse démontre que le trouble d'anxiété social est une comorbidité prévalente dans la schizophrénie, liée à la fois à la représentation clinique de la schizophrénie et au rang social (i.e. comment ils se comparent aux autres vis-à-vis leurs attributs personnels (chapitre 1). Globalement chez les patients atteints de schizophrénie, il est démontré que le traitement du contexte est une composante importante reliée aux déficits de théorie de l'esprit (chapitre 2). De plus, des résultats d'analyse IRMf démontrent que les patients atteints de schizophrénie présentent des activations altérées dans des régions du cerveau, telles que la jonction temporo-pariétale droite et le cortex cingulaire postérieur, lors du traitement du contexte dans des scénarios sociaux et non sociaux (chapitre 2, chapitre 3). Plus précisément, le chapitre 4 souligne que les patients ont une capacité réduite à moduler les réseaux cérébraux à grande échelle en réponse à des types de contexte différents. Le traitement du contexte peut représenter un déficit fondamental en schizophrénie qui pourrait être une cible lors d'interventions futures visant à améliorer les capacités sociales. Globalement, cette thèse souligne l'importance de prendre en compte l'hétérogénéité à la fois dans la schizophrénie et dans les tâches de la théorie de l'esprit dans de futures recherches sur le traitement social de la schizophrénie, en soulignant spécifiquement le rôle important du trouble de l'anxiété sociale et du traitement du contexte.

Abstract

Schizophrenia is a highly disabling disorder characterized by significant social deficits that impair one's ability to interact with and understand others. Specifically, impairments in Theory of Mind, i.e. the ability to infer the mental states of others, are an important predictor of community functioning in schizophrenia. Delineating the factors underlying social deficits in schizophrenia is thus crucial to developing improved treatment targets for functioning. Heterogeneity in the clinical presentation of schizophrenia may influence one's social abilities. For instance, many patients also present with social anxiety, and this comorbid presentation may further affect their abilities to integrate in the social world. Additionally, heterogeneity in the types of tasks used to measure social deficits, and notably, the degree to which these tasks rely on context, may affect deficits observed in schizophrenia. The present thesis describes three studies that aim to pinpoint whether these illness- and task-related components play a role in social deficits in schizophrenia, with a particular focus on Theory of Mind abilities.

This thesis demonstrates that social anxiety disorder is a prevalent comorbidity in schizophrenia related to both the clinical presentation of schizophrenia and to social rank (i.e. how they rank themselves compared to others on personal attributes; Chapter 1). In patients with schizophrenia overall, results also highlight that context processing is an important component related to deficits on Theory of Mind tasks (Chapter 2). Additionally, fMRI results demonstrate that patients with schizophrenia display altered activation in brain regions (e.g. right temporo-parietal junction, posterior cingulate cortex) during processing context in social and non-social scenarios (Chapter 2, Chapter 3). Specifically, Chapter 3 highlights that patients have a reduced ability to modulate large-scale brain networks in response to different types of context. Context processing may represent a core deficit in schizophrenia that could be a target in future interventions to improve social abilities. Overall, this thesis underlines the importance of considering heterogeneity in both schizophrenia and in Theory of Mind tasks in future research of social processing in schizophrenia, specifically highlighting the important role of social anxiety disorder and context processing.

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List of abbreviations

ACC: anterior cingulate cortex

BOLD: Blood Oxygen Level Dependent

Con: congruent conditions (REMICS task)

COST: Combined Stories test

CPCA: Constrained Principal Component Analysis

dlPFC: dorsolateral prefrontal cortex

dmPFC: dorsal medial prefrontal cortex

DMN: Default Mode Network

DSM: Diagnostic and Statistical Manual for Mental Disorders

dTPJ: dorsal temporo-parietal junction

EPI: echo-planar imaging

FEF: frontal eye field

fMRI: functional magnetic resonance imaging

FP-PFC: frontopolar prefrontal cortex

HC: healthy control

HRF: hemodynamic response function

ICD: International Classification of Disease and Related Health Problems

Inc: incongruent conditions (REMICS task)

LSAS: Liebowitz Social Anxiety Scale

MNI: Montreal Neurological Institute

mPFC: medial prefrontal cortex

PANSS: Positive and Negative Syndrome Scale

PET: positron emission tomography

PCC: posterior cingulate cortex

PFC: prefrontal cortex

Phy: physical conditions (REMICS task)

PhyCon: physical congruent condition (REMICS task)

PhyInc: physical incongruent condition (REMICS task)

SAD: social anxiety disorder

SCID: Structured Clinical Interview

SCOPE: Social Cognition Psychometric Evaluation Study

SCS: Social Comparison Scale

SMA: supplementary motor cortex (SMA)

Soc: social conditions (REMICS task)

SocCon: social congruent condition (REMICS task)

SocInc: social incongruent condition (REMICS task)

SPM: Statistical Parametric Mapping

SZ: schizophrenia

SZ+: individuals with schizophrenia plus social anxiety disorder

SZ-: individuals with schizophrenia minus social anxiety disorder

SZ-SAD: individuals with schizophrenia without social anxiety disorder

SZ+SAD: individuals with schizophrenia plus comorbid social anxiety disorder

ToM: Theory of Mind

TPJ: temporo-parietal junction

TTG: transverse temporal gyrus

vlPFC: ventrolateral prefrontal cortex

vmPFC: ventral medial prefrontal cortex

vTPJ: ventral temporo-parietal junction

WCST: Wisconsin Card Sorting test

“However, it is critical to be aware that the path schizophrenia pursues is particular to each person afflicted. Frequently, there is no attempt made to explore beyond the illness. It is often forgotten that there is a person behind the condition, with a fundamental need to be understood. [..] We must be seen as individuals and not regarded as just a collection of symptoms. With the instigation of more constructive approaches and inspired care, our pain and anguish may begin to be contained. Only then will the balance be redressed and societies' ignorance brought to an end.”

Anonymous, First-person account (Schizophrenia Bulletin, 2(4), 1996)

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Foreword

The present thesis details three studies completed by the first author between 2013 to 2018 as part of her doctoral thesis in Neurobiologie at Université Laval.

The first study is detailed in the article "Social anxiety disorder in recent onset schizophrenia spectrum disorders: The relation with symptomology, anxiety, and social rank," which was published in *Psychiatry Research* in 2015. This study assesses 42 patients with schizophrenia who were recruited from the Clinique Notre-Dame-des-Victoires of the Institut Universitaire en Santé Mentale de Québec to determine the role of social anxiety disorder comorbidity in schizophrenia. This project represents a collaboration with Dr. Amélie Achim and Dr. Marc-André Roy. Participant recruitment and testing was supervised by Dr. Amélie Achim and Dr. Marc-André Roy, and data analysis, interpretation, manuscript preparation and revision was performed by the first author.

The second study is titled "Deficits on ToM tasks in individuals with schizophrenia: More than just errors in social information processing" and presents results from 19 healthy control participants and 25 patients with schizophrenia recruited from the local community and outpatient clinics of the Centre Intégré universitaire de santé et de services sociaux de la Capitale-National. This study reports altered brain activation in patients with schizophrenia as compared to healthy controls while performing an fMRI task assessing social and context-based processing. fMRI results from this task for the 19 control participants were reported in the article published in *Cortex* in 2016 by Lavoie, Vistoli, Sutliff, Jackson, & Achim (2016) titled "Social representations and contextual adjustments as two distinct components of the Theory of Mind brain network: Evidence from the REMICS task."

The final study reported in this thesis is titled "Functional connectivity analysis reveals disruption of large-scale networks during a ToM task in patients with schizophrenia." This study presents an additional fMRI analysis using Constrained Principal Component Analysis (CPCA) with the same participants as the second study (with the addition of one more healthy control, i.e. a total of 20 participants in the control group).

The second and third studies were part of a project that was a collaborative effort between the laboratories of Dr. Amélie Achim and Dr. Philip Jackson. The recruitment of participants and testing was performed by Dr. Damien Vistoli, Dr. Marie-Audrey Lavoie, and the first author, with additional collaboration from Élisabeth Thibaudeau and Andréanne

Parent. For these studies, the first author was responsible for database management, data analysis, interpretation of clinical, cognitive, and fMRI results, as well as the development of the manuscripts.

General Introduction

Schizophrenia is a highly disabling disorder that affects 0.3 to 0.7% of the population worldwide (American Psychiatric Association, 2013; Murray & Lopez, 1997). Individuals with schizophrenia present with a combination of cognitive, behavioral, and emotional disturbances, as well as impaired functioning (American Psychiatric Association, 2013). Particularly, impaired social deficits are a hallmark of the disorder. Individuals with schizophrenia are thus less likely to have meaningful social relationships (MacCabe, Koupil, & Leon, 2009; Stevens, Mcnichol, & Magalhaes, 2009), to attain the same level of education as their healthy peers (Kessler, Foster, Saunders, & Stang, 1995), and to hold employment throughout adulthood (Harvey et al., 2012). Social deficits persist even after remission in patients with schizophrenia (Bora, Yücel, & Pantelis, 2009; Fiszdon, Fanning, Johannesen, & Bell, 2013) and thus remain an obstacle to improved functioning and re-integration within the community in schizophrenia.

1.1 Schizophrenia

1.1.1 Clinical presentation

Individuals with schizophrenia often experience a prodromal period in childhood and/or early adolescence preceding clinical diagnosis. During this period, individuals may exhibit behavioral and affective disturbances, such as anxiety or depression, as well as intermittent psychotic symptoms (Addington et al., 2015; Ruhrmann et al., 2010). Although these symptoms themselves are not severe enough or of sufficient duration to constitute a diagnosis of schizophrenia, they are typically associated with reduced quality of life and social impairments (Larson, Walker, & Compton, 2011; McGlashan, Miller, & Woods, 2001; Schultze-Lutter, Ruhrmann, Berning, Maier, & Klosterkötter, 2010).

Clinical schizophrenia tends to emerge in late adolescence to early adulthood, with the peak age of onset in the early-to-mid 20's for males and late 20's for females (American Psychiatric Association, 2013). The trajectory of schizophrenia varies greatly from person to person, but the majority of cases present slowly and insidiously with periods of symptom exacerbations, followed by periods of remission (American Psychiatric Association, 2013). The majority of individuals with schizophrenia tend to have lifelong impairments (Harrison et al., 2001; Jobe & Harrow, 2005; Lang, Kösters, Lang, Becker, & Jäger, 2013).

Schizophrenia symptoms were traditionally categorized into at least two groups: positive symptoms (i.e. an augmentation of typical cognition) and negative symptoms (i.e. a reduction of typical cognition). Positive symptoms include hallucinations and delusions. Hallucinations can take visual or auditory form, although auditory is the most frequently reported among patients (Bracha, Wolkowitz, Lohr, Karson, & Bigelow, 1989). Delusions can present as bizarre, persecutory, or grandiose, with persecutory being the most common (Bentall, Corcoran, Howard, Blackwood, & Kinderman, 2001; Garety, Everitt, & Hemsley, 1988). Common negative symptoms of schizophrenia include flattened affect, stereotyped thinking, and avolition. Although positive symptoms are perhaps the most dramatic symptoms of the disorder, negative symptoms are more powerful predictors of a poorer outcome and are an important feature of the illness (Fervaha, Foussias, Agid, & Remington, 2014; Verma, Subramaniam, Abdin, Poon, & Chong, 2012).

1.1.1.1 Measuring & diagnosing schizophrenia: Assessing symptoms

A diagnosis of schizophrenia is made on clinical presentation as well as chronology of symptoms and disabilities, as there is currently no neurobiological marker which definitively identifies schizophrenia. Therefore, when faced with a person presenting with symptoms of schizophrenia, clinicians must turn to established guidelines, such as the Diagnostic and Statistical Manual for Mental Disorders V (DSM-5; American Psychiatric Association, 2013) or the International Classification of Disease and Related Health Problems 10 (ICD-10; World Health Organization, 1992). These guidelines are based on decades of research and have been developed by some of the leading experts in the field. The DSM-5 criteria are the most commonly used in Canada and the United States and will therefore be the primary source addressed in this thesis. The DSM-5 lists six main guidelines (A-F) for a schizophrenia diagnosis: (A) a person presents with two of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms; (B) these symptoms are associated with reduced functioning in work, interpersonal relations or self-care; (C) the disturbance lasts for at least six months; (D) the disturbance is not better attributable to bipolar or depressive disorder; (E) the disturbance is not better attributable to physiological effects of a substance or another medical condition;

and lastly, (F) the disturbance is not better attributable to autism spectrum disorder or a communication disorder (American Psychiatric Association, 2013).

The DSM-5 guidelines for diagnosis highlight that there is not one clinical symptom that can be used to identify schizophrenia. An individual with schizophrenia may present with predominantly psychotic symptoms, predominantly negative symptoms, or a mix of the two, and two patients with schizophrenia may not have a single symptom in common. Although there have previously been attempts to identify subtypes of schizophrenia based on similar types of symptoms (i.e. catatonic, disorganized, or deficit syndrome types), decades of research has not found a standard method to categorize individuals into subtypes, nor has it found strong evidence that there is homogeneity among the subtypes (Braff, Ryan, Rissling, & Carpenter, 2013; Heckers, Tandon, & Bustillo, 2010). As such, in the 2013 upgrade of the DSM-IV to the DSM-5, these subtype classifications were removed (American Psychiatric Association, 2013).

Within the DSM-5, schizophrenia is categorized along the broader category of schizophrenia spectrum disorders, which includes related disorders, such as schizophreniform, schizoaffective, and delusional disorders (American Psychiatric Association, 2013). Schizophrenia spectrum disorders have unique diagnostic features but are similar in that they feature psychotic symptoms, accompanied by substantial impairments in functioning. Additionally, there is growing evidence that schizophrenia spectrum disorders carry common genetic markers (for a review, see Owen, Craddock, & Jablensky, 2007), leading some researchers to question the usefulness of diagnosing specific disorders on the schizophrenia spectrum. Instead, they propose that disorders of the schizophrenia spectrum should be looked at just as they are called -- on a spectrum (Heckers, 2009; Malhi, Green, Fagiolini, Peselow, & Kumari, 2008). Such an approach to schizophrenia has been shown to have greater validity (Peralta & Cuesta, 2008), as well as to provide a more detailed description of clinical characteristics which can be used for improved treatment recommendations (van Os et al., 1999).

Importantly, differences in patients' symptomatology, have large impacts on long-term outcomes (Fenton & Mcglashan, 1991; Joseph Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009). Symptoms affect an individual's treatment needs (P. J. Weiden, 2007), occupational status (Bejerholm & Eklund, 2005), and social functioning (Lysaker &

Davis, 2004).

In research settings, clinical symptoms for schizophrenia-related disorders are often measured via semi-structured interviews. These interviews contain strategic questions which allow the researcher to gain the information needed from the patient to rate the severity of schizophrenia symptoms in a presenting patient. For instance, the Positive and Negative Syndrome scale (PANSS) is a brief interview that takes around 45 minutes to administer and assesses the severity of 30 common symptoms of schizophrenia (Kay, Fiszbein, & Opler, 1987). Each symptom is rated on a scale from 1 (the symptom is absent) to 7 (the symptom is present and is extreme). The PANSS divides symptoms into 'positive' and 'negative' categories, as well as a third category for 'general psychopathology'. Within this third category of the PANSS are symptoms such as disorganization, poor attention, lack of judgment and insight, social avoidance, and anxiety (Kay et al., 1987). However, to look more closely at the symptomatology of patients, several studies have performed factor analyses and suggested that PANSS is more accurately examined using five subcategories, adding categories such as disorganization/anxiety, excitement/hostility, or cognitive symptoms (Lehoux, Gobeil, Lefèbvre, Maziade, & Roy, 2009; van der Gaag et al., 2006).

The idea that the complexity of schizophrenia expands beyond rigid categorical boundaries has been acknowledged in the 2013 update of the DSM-5 (American Psychiatric Association, 2013). Diagnostic guidelines for schizophrenia now recommend that patients be evaluated on eight dimensions, which include, in addition to classic psychotic symptoms (e.g., hallucinations, delusions), depression, mania, and impaired cognition. These factorial or dimensional methods of symptom assessment can have important implications for studies of anxiety and cognitive disturbances in schizophrenia, areas which have until recently been largely underrepresented in the schizophrenia literature.

1.1.1.1.1 The importance of cognitive symptoms

Cognition is the sum of all processes necessary for information acquisition and processing (M. Green, Horan, & Lee, 2015; Heinrichs, 2005; E. K. Miller & Wallis, 2010). As can be deduced from this broad definition, cognition encapsulates processes from basic memory to executive function to cognition required for social interactions (i.e. Theory of Mind; see Section 1.2.2). In schizophrenia, cognitive deficits are increasingly recognized as an important feature to understand the pathophysiology of schizophrenia and to develop treatments that will improve patients' lives (Cannon, 2015; M. Green et al., 2015; Nuechterlein et al., 2008). Cognitive deficits are present in unaffected first-degree relatives (Lavoie et al., 2013; Snitz, MacDonald, & Carter, 2006) and are present before the onset of psychotic symptoms in patients who later develop schizophrenia (Hambrecht, Lammertink, Klosterkötter, Matuschek, & Pukrop, 2002; Simon et al., 2007). These cognitive deficits also last throughout the course of the disorder (Fioravanti, Bianchi, & Cinti, 2012; Savla, Vella, Armstrong, Penn, & Twamley, 2013), and even persist in remission (Balogh, Égerházi, & Berecz, 2015; Mehta et al., 2013). Thus, in contrast to positive and negative symptoms which fluctuate over time, deficits in cognition remain a stable disabling feature in individuals with schizophrenia.

1.1.1.1.2 Comorbid conditions

In addition to the classic symptoms of schizophrenia, patients often present with comorbid symptomatology (American Psychiatric Association, 2013). The complex, encompassing symptoms of schizophrenia, however, can make it difficult to determine if a presenting symptom is related to schizophrenia or if it is, rather, part of a distinct, comorbid disorder. For instance, while anxiety is a classic symptom of schizophrenia (contained within the 'general psychopathology' subsection of the PANSS), comorbid anxiety disorders are also quite common in schizophrenia, with prevalence rates in schizophrenia of 12.1% for obsessive-compulsive disorder (Achim et al., 2011) and up to 47.5% in social anxiety disorder (Roy et al., 2015). To make a comorbid diagnosis such as an anxiety disorder in schizophrenia, the DSM-5 states that the symptoms should not be better accounted for by psychopathology linked to schizophrenia (American Psychiatric Association, 2013). Therefore, the diagnostic criteria for the additional disorder should be met in full and not restricted to symptoms of schizophrenia.

1.1.2 The schizophrenic brain

1.1.2.1 Genes and the environment: the neurodevelopmental model

Schizophrenia is believed to arise from a complex interplay between genetic and environmental factors (Tsuang, Stone, & Faraone, 2001; Van Os, Rutten, & Poulton, 2008).

While the exact mechanism by which genetic and environmental risks ultimately lead to schizophrenia is unknown, a leading explanation is the neurodevelopmental model of schizophrenia, which states that genetic and environmental factors combine to alter vital neurodevelopmental processes early in life, eventually leading to long-term structural and functional abnormalities (Murray & Lewis, 1987; Rapoport, Giedd, & Gogtay, 2012; Singh, McDonald, Murphy, & O'Reilly, 2004; Tsuang et al., 2001; Weinberger, 1987).

During normal brain development, there are several vital stages, at which environmental insults could alter the trajectory of brain development. For instance, given that brain development begins as early as the second gestational week (Stiles & Jernigan, 2010), risk factors occurring early in the prenatal stage could lead to structural and functional complications of schizophrenia later in life (Murray, Jones, & O'Callaghan, 1991). For instance, prenatal exposure to influenza (Brown & Derkits, 2010), maternal stress (Malaspina et al., 2008; van Os & Selten, 1998), and maternal nutritional deficiency (Brown & Susser, 2008) have all shown an association with increased schizophrenia risk. Postnatal brain development is marked by an overproduction of synapses and gray matter as the brain rapidly develops, followed by pruning processes where redundant and inefficient connections are eliminated in the favor of optimal brain functioning (Chechik, Meilijson, & Ruppin, 1999). Pruning within the prefrontal cortex (PFC) and association areas continues through adolescence, with the dorsolateral prefrontal cortex (dlPFC), important for higher-level functions such as executive functions and decision-making, being the last brain region to fully mature (Gogtay et al., 2004; Huttenlocher & Dabholkar, 1997). These neurodevelopmental processes may be altered by various factors that have shown an association with schizophrenia, including early childhood trauma (Read, Van Os, Morrison, & Ross, 2005) social defeat and isolation (Selten, Van Der Ven, Rutten, & Cantor-Graae, 2013), psychosocial stress (Pruessner, Cullen, Aas, & Walker, 2017), and drug abuse during adolescence (Henquet, Murray, Linszen, & Van Os, 2005). In adolescence, excessive synaptic pruning in the PFC may result in a loss of plasticity and altered neuronal communication associated with symptoms of schizophrenia (Feinberg, 1982; Keshavan & Hogarty, 1999; Mcglashan & Hoffman, 2000). Postmortem findings in schizophrenia do in fact show reduced dendritic spine density on the pyramidal cells of the prefrontal cortex, suggesting that pruning may be an important neurodevelopmental process associated with schizophrenia (Glantz & Lewis, 2000).

Notably, environmental factors do not, on their own, lead to schizophrenia, as brain development proceeds based on programmed instructions within the genetic code. Large-scale genetic studies in recent years have unveiled several genetic factors that are associated with increased schizophrenia risk (e.g. the International Schizophrenia Consortium, 2009 and (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Many of these genetic mutations are implicated in processes vital for healthy brain development, such as synaptic plasticity and glutamate signaling (for a review of genetic studies and findings in schizophrenia, see Kavanagh, Tansey, O'Donovan, & Owen, 2015). Hence, the current state of the literature suggests that it is a combination of environmental and genetic susceptibility that may alter important developmental processes and eventually lead to the neural and, as a consequence, behavioral abnormalities associated with schizophrenia (Singh et al., 2004).

1.1.2.2 Gray and white matter abnormalities

Individuals with schizophrenia show extensive structural brain alterations. Although there have been hundreds of studies assessing structural abnormalities in schizophrenia, a systematic review (Shepherd, Laurens, Matheson, Carr, & Green, 2012) examined the evidence of previous reports, as well as the quality of those reports, and showed that the most common brain abnormalities found throughout the course of schizophrenia include gray matter reductions in the anterior cingulate, medial and inferior frontal regions, temporal lobes, hippocampus and amygdala, thalamus, and insula. Reduced white matter integrity is also observed in several long-range tracts vital to inter-regional communication within the brain. These tracts include those connecting frontal and temporal regions (i.e. the uncinate fasciculus; Burns et al., 2003; Mori et al., 2007), frontal and parietal regions (i.e. the arcuate fasciculus; Burns et al., 2003), and frontal and striatal regions (de Leeuw, Bohlken, Mandl, Kahn, & Vink, 2015).

While gray and white matter abnormalities have been observed in both first episode psychosis and chronic schizophrenia, factors such as the duration of illness and long-term use of antipsychotic medications may also contribute to progressive structural decline in some brain areas (Bora et al., 2011; Pantelis et al., 2005). Furthermore, the role of symptoms in these abnormalities also remains unclear (Shepherd et al., 2012), but a meta-analysis by Bora et al (2011) of 79 studies suggests an association between the level of negative symptoms and gray matter loss in schizophrenia.

1.1.2.3 Functional abnormalities

Given widespread structural abnormalities, one may also expect to find functional abnormalities associated with these alterations. Unfortunately, there is no simple definitive relationship between reduced gray matter or white matter integrity and functional consequences, due to the complexities of the neuronal organization and communications (Messé, Rudrauf, Benali, & Marrelec, 2014). [1] There are, however, several streams of research that have aimed to assess functional abnormalities associated with schizophrenia. While this research is exhaustive and has uncovered many interesting findings in schizophrenia, the full spectrum of findings is outside the scope of this section; this thesis will provide a brief overview of some of the most common and potentially relevant findings.

One of the most commonly studied functional abnormalities in schizophrenia (Karlsgodt, Sun, & Cannon, 2010) are alterations in the prefrontal cortex. Particularly, a common finding is that individuals with schizophrenia show reduced activation within the dlPFC during both executive function and memory tasks (Barch & Ceaser, 2012; Kraguljac, Srivastava, & Lahti, 2013; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Furthermore, during memory encoding and retrieval tasks, patients also display abnormal activation in the medial temporal lobe, including the hippocampus and parahippocampal gyrus; however, some studies have found reduced activation (Heckers et al., 1998, 1999), while others have found increased activation in these regions (Ragland et al., 2009) in schizophrenia. Given that altered regional activation of prefrontal and temporal regions are both frequently found together in schizophrenia, it has also been suggested that patients with schizophrenia experience abnormal top-down control from the frontal cortex, leading to compensatory

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[1] An interesting way to visualize the relation between structure and function within the brain is to think of a system of roads (Messé et al., 2014). In this metaphor, the structural anatomy, including the shape and clustering of the neurons are the 'roads' while the electrical and chemical signals that pass through this structure and support various cognitive functions are the 'traffic' passing along these roads. Importantly, although the two are related, one cannot predict the other.

mechanisms in the temporal lobe (Kraguljac et al., 2013). In patients with schizophrenia, reduced activation of the anterior cingulate cortex (ACC), a region that is central in error-detection and cognitive control, is also a consistent finding among cognitive tasks (Adams & David, 2007). This region may be a vital part of a control loop that provides feedback to the lateral prefrontal cortex to modulate future cognitive processing (Lesh, Niendam, Minzenberg, & Carter, 2011).

To gain a more global view of how brain regions interact in schizophrenia, studies of resting-state connectivity (i.e. intrinsic connectivity in the absence of a specific cognitive stimulus) have highlighted important alterations in two networks (see Sheffield & Barch, 2016 for a review): (1) a circuit linking the PFC (i.e. mPFC, ACC, dlPFC), cerebellum, and thalamus which supports cognitive control and error monitoring (Ide & Li, 2011) and (2) a task-negative network whose activity decreases in response to cognitive load (Raichle et al., 2001). The task-negative network, commonly referred to the Default Mode Network (DMN; (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001) consists of nodes in the mPFC and posterior cingulate cortex (PCC) and is activated in response to 'stimulus-independent thought' but deactivated during cognitive tasks. Importantly, suppression of this network has been associated with better cognitive performance on tasks that require attention to external stimuli (Daselaar et al., 2009; Daselaar, Veltman, & Witter, 2004). In schizophrenia, this network has been shown to be altered at rest (Broyd et al., 2009; Littow et al., 2015; Mingoia et al., 2012; Wang et al., 2015), and alterations in the DMN have been associated with reduced cognitive performance in schizophrenia (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009; Zhou et al., 2016).

1.1.2.4 Neurotransmitter function

Proposed mechanisms for relating environmental and genetic risk factors to the presentation of schizophrenia are linked to aberrant neurotransmitter function. Altered dopamine levels are one of the most consistent findings in the schizophrenic brain (Howes & Kapur, 2009; Howes, McCutcheon, Owen, & Murray, 2017; Winterer & Weinberger, 2004). While the development of dopaminergic neurons is under genetic control (Blaess & Ang, 2015), the release of dopamine may be increased in response to environmental factors, such as social stressors (Cabib & Puglisi-Allegra, 1996) and drugs of abuse (Laruelle et al., 1996).

Importantly, chronic exposure to these factors, and as a result, chronic dopamine release, could lead to a sensitization process that disrupts the healthy dopaminergic system (Gresch, Sved, Zigmond, & Finlay, 1994; Valenti, Gill, & Grace, 2012).

Excess production of dopamine and dopamine D2 receptors contributes to increased dopamine levels in the striatum, which in turn, send dopaminergic projections to the limbic system via the mesolimbic dopamine - a system that is vital to healthy motivation, learning, and reward (Abi-Dargham et al., 2000; Howes, McCutcheon, & Stone, 2015; Kegeles et al., 2010). Within the mesolimbic circuit, phasic dopamine is typically released when an individual is faced with contextually salient stimuli (Berridge & Robinson, 1998; Smith, Berridge, & Aldridge, 2011). In schizophrenia, however, excess dopamine results in dopamine release in response to neutral stimuli or even independent of stimuli (Heinz & Schlagenhauf, 2010; Kapur, 2003). This dysfunctional dopamine system could also lead to aberrant assignment of salience to external objects and internal representations and eventually to positive symptoms of schizophrenia (Kapur, 2003). Indeed, hallucinations have been linked to amplified, aberrant self-percepts, arising from excess dopamine in this circuit (Bentall, 1990; Fletcher & Frith, 2009; Grossberg, 2000).

In contrast to the hyperdopaminergic input of the mesolimbic system, hypodopaminergic input within the mesocortical circuit, which projects from the striatum to the prefrontal cortex, may contribute to negative and cognitive symptom dimensions (Goldman-Rakic, Castner, Svensson, Siever, & Williams, 2004; Weinberger, 1987). In schizophrenia, this reduced dopaminergic transmission, particularly in the dlPFC, is associated with reduced cognitive performance, as well as increased negative symptoms such as flat affect, decreased motivation, and reduced spontaneity (Abi-Dargham et al., 2002; Okubo et al., 1997; Rao et al., 2018).

In addition to dopamine, there is evidence for the role of other neurotransmitters in schizophrenia. For instance, glutamate and particularly hypofunction of its ionotropic receptor, NMDA, have been linked to the pathophysiology of schizophrenia (Stone, Morrison, & Pilowsky, 2007). One of the most compelling lines of evidence comes from data showing that the administration of phencyclidine (PCP) and ketamine (NMDA antagonists) leads to symptoms of schizophrenia, including positive, negative, and cognitive symptoms (Javitt, 2007; Krystal et al., 1994). Research suggests that altered NMDA receptor function occurs on interneurons within the thalamus and basal ganglia and results in disinhibition of GABA-ergic projections and elevated levels of glutamate and acetylcholine in the cortex (Olney & Farber, 1995). In rodents, this excessive glutamate release leads to excitotoxicity and ultimately neurodegenerative changes, which could account for reduced gray matter in schizophrenia (Olney & Farber, 1995).

As neurotransmitters function in a delicate balance within the brain, dopaminergic neurons may be sensitive to altered glutamate levels. Particularly, glutamatergic neurons have been shown to regulate dopaminergic projections in the midbrain (D. Miller & Abercrombie, 1996). Studies also show that administration of the NMDA antagonists PCP and ketamine are linked to altered activity at dopamine D2 and D3 receptors (Aalto et al., 2005; Kegeles et al., 2000). Therefore, although the exact mechanisms underlying neurotransmitter function in the development and maintenance in schizophrenia is unknown, it appears likely that it is linked, at least in part, to altered activity in both dopaminergic and glutamatergic systems.

1.2 Social deficits in schizophrenia

Humans are intelligent, social beings whose ability to thrive depends on the successful navigation through social situations in daily life. Although for many individuals, the understanding of social situations is an immediate, effortless task, for many individuals with schizophrenia, their illness is accompanied by significant social deficits which impair this ability to easily interact with and understand others (Hooley, 2010; Penn, Corrigan, Bentall, Racenstein, & Newman, 1997; Savla et al., 2013). This begs the question: how are humans normally able to seamlessly navigate the social world? Simulation theory posits that, given that each person herself is a social being, she too experiences emotions and actions and can therefore use her own mind as a model for other’s thoughts and behaviors (Adolphs, 2002; Davies & Stone, 1995; J. P. Mitchell, Banaji, & Macrae, 2005). Essentially, we may then intuitively construct simulations of others’ mental states based at least in part by our own. This view highlights the importance of self-perception and the first-person account in understanding others. Therefore, in an effort to understand social deficits in schizophrenia, this introduction will discuss the current literature on both perceiving the self and perceiving others.

1.2.1 Perceiving the self

Disturbances in the sense of self are recognized as a fundamental feature of schizophrenia (Bleuler, 1911; Kraepelin, 1896; Lysaker & Lysaker, 2010; Mishara, Lysaker, & Schwartz, 2014; Sass & Parnas, 2003). Kraepelin (1896) famously compared a person with schizophrenia to 'an orchestra without a conductor,' reflecting that these individuals often experience a fragmented sense of self, with a loss of binding between perceptions, thoughts, and experiences. As reviewed in Nelson & Raballo (2015), deficits in the sense of self experienced by individuals with schizophrenia encompass the two generally accepted levels of the 'self': (1) the basic self, i.e. the implicit, self-present, temporally persistent, embodied being; and (2) the social self, i.e. the social identity, forward-facing self, including one's narrative view of the self.

Specifically, individuals with schizophrenia tend to experience separation from one's own thoughts (i.e. thinking that thoughts are external from one's body; Sass & Parnas, 2003) and difficulty in monitoring their own actions and perceptions[2] (Blakemore & Frith, 2003; Frith, Blakemore, & Wolpert, 2000). These self-monitoring deficits in schizophrenia have been observed in regards to self-generated speech (Johns et al., 2001; Keefe, Arnold, Bayen, & Harvey, 1999), touch (Blakemore, Smith, Steel, Johnstone, & Frith, 2000) and movement (Knoblich, Stottmeister, & Kircher, 2004). Furthermore, impairments in attributing thoughts and perceptions to oneself may in fact lead to difficulties in social situations, as individuals with schizophrenia have also shown difficulties distinguishing the self from the other's perspective which correlate with deficits in social cognition (Fisher, McCoy, Poole, & Vinogradov, 2008). Indeed, there also appears to be overlap in the brain regions that are responsible for self-processing and those that are responsible for processing the thoughts and emotions of others (e.g. Mitchell et al. 2005; discussed in more detail in Section 1.4.3).

In regard to the social self, individuals with schizophrenia express negative self-percepts and reduced self-esteem, which may be related, among other factors, to positive symptomatology (Barrowclough et al., 2003; Bentall et al., 2001; Garety, Kuipers, Fowler,

[2] Deficits in self-monitoring may be an outcome of a dysregulated dopaminergic system, according to the aberrant salience model, as mentioned briefly in section 1.1.2.4 (see Kapur, 2003 for further details).

Freeman, & Bebbington, 2001). Furthermore, research by Birchwood and colleagues shows that stigma associated with a schizophrenia diagnosis affects the way that individuals with schizophrenia view themselves and present themselves to the others (Birchwood & Iqbal, 1998; Iqbal, Birchwood, Chadwick, & Trower, 2000). Other research highlights that individuals with schizophrenia tend to judge themselves based on how they compare to others, and these self-other comparisons influence how they construe themselves in a social context (Finlay, Dinos, & Lyons, 2001). Together, these aspects contribute to alterations in the sense of self in schizophrenia and are important factors in considering how patients with schizophrenia interact in our social world.

1.2.2 Perceiving others: Social cognition

Social cognition refers to those cognitive abilities that are employed in social interactions, including perceiving, encoding, storing, retrieving, and regulating information about others (M. Green et al., 2008; M. Green & Harvey, 2014). As social cognition has been gaining more attention in the literature in recent years (M. Green & Leitman, 2008), the Social Cognition Psychometric Evaluation Study (SCOPE) was initiated with the collaboration of experts in the social cognition research, to develop a consensus on critical domains of social cognition (Pinkham et al., 2014). Therefore, this thesis will focus only on domains of social cognition determined by the SCOPE initiative: social perception, emotion processing, and Theory of Mind (ToM).[3]

For a successful social encounter in a given environment, these social cognitive processes must work together. For instance, imagine that on your morning walk to work, a friendly woman approaches you on the street. The most basic level of social cognition is to merely perceive the social situation surrounding you - the woman's face, her voice, her posture. This process of identifying and decoding social cues is known as **social perception**. Importantly, it also involves understanding and applying certain social norms (sometimes

[3] The SCOPE panel also identified attribution bias, social reciprocity, and social metacognition as unique domains within social cognition. Attribution bias is left out here, as studies in SZ continue to be sparse and heterogeneous (Savla et al., 2012). Similarly, social reciprocity and social metacognition are new terms in the field, with little consensus on their definition and measurements (Pinkham et al, 2014). It is sure that in upcoming years, there will be fruitful literature on these domains to discuss.

referred to as social knowledge). For instance, say the friendly woman approached you with a hug while saying, "It has been too long!" Social rules, here, would indicate that this woman is someone with whom you were once close with, hence the hug. You would know that the socially normative response would thus be to respond in a friendly manner. At the same moment you are decoding the social cues, you are processing the emotions on the woman's face - she has raised cheeks, relaxed eyebrows, and a wide smile. This suggests she is happy, or even excited. This action of processing physical emotional cues is the **emotion processing** domain in social cognition. Now, lastly, from this encounter - What is this women's intention? Why is she approaching you on the street? This process of inferring the woman's mental state based on surrounding context (i.e., the location, other greetings or small talk she may have voiced during your encounter) and often previous context (i.e., do you remember meeting with her before? what types of interactions have you had in the past) is referred to as **Theory of Mind (ToM)**.

Deficits have been reported in all three of these domains of social cognition in individuals with schizophrenia. In terms of social perception, studies have shown that individuals with schizophrenia have difficulty in detecting social cues in another person's gait (Peterman et al., 2014), posture (Walther et al., 2015), and body movements (Walther et al., 2015). Other reports found that these individuals also had difficulty in using social knowledge to make character judgements (Champagne-Lavau & Charest, 2015). A meta-analysis by Savla and colleagues (2012) of 13 published studies showed an overall large effect-size in social perception ($g= 1.04$). Similarly, several studies have observed deficits in emotion processing in schizophrenia (Borod et al., 1993; Chen et al., 2012; Green et al., 2011; Hall et al., 2004 and others). Importantly, these reports show deficits in both positive and negative emotions, suggesting an overall deficit in emotion processing in schizophrenia. This is also supported by meta-analyses of emotional processing in schizophrenia (Chan, Li, Cheung, & Gong, 2010; Hoekert, Kahn, Pijnenborg, & Aleman, 2007; Savla et al., 2013). In terms of ToM, deficits in schizophrenia are robust and well-replicated, with large effect sizes being reported in three separate meta-analyses (Bora, Yucel, & Pantelis, 2009; Savla et al., 2013; Sprong, Schothorst, Vos, Hox, & Van Engeland, 2007). These studies report important deficits in ToM abilities in inferring others' emotions, intentions, and beliefs in social situations. Overall, given these deficits, social cognition remains an important area of study in schizophrenia.

1.2.2.1 Theory of Mind in schizophrenia

1.2.2.1.1 The relationship between ToM and functioning

Schizophrenia is associated with robust impairments in functional outcomes (i.e. social skills, community functioning), which are relatively resistant to antipsychotic medications (Addington & Addington, 2000; Pinkham, Penn, Perkins, & Lieberman, 2003). In the search to identify treatment targets that can be used to improve functioning, reviews have highlighted that social cognition is importantly related to everyday functioning in SZ (Brekke, Hoe, Long, & Green, 2007; Couture, Penn, & Roberts, 2006; Penn, Sanna, & Roberts, 2008). Furthermore, Fett et al., (2011) performed a meta-analysis of 52 studies to assess the impact of multiple social cognitive variables on domains of functioning and showed that social cognition abilities accounted for 16% of the variance in community functioning. Among the social cognition domains, ToM was the greatest predictor of community functioning, and was a greater predictor than any other neurocognitive domain. Given that community functioning requires interpersonal relations, it may be that ToM is a specific determinant with real-world implications.

1.2.2.1.2 Operationalizing ToM for behavioral study

According to Premack & Woodruff who coined the term “Theory of Mind” in 1978, others’ mental states of others are not directly observable, and therefore, we must thus implement a system of inferences by integrating surrounding information to form a mental model in order to infer the intentions, feelings, or beliefs of others. Although this definition of ToM is largely agreed upon by researchers today, it is important to note that this definition is broad, and as a result, researchers have operationalized ToM in various ways. Importantly, the method in which ToM is operationalized and measured in research (i.e. ToM tasks) drives what we know about ToM in health and in schizophrenia. Therefore, it is important to explore the types of ToM tasks that have informed our knowledge of ToM deficits in schizophrenia.

Typically, behavioral tasks of ToM begin by presenting participants with a relatable social situation and conclude by requiring participants to make a judgment about the mental state of one of the characters. This judgment can be in regard to the intentions, emotions, or beliefs of a character. Oftentimes, ToM tasks also include the addition of contextual details regarding the social situation that create added complexity. For example, a classic example of a ToM task is the Sally-Anne task (Baron-Cohen, Leslie, & Frith, 1985), in which participants view a sequence of illustrations that is accompanied by two props (Sally and Anne dolls), as well as narration by the tester to explain the situation. In the task, Sally places her marble into her basket. Then she leaves the room, and while Sally is gone, Anne moves the marble into her box. Then, Sally returns to the room, and the judgment that participants are asked to make is: "Where will Sally look for her marble?" To be able to answer this question correctly (i.e. that Sally will in fact look for her marble in her basket), the participant must understand the mental state of Sally, taking into account the context that Sally does not know that Anne has moved her marble from its original location. Generally speaking, this type of task is often referred to as a False-belief task, as it requires participants to answer while taking into account the false-belief (a belief which differs from reality; i.e. the location of the marble in this case of Sally and Anne) of one of the characters.

Another common task used to study ToM in schizophrenia is a comic-strip task (e.g. (Brüne, 2003; Brunet, Sarfati, Hardy-Baylé, & Decety, 2003; Sarfati, Hardy-Baylé, Besche, & Widloecher, 1997). This task, although it has several variations, presents a sequence of illustrations as a comic-strip, underneath which are three additional images that serve as possible endings to the comic-strip. Participants are asked to choose among these three images which represents the most logical ending given the Comic-strip sequence. In the original version, the ending illustration requires the participant to successfully understand the character's intentions. Other common ToM tasks in schizophrenia include the Hinting task (in which participants have to infer the real meaning of a character's speech from a 'hint' or indirect speech; Corcoran, Mercer, & Frith, 1995) and the Reading the Mind in the Eyes task (in which participants have to infer what complex emotion an individual is expressing by looking only at his or her eyes; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001)[4].

[4] The Reading the Mind in the Eyes task, unlike the majority of ToM tasks, does not present context. In this case, for instance, eyes are presented displaying an emotion, but the participant does not receive any information regarding the social situation surrounding the emotion. Although some authors have argued that the Reading the Mind in the Eyes task therefore invokes a different type of processing (Bora et al., 2009; Lavoie et al., 2014), this task is still studied by the majority of researchers as a ToM task (including the recent SCOPE initiative; Pinkham et al., 2014). Therefore, the present thesis will continue to treat this task, albeit cautiously, as a measure of ToM.

Given the amount of variation between methods of operationalizing ToM, it may be disadvantageous to refer to what we measure as ToM as a monolithic process. Kosmidis and colleagues (2011) examined correlations among scores of seven ToM tasks in patients with schizophrenia and healthy controls and showed that most ToM tests were relatively independent of one another in both groups. ToM may thus be best understood as a multidimensional process involving multiple components, which are addressed more or less depending on the task type. The question of how to best define the components, however, remains to be determined. Some have suggested ToM be divided into cognitive and affective components (Scherzer, Leveillé, Achim, Boisseau, & Stip, 2012; Shamay-Tsoory, Aharon-Peretz, & Levkovitz, 2007), while others have proposed a division of ToM into components based on the amount of context and the content utilized (Achim, Guitton, Jackson, Boutin, & Monetta, 2013; Bell, Langdon, Seigert, & Ellis, 2010). Overall, given the heterogeneous definitions of ToM and the tasks being used in research, it is important to identify the specific cognitive processes involved in completing various ToM tasks in an effort to construct a definition of ToM that can be applied to future investigations of ToM (Schaafsma, Pfaff, Spunt, & Adolphs, 2015). Recent studies have begun to take on this challenge in healthy individuals (Lavoie, Vistoli, Sutliff, Jackson, & Achim, 2016; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014; Schuwerk, Schurz, Müller, Rupprecht, & Sommer, 2016), and the present thesis seeks to address this issue particularly in terms of ToM deficits in patients with schizophrenia.

1.2.2.2 Task-related factors in social deficits

In a meta-analysis of 29 behavioral studies of ToM in schizophrenia, (Sprong et al., 2007) examined effect sizes four types of ToM tasks: first-order false-belief tasks (tasks that test the participant's ability to understand the false-belief of a character), second-order false belief tasks (tasks that test the participant's ability to understand a character's false belief of another), tasks assessing indirect speech (i.e. the Hinting task), and what the authors referred to as intention-inference tasks (i.e. the Comic-strip task). The results showed a similar range of significant impairment in all tasks (Cohen's d's = -0.96 to-1.44). However, the authors reported significant heterogeneity within categories, suggesting that the method of grouping tasks was not optimal. Subsequently, Bora et al (2009) published a meta-analysis of 36 published studies, which contained many of the same studies reported in Sprong (2007), and they also found heterogeneity in the false-belief tasks. Importantly, these meta-analyses suggest that even among one 'type of task,' the level of ToM deficits in schizophrenia can vary, and it remains unclear what aspects of these tasks are difficult for individuals with schizophrenia.

Interestingly, a recent meta-analysis by Lavoie et al (2014) of siblings of individuals with schizophrenia highlighted important differences between performance of contextualized ToM tasks versus decontextualized ToM tasks (i.e. Reading the Mind in the Eyes), with siblings showing larger deficits compared to controls on tasks that required context integration into the social inference than those that did not (Cohen's d = 0.62 and 0.32, respectively). In accordance with these findings, recent behavioral studies highlight that in fact, individuals with schizophrenia have reduced ability to integrate context into inferences (Champagne-Lavau & Charest, 2015; Chung, Mathews, & Barch, 2011; M. J. Green, Waldron, Simpson, & Coltheart, 2008; Riveros et al., 2010). Given that tasks often vary in the amount of context presented during a ToM task, this could underlie some of the heterogeneity shown within categories of ToM tasks. Taking into account the level of context involved in ToM tasks would thus be an important step in understanding the processes affecting ToM deficits in schizophrenia.

1.2.2.3 Illness-related factors in social deficits

Social deficits in schizophrenia have been suggested to be a trait-related characteristic and core feature of the disorder itself (e.g. Bora, Yücel, et al., 2009; Charernboon & Patumanond, 2017; Martin, Robinson, Dzafic, Reutens, & Mowry, 2014; David L. Penn, Sanna, & Roberts, 2008). This concept is primarily supported by findings that social cognitive deficits are observed even in the absence of prominent symptoms, such as in the prodromal phase and in remission (M. Green et al., 2012; Herold, Tényi, Lénárd, & Trixler, 2002; T. Y. Lee, Hong, Shin, & Kwon, 2015; Mehta et al., 2013) and to a lesser degree, in unaffected first-degree relatives (Bora & Pantelis, 2013; Lavoie et al., 2013, 2014). Furthermore, a recent neuroimaging study of 63 unaffected relatives showed that these individuals also present with altered neural activity associated with ToM task performance, further suggesting hereditary components of ToM (Mohnke et al., 2015). However, molecular investigations of the genetic bases of social abilities are quite recent (Warrier & Baron-Cohen, 2018; Xia, Wu, & Su, 2012) and therefore, studies of social abilities, and particularly of ToM as an endophenotype in schizophrenia have been deemed 'premature' (R. L. Mitchell & Young, 2016). For instance, contrary to the idea that social deficits are trait-related characteristics of schizophrenia, several studies have found evidence that ToM abilities in schizophrenia are related to specific characteristics of the illness, including neurocognitive deficits and symptom presentation (e.g. Abdel-Hamid et al., 2009; Balogh et al., 2015; Bora, Eryavuz, Kayahan, Sungu, & Veznedaroglu, 2006; Brüne, 2005; Buck, Healey, Gagen, Roberts, & Penn, 2016; Koelkebeck et al., 2010; Majorek et al., 2009; Roux, Forgeot d'Arc, Passerieux, & Ramus, 2014), as well as social anxiety (Achim, et al., 2013). Therefore, in order to thoroughly explore mechanisms that may lead to social deficits in schizophrenia, this thesis will review those illness-related aspects that have been proposed to play a role.

1.2.2.3.1 Non-social cognitive deficits

In contrast to social cognition, non-social cognition includes domains such as general information processing, memory, and attention. Individuals with schizophrenia are impaired in multiple areas of non-social, including attention, executive functioning, memory, and processing speed (Albus et al., 2002; Cannon, 2015; Hill et al., 2004; Hughes et al., 2003; Schaefer, Giangrande, Weinberger, & Dickinson, 2013), with the greatest impairments are observed in episodic memory and processing speed (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014; Schaefer et al., 2013). As ToM is a higher-level social cognitive process, most studies have assessed the relation of non-social cognition and ToM. For instance, Bora et al. (2006) showed that ToM task performance correlated with measures of processing speed and working memory. Similarly, Koelkebeck et al. (2010) showed a correlation with ToM task performance with non-social reasoning and verbal memory in schizophrenia. However, importantly, meta-analytic data suggests that when these non-social cognitive deficits are controlled for, the difference in ToM performance between individuals with schizophrenia and healthy controls remains significant (Pickup, 2008; Sprong et al., 2007). Hence, while non-social cognitive deficits may partly underlie ToM deficits in SZ, there are likely other illness- and task-related factors that are involved.

1.2.2.3.2 Symptomatology

Early reports of social deficits in patients with schizophrenia suggested a link with symptomatology (Bentall, Kinderman, & Kaney, 1994; Frith & Corcoran, 1996; Christopher D Frith, 1992). For instance, Frith (1992) hypothesized that social deficits in schizophrenia are in part linked to individuals' inability to recognize their thoughts and beliefs as their own, as well as to understand social and contextual signals, leading to the abnormal attribution of salience and agency (previously discussed in more detail in Sections 1.1.2.4 and 1.2.1, respectively). According to Frith's model, patients with predominantly negative or disorganized symptoms would be unable to acknowledge and represent the mental states of others and would therefore present with the greatest deficits. Patients with paranoid symptoms, on the other hand, would be able to acknowledge that others have mental states, but would still make incorrect mental state judgments due to their inability to use surrounding context to make a correct inference. Frith's model gained some support from empirical studies which showed that the subgroups of patients displaying prominent negative and psychotic symptoms had greater ToM deficits than other subgroups of patients (i.e. those with prominent passivity symptoms and those in remission; Corcoran et al., 1995; Frith and Corcoran, 1996). However, later researchers failed to find a relation of positive symptoms and ToM (Langdon, Coltheart, Ward, & Catts, 2001; Mazza, De Risio, Surian, Roncone, & Casacchia, 2001). This may be due to differences in the level of symptoms present in the patient samples, as Langdon et al., 2001 reported that the sample presented with relatively mild symptoms. Impaired ToM function could create a vulnerability to lapse into psychotic symptoms, which would render any association between ToM and positive symptoms most noticeable during acute states of the illness.

A downfall of early studies examining symptomatology in relation to social deficits in schizophrenia (e.g. Frith, 1992) is that researchers often divided patients into subgroups based on their primary symptom presentation but did not assess the relation of severity of symptoms or co-occurring types of symptoms. More recent studies instead tend to examine the relation between symptomatology and social cognition measures via correlation analyses to provide further details (e.g. Abdel-Hamid et al., 2009; Couture, Granholm, & Fish, 2011; Greig, Bryson, & Bell, 2004). These studies have shown mixed results for the association between symptomatology and ToM deficits, which is complicated by the use of different symptom scales and factor analyses methods to create symptom clusters. It is important to note that often these studies merely report that no significant relation was observed between ToM abilities and symptoms, without providing statistical details. In fact, several studies simply report 'no correlation' between ToM scores and symptom levels for at least one symptom domain (e.g. Abramowitz, Ginger, Gollan, & Smith, 2014; Bâ, Zanello, Varnier, Koellner, & Merlo, 2008; Ho et al., 2015; Rossell & Rheenen, 2013). Based on the heterogeneous results in the literature, it is unlikely that ToM deficits are entirely a product of a specific type of symptoms of schizophrenia. However, it may be that particular symptoms, if severe enough, could be related to an exacerbation of already present deficits, which may lead to significant relations in some patient samples.

Another possible factor involved in the contradicting findings of the relation between ToM deficits and symptoms is the role of antipsychotics, which are helpful in improving some symptoms of schizophrenia but have little effect on improving social abilities (Sergi et al., 2007). While the majority of patients with schizophrenia are on antipsychotic medications of some kind, a meta-analysis of ToM studies by Bora et al. (2009) showed that only 10 of 36 studies reported the medication details of their participants. However, given that studies report ToM deficits in never-medicated first-degree relatives and high-risk individuals (Bora & Pantelis, 2013), it is unlikely that antipsychotic medication has an important impact on observed ToM deficits in schizophrenia.

1.2.2.3.3 Comorbid social anxiety

Among individuals with schizophrenia, those who also present with comorbid social anxiety disorder (SZ+SAD) exhibit greater social deficits than individuals with schizophrenia without social anxiety disorder (SZ-SAD; Voges & Addington, 2005). Individuals with SZ+SAD, in addition to experiencing classic schizophrenia symptoms, also present with the hallmarks of primary social anxiety: a fear of judgment from others, a strong desire to project a positive impression of oneself to others, and significant anxiety regarding the ability to do so (Clark & Wells, 1995). As a result, individuals with SZ+SAD experience greater disturbances in the sense of self. For instance, compared to individuals with SZ-SAD, this comorbid group exhibits reduced self-esteem (Gumley, Grady, Power, & Schwannauer, 2004; Voges & Addington, 2005) and greater feelings of blame, entrapment, and shame associated with their diagnosis (Birchwood et al., 2007; Voges & Addington, 2005).

In other domains of social cognition, however, Achim et al. (2013) showed that individuals with SZ+SAD showed fewer encompassing deficits than patients with only SZ-SAD. Both groups were impaired in ToM, but only the group with SZ-SAD was also impaired in non-social reasoning compared to healthy controls. Importantly, only in the SZ-SAD group, general reasoning abilities had a significant influence on their ToM abilities. This suggests that the presentation of SAD may have important impacts on social deficits in schizophrenia. These differences represent an important area of study, as SAD is one of the most common comorbid disorders in SZ (Achim et al., 2011; Roy et al., 2015), and individuals with SZ+SAD tend to have worse outcomes than those with schizophrenia only (Pallanti, Quercioli, & Hollander, 2004; Romm, Melle, Thoresen, Andreassen, & Rossberg, 2012; Voges & Addington, 2005).

1.3 Neuroimaging and social cognition

Further evidence for the role of context in ToM comes from neuroimaging studies elucidating brain activation involved in ToM tasks. A variety of techniques can be employed to measure and visualize brain activation, each with its own advantages and disadvantages, depending on the target processes to be measured. Of the available techniques, there is typically a trade-off between spatial and temporal resolution. For instance, while electroencephalography (EEG) can detect changes in brain activity within a millisecond, it is only able measure activation from superficial layers of the cortex and thus is not ideal for measuring midline or subcortical structures (Cuffin & Cohen, 1979). Similarly, while magnetoencephalography (MEG) can detect activation deeper in the cortex than EEG, the localization of the source of activation is limited (Hämäläinen, Hari, IImoniemi, Knuutila, & Lounasmaa, 1993). Positron Emission Tomography (PET), on the other hand, has a good spatial resolution (a few millimeters) but a poor temporal resolution (a few seconds to a few minutes; (Gosseries et al., 2008). For ToM studies it is important to understand the specific brain areas that are activated during a task but the temporal precision may be less critical given that ToM trials tend to involve longer, higher-level cognitive processing. As such, PET has indeed been used in several ToM studies (e.g. Andreasen, Calarge, Calage, & O'Leary, 2008; Brunet et al., 2003). The primary disadvantage of PET, however, is that it is an invasive technique that requires injection of a radioactive isotope (Gosseries et al., 2008). Functional magnetic resonance imaging (fMRI) has similar spatial and temporal resolution as PET. Moreover, it has the additional advantage that it is non-invasive and is therefore less difficult and costly to perform, ultimately making it the most common form of neuroimaging used in ToM investigations. Therefore, in this section, I will discuss further how fMRI can be used as an innovative tool to understand ToM in health and schizophrenia.

1.3.1 fMRI basics: the BOLD response and neural activity

fMRI provides a means to visualize brain function in health and disease that is based on the coupling of cerebral blood flow, energy demands, and neuronal activity (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Kwongt et al., 1992; Ogawa, Lee, Kay, & Tank, 1990). When processing information, neuronal activity increases within specific brain regions, and in order to meet this metabolic demand, neurons must utilize oxygen from the blood supply. Importantly, as the ratio between oxygenated and deoxygenated hemoglobin changes within a given area in the brain, this results in systematic changes to the MR signal. These changes, known as the Blood Oxygen Level Dependent (BOLD) response, can be summarized as a series of phases: (1) an initial dip in activity as the neurons deplete oxygen stores from the available blood supply (Devor et al., 2005); (2) an increase in signal as the venous supply overcompensates with oxygenated hemoglobin (P. Fox & Raichle, 1986; P. Fox, Raichle, Mintun, & Denec, 1988); (3) a decrease in signal and dip below baseline, or undershoot, as the neuronal activity ceases (Buxton, Wong, & Frank, 1997; Frahm, Krüger, Merboldt, & Kleinschmidt, 1996; Logothetis, Guggenberger, Peled, & Pauls, 1999). Overall, the typical BOLD response (to a short stimulus or event) may last a total of 25 seconds (see Figure 1.1 for visualization of the BOLD response curve).

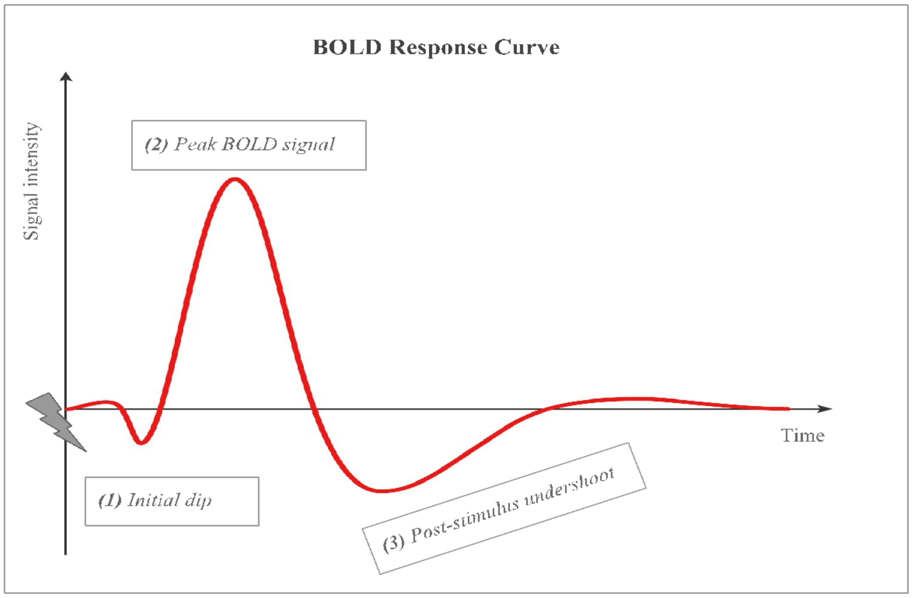

Figure 0.1 Outline of the BOLD response curve.

The above figure indicates the three known phases of the BOLD response curve over time, following a stimulus, lasting about 25 seconds total for a short stimulus.

Importantly, the BOLD response is not a direct measure of neuronal activity, as is the case with neurophysiological recordings. The BOLD response is thus linearly correlated with neural activity - rather than reflective of the activity itself (Mathiesen, Caesar, Akgören, & Lauritzen, 1998; Ogawa et al., 2000; Rees, Friston, & Koch, 2000). An innovative study by Logothetis and colleagues (2001) used single-cell recordings, multi-unit recordings, and local field potential recordings in anesthetized monkeys to determine the specific neural activity that relates to the BOLD signal. Results showed that the BOLD signal was in fact most related to postsynaptic activity and integrative activity occurring at the cell body of the neuron. Therefore, rather than being tied specifically to the firing of individual neurons, the BOLD response is associated with integrative intracortical processing (Logothetis, 2003; Logothetis et al., 2001). It is therefore a useful tool to broadly assess levels of activation in brain regions associated with information processing in both health and disease.

1.3.1.1 fMRI analysis for social cognition studies

In neuroscience research, the BOLD response is used to analyze the brain activation associated with cognitive tasks developed specifically for fMRI. The classic method of fMRI data analysis used in these tasks is the subtraction method, whereby activity from a control condition can be subtracted from the activity associated with an experimental condition (Logothetis, 2008). For instance, in ToM research, one of the tasks is the False-belief vs False-photograph task. This task presents a social situation where a character has a false-belief about another and then asks the participant to make a judgment about the mental state of the character, similar in style to the Sally-Anne task described above in Section 1.2.2.1.2. However, it differs in that it adds a False-photograph condition, which presents a story of a photograph (rather than a social situation) and then asks the participant to make a judgment on the physical characteristics of the photograph (see Figure 1.2 for an example; Lee et al., 2011). In fMRI tasks, then, studies report the brain activation that is greater in the False-belief condition than in the False-photograph condition, ideally pinpointing those social cognitive processes involved specifically in false-belief judgments.

Condition	**Vignette**	**Question**
False-belief	David knows that Ethan is very scared of spiders. Ethan, alone in the attic, sees a shadow move and thinks it is a burglar. David hears Ethan cry for help	David assumes Ethan thinks he has seen ________. A spider / A burglar
False-photograph	Amy made a drawing of a treehouse three years ago. That was before the storm. We built a new treehouse last summer, but we painted it red instead of blue.	The treehouse in Amy's drawing is ___________. Red / Blue

Figure 0.2 Example of False-belief vs. False-photograph task, *provided in Lee et al., 2011.*

While the subtraction method has driven results that improved our understanding of cognition and social cognition, more specifically, there are some limitations that should be discussed. First, there is a risk that this method could subtract out functionally significant processes that are shared between tasks. Although researchers attempt to avoid this by developing experimental and control conditions that target particular processes, there is typically no formal analysis done to verify this assumption (Logothetis, 2008; Poeppel, 1996). Domain general processes, such as cognitive control and attention involved in the experimental task may thus be overlooked because they are shared in the control task[5] (Hartwright, Hansen, & Apperly, 2016; Schurz & Tholen, 2016). Second, while this method highlights individual brain regions that are activated in one task versus another, it does not provide information about connectivity among these regions and the large-scale networks involved. This is an important point given that cognition likely arises from dynamic interactions between brain areas, rather than from isolated functions of specific brain areas. Functional connectivity analysis of ToM tasks may be an important supplement to contrast-based techniques to allow for the identification of large-scale brain networks that may be involved in ToM (for a review of available connectivity techniques and their application, see Bressler & Menon, 2010).

The majority of fMRI studies of social cognition in schizophrenia utilize the subtraction method as discussed above. I will discuss some of those findings for ToM below.

1.3.2 fMRI studies of social cognition in healthy participants

1.3.2.1 Social perception

The majority of social perception tasks require individuals to decode stimuli such as human faces or bodies and compare brain activation to control, non-social stimuli (e.g. houses). These studies suggest that first basic visual processing occurs in the inferior occipital gyrus (Haxby, Hoffman, & Gobbini, 2000). Additionally, in response to invariant features of faces and the perception of an individual's identity, the lateral fusiform gyrus is activated, while the changeable aspects of the face, such as eye gaze, expression, and lip movement are associated with activation of the superior temporal sulcus (Hoffman & Haxby, 2000).

Tasks that require identifying and using social norms (i.e. social knowledge) are much less common, but fMRI studies suggest that this ability may be supported by activation in areas of the lateral prefrontal cortex (Zinchenko & Arsalidou, 2017).

[5] Conjunction analyses, however, can identify the regions of common activation between control and ToM tasks and/or among groups (Friston, Holmes, Price, Büchel, & Worsley, 1999). However, to my knowledge, this technique has not previously been used in a published study of ToM in schizophrenia.

1.3.2.2 Emotion processing

For emotion processing, a more extended neural system is activated in addition to those regions involved in detecting the social cues. Importantly, regions of the limbic system are involved in perceiving emotion, as well as providing feedback to brain regions involved in visual processing and higher-order cognition (Pessoa & Adolphs, 2010). For instance, within this system, the amygdala is associated with activation to both negative and positive emotions (Sergerie, Chochol, & Armony, 2008) and may be involved in generally salient social stimuli processing (Bzdok et al., 2011). Other regions of this network include the anterior insula, which is associated with emotions of disgust (Calder et al., 2007; Wicker et al., 2003), as well as with general emotional awareness, pain, and salience (Gu, Hof, Friston, & Fan, 2013; Legrain, Iannetti, Plaghki, & Mouraux, 2011; Orenius et al., 2017). Furthermore, the explicit judgment of an expressed emotion is associated with activation in the lateral frontal cortex, including the vlPFC, dlPFC, and orbitofrontal cortex (Berthoz et al., 2002; Zinchenko & Arsalidou, 2017).

1.3.2.3 Theory of Mind

Studies of the neural bases of ToM, activation has been primarily found in the medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus (IFG), temporo-parietal junction (TPJ), precuneus, and temporal poles (Carrington & Bailey, 2009; Frith & Frith, 2007; Mar, 2011; Schurz et al., 2014). Each of these regions represents an important theoretically relevant component of ToM processing, which can be examined individually to make a case for the complexity of ToM processing. The mPFC, for example, is activated in response to both tasks that require self-referential thought and those that require reasoning about the mental states of others (Denny, Kober, Wager, & Ochsner, 2012; J. P. Mitchell et al., 2005), but has also been implicated in information processing (Botvinick, Cohen, & Carter, 2004), cognitive monitoring of performance/error-processing (Hartwright, Apperly, & Hansen, 2014), and learning associations between stories and context (Euston, Gruber, & McNaughton, 2012). More recent evidence also implicates the IFG in inhibiting the perspective of the self in favor of taking the perspective of another (Hartwright, Apperly, & Hansen, 2015, 2012; Samson, Houthuys, & Humphreys, 2015). The TPJ has been hypothesized to play a role in attentional re-orienting by a number of studies, as it is involved in processing task-relevant stimuli, particularly those that are unexpected (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002), but has recently been proposed to have a role in contextual updating (Geng & Vossel, 2013).

An influential meta-analysis by Schurz et al (2014) gathered the results of 73 studies of healthy individuals completing a ToM tasks to address how the brain regions recruited changed as a result of the ToM task implemented by the study. While the results of the full 73 studies showed the complete set of abovementioned regions, the results based on task-type, highlighted important variation in brain activation between tasks. For instance, when the studies using the Reading the Mind in the Eyes task (k=10) were combined, there was no longer statistically significant activation in the mPFC or dorsolateral prefrontal cortex, although activation remained in the inferior frontal gyrus. Those studies using more complex tasks, such as the False-belief task (k=15), however, showed activation in these important prefrontal regions in this meta-analysis[6]. Overall, results of this meta-analysis support behavioral results in suggesting that ToM involves multiple components that need to be better understood.

In order to understand what processes could be responsible for activating varied brain regions among types of ToM tasks, it would be useful to look at the recent study published by Lavoie et al., (2016). This study used a novel fMRI task that orthogonally manipulated the social (social vs. physical inferences) and contextual aspects (added context that required participants to adjust their initial inference about the cause of the event or context that confirmed their initial inference about the cause of the event) related to ToM judgments. Lavoie et al. (2016) found that the Social Adjustment vs. Physical Conformation contrast showed activation in brain regions highlighted in the meta-analysis of 73 ToM studies in health as well as the meta-analysis of 15 studies specifically using the False-belief vs. False-photograph condition (Schurz et al., 2014; see Figure 1.3 for a comparison of healthy ToM brain activation found in Schurz et al., 2014 and Lavoie et al., 2016). These results suggest that overall ToM conditions, as well as the False-belief vs. False-photograph task (one of the

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[6] In grouping similar tasks together, this meta-analysis also assessed the control conditions and did not include those with less stringent control conditions in the main task analyses. Heterogeneity analyses were also conducted; for the Reading the Mind in the Eyes task, no significant heterogeneity was found, and for the False-belief task, heterogeneity was found only in a peak in the precuneus.

most common tasks, often referred to as the localizer task for ToM in health) is comprised of both social and contextual processing in healthy individuals.

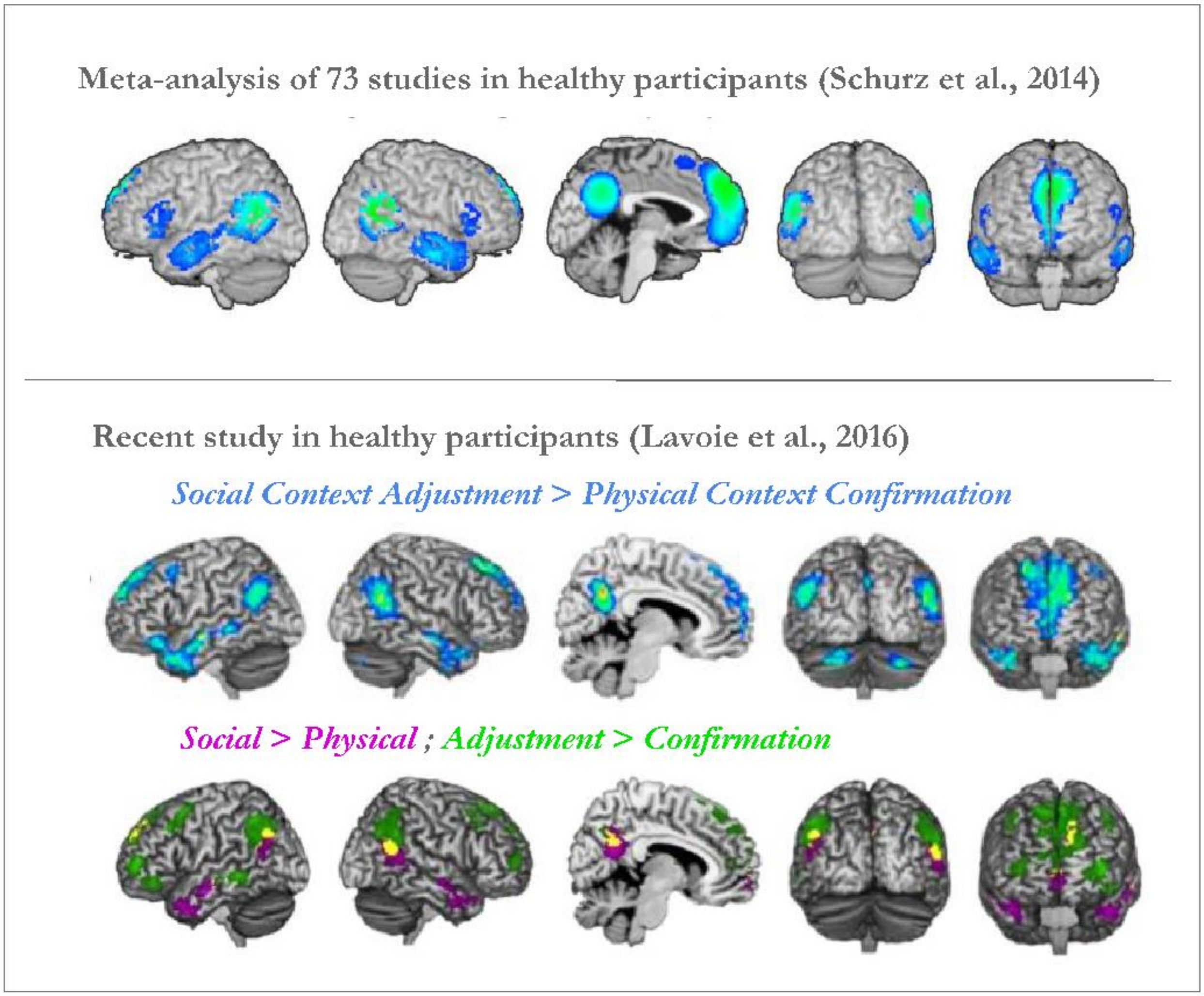

Figure 0.3 ToM task-related activation in health.

(Top) Brain activation associated with pooled meta-analysis of 73 studies by Schurz et al., 2014 using ToM tasks in healthy participants and **(Bottom)** Brain activation observed in recent study by Lavoie et al., 2016 of healthy participants using the contrasts: (blue) social inferences plus context that required an individual to update an initial inference about the cause of the event > physical inferences plus context that confirmed an initial inference about the cause of the event and (purple) social inferences versus physical inferences and (green) all inferences that contained context that required an inference to be updated versus all inferences that contained context that confirmed an inference.

1.3.3 fMRI studies of social cognition deficits in schizophrenia

1.3.3.1 Social perception in schizophrenia

Social perception is less studied in schizophrenia using fMRI. However, two studies showed that patients with schizophrenia had similar activation of the fusiform gyrus compared to controls during the perception of non-affective faces (vs. non-social stimuli; Walther et al., 2009; Yoon, D'Esposito, & Carter, 2006). Furthermore, a study by Bjorkquist & Herbener, (2013) found that patients with schizophrenia had reduced activation in occipital and temporal regions (i.e. the middle occipital gyri and right inferior temporal gyrus extending the right middle temporal gyrus), but this difference was found only for emotional social content. Therefore, it is unclear if this is due strictly to emotion processing alterations at the neural level.

As for social knowledge and the use of social norms, there is a lack of clear evidence in schizophrenia; however, given the importance of the lateral prefrontal cortices in healthy individuals (Zinchenko & Arsalidou, 2017), an area affected in many studies of cognition in schizophrenia (Billeke & Aboitiz, 2013), patients may also show deficits in this region during social knowledge tasks. Given that social knowledge was recently identified as an important component of social cognition in the SCOPE panel results (Pinkham et al., 2014), it is likely that studies in the future will examine this aspect further.

1.3.3.2 Emotion processing in schizophrenia

A recent meta-analysis of emotion recognition tasks (Jáni & Kašpárek, 2017) highlighted that patients with schizophrenia displayed altered activation in a variety of regions compared to healthy participants. Findings included reduced activity in the amygdala, insula, and vlPFC and increased activity in the cuneus, inferior parietal lobe, and dlPFC. Given that patients showed increased activation in regions that are not typically associated with emotional face recognition (i.e. cuneus and inferior parietal lobe), it may be that these individuals recruit additional brain regions in order to compensate for reduced activation in core regions associated with face processing (M. Green et al., 2015).

1.3.3.3 Theory of Mind in schizophrenia

For the fMRI investigation of ToM in schizophrenia, a recent meta-analysis (Kronbichler, Tschernegg, Martin, Schurz, & Kronbichler, 2017) report a total of 21 studies of ToM published that matched their inclusion criteria. Combined, these studies report a mix of under- and over-activation within the mPFC and TPJ. The earliest fMRI study reported in this meta-analysis (Russell et al., 2000) assessed five patients and seven healthy controls using an fMRI-adapted version of the Reading the Mind in the Eyes task (with a gender identification condition as the control condition). Results of this study showed a significant underactivation in the schizophrenia group compared to the control group, within the left inferior frontal gyrus. Although the Reading the Mind in the Eyes task is one of the most commonly used behavioral tasks, only one other study to date used this assessment to study ToM-related brain activation in schizophrenia. This study by De Achával et al. (2012) also found reduced activation in the inferior frontal gyrus, however, in this group, reduced activation was shown in the right hemisphere, along with deactivation in the right middle frontal gyrus and the TPJ. This is fitting with the study by Schurz et al (2014) who showed that the Reading the Mind in the Eyes task recruited the IFG in healthy controls. This may be related to difficulties in self-perceptive inhibition in schizophrenia and reduced mirror neuron function in schizophrenia which implicate the IFG and are commonly affected in schizophrenia (Enticott, Johnston, Herring, Hoy, & Fitzgerald, 2008; A. van der Weiden, Prikken, & van Haren, 2015).

Similarly, false-belief tasks, which are commonly used to assess behavioral ToM in schizophrenia and have been associated with healthy activation in the full 'reported ToM network' in healthy subjects, have only been used in fMRI studies of schizophrenia in two published reports. Lee, Quintana, Nori, & Green, (2011), for instance, showed that during a verbal false-belief task (vs. false-photograph; see example in Figure 1.2) patients with schizophrenia showed reduced activation in the mPFC, precuneus, and TPJ. Dodell-Feder and colleagues (2014) used a similar task and also found only reduced activation in the mPFC. Interestingly, Dodell-Feder also identified that activity within the mPFC during the ToM task mediated the relationship between social anhedonia (i.e. disinterest in social interactions) and social functioning.

The most common tasks used in schizophrenia research are cartoon/comic-strip tasks. Walter et al. (2009), for instance, showed reduced activation in individuals with schizophrenia within a region of the TPJ during a comic strip intention task, while Brune et al., (2008) showed increased activation in the TPJ in patients during a similar task. Interestingly, (Ciaramidaro et al., 2015) showed that dysfunctional activation in the mPFC and observed in their contrast analysis was due to increased activation in the control condition (a physical causality condition which used physical objects without characters) for patients with schizophrenia versus controls, highlighting the potential confound of non-social cognition in results of social cognition fMRI studies.

1.4 Objectives and hypotheses

Together, the presented literature highlights two major points that need to be addressed in the path towards understanding social deficits in schizophrenia. First, there is heterogeneity in the disorder presentation among individuals with schizophrenia. In addition to differences in classic schizophrenia symptomatology, a significant portion of patients present with comorbid social anxiety disorder which further impacts their ability to integrate in our social world. Second, there is heterogeneity among the tasks used to assess ToM and the resulting brain activation associated with ToM processing in schizophrenia. A possible variable affecting this variance is the degree to which the tasks rely on context in social situations. Accordingly, the overarching goal of the present thesis is to pinpoint whether these illness-related and task-related components play a role in social deficits in schizophrenia, and if so, to identify which of these factors may make high level social cognitive tasks (i.e. ToM) difficult in patients with schizophrenia. Specifically, the thesis will address this goal with three targeted objectives:

1. To determine the role of comorbid social anxiety disorder in schizophrenia on the perception of self and symptomatology;
2. To pinpoint important mechanisms underlying ToM deficits in schizophrenia, including (a) if ToM deficits in schizophrenia are related to social anxiety and clinical presentation of symptomatology and (b) if ToM deficits are related to alterations in social processing, context processing, or to both social and contextual processing;
3. To identify brain networks involved in performing a ToM task in schizophrenia and determine if these networks are related to social and/or context processing or

are generally affected in schizophrenia regardless of the task.

To address these three objectives, I present two main projects. The first is a clinical research study of individuals with schizophrenia who were divided into two groups: patients with schizophrenia who meet the full diagnostic criteria of social anxiety disorder (SZ+SAD) and patients with schizophrenia who do not meet the diagnostic criteria for social anxiety disorder (SZ-SAD) (Chapter 1). Here, I examine their symptomatology via the PANSS and self-perceptions via a well-recognized self-report scale that requires individuals to rank how they view themselves in comparison to others. I hypothesize that this comorbid group will have lower levels of perceived social rank, which will be correlated with social anxiety in this group. Overall, I expect this study will highlight the importance of social anxiety in the study of social deficits in schizophrenia.

The second project includes two studies of original research, employing fMRI, a ToM task, and clinical and cognitive measures. In this project, I examine behavioral correlations of ToM scores in schizophrenia with clinical characteristics, including levels of symptoms and social anxiety. I also examine the relation of ToM scores with behavioral performance on social and context manipulations of the fMRI task. The design of the fMRI ToM task in this study was developed by my colleagues in the laboratory of Dr. Amélie Achim and has been previously reported in healthy controls (discussed in Section 1.3.3.3). Briefly, using this task and a standard subtraction method, I evaluate the brain regions activated during social and contextual processes in individuals with schizophrenia (Chapter 2). Additionally, in order to understand other processes that are involved in completing the task, I also examine activation related to this ToM task using functional connectivity analysis (Chapter 3). I expect that, overall, the project will highlight that context plays an important role in ToM deficits in patients with schizophrenia. Furthermore, when examining the functional networks involved, I expect that networks involved in basic non-social cognition, such as attention and information processing will be less activated in patients with schizophrenia, particularly during the conditions that rely heavily on context integration.

Chapter 1: Social anxiety disorder in recent onset schizophrenia spectrum disorders: The relation with symptomology, anxiety, and social rank

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2.1 Résumé

Le trouble d'anxiété sociale (TAS) est une comorbidité courante de la schizophrénie, mais son lien avec les symptômes et la perception de soi demeure en question. Quarante-deux patients atteints de schizophrénie d'apparition récente ont été évalués avec le TAS, les symptômes (PANSS; modèle à 5 facteurs) et les perceptions du rang social (échelle de comparaison sociale; SCS). Dix-huit patients remplissaient les critères de diagnostic du TAS (SZ+) et 24 patients n'y répondaient pas (SZ-). Le groupe SZ- présentait des symptômes plus graves que le groupe SZ+ sur le facteur PANSS Cognitive / Disorganization, notamment des symptômes d'attention et de pensée abstraite. Le groupe SZ+ présentait des symptômes plus graves d'anxiété et de suspicion / de persécution. Les évaluations des symptômes d'anxiété sociale et les symptômes n'étaient corrélés que dans le groupe SZ-. La perception du rang social, qui était réduite chez les patients SZ+, démontre une corrélation avec le facteur de symptôme positif chez les patients SZ-. Ces résultats, bien que préliminaires, suggèrent que SZ+ et SZ- pourraient avoir des profils cliniques différents qui seraient importants de prendre en compte lors de l'adaptation de traitements.

2.2 Abstract

Social anxiety disorder (SAD) represents a common comorbidity in schizophrenia, but questions remain regarding how this comorbidity is related to symptomology and self-perceptions. Forty-two patients with recent-onset schizophrenia were evaluated for SAD, and assessed with the Positive and Negative Syndrome Scale (PANSS), as well as the Social Comparison Scale (SCS), which assessed how participants perceived themselves in relation with others (i.e. social rank). Eighteen patients met the full diagnostic criteria for SAD (SZ+) while 24 patients did not (SZ-). Analysis of symptoms using a five-factor model of the PANSS revealed that the SZ- group had more severe symptoms than SZ+ on the Cognitive/Disorganization factor. Further exploratory analyses of individual symptoms demonstrated that the SZ- group was more affected in attention, abstract thinking, and cognitive disorganization (Cognitive/Disorganization symptoms), while the SZ+ group was more severely affected in anxiety, suspiciousness/persecution, and active social avoidance. Interestingly, severity of social anxiety symptom ratings correlated with certain PANSS symptoms only in the SZ- group. Perception of social rank, which was reduced in SZ+ patients, displayed only a trend level correlation with the Positive symptom factor in the SZ- group. Overall, the results, while preliminary, nonetheless suggest that SZ+ and SZ- may have different clinical profiles that could be important to consider when tailoring treatments for these patients.

2.3 Introduction

Social anxiety disorder (SAD) is the most common comorbid anxiety disorder among persons with schizophrenia, with a mean prevalence rate of 14.9% reported in a recent meta-analysis (Achim et al., 2011). Patients with schizophrenia display similar characteristics as patients with SAD, including anxiety, social avoidance/isolation, and suspiciousness/persecution; however, such behaviors are often inherent characteristics of the disorder (i.e. related to hallucinations, delusions, etc.). This can be distinguished from characteristics of SAD, as according to the DSM-IV, the main diagnostic criteria for SAD is an important fear or anxiety of social situations in which individuals may be exposed to scrutiny of others (American Psychiatric Association, 2013). Core features of SAD include a fear of judgment, a strong desire to project a positive impression of oneself to others, and significant anxiety regarding the ability to do so (Clark and Wells, 1995). In patients with SAD, this leads to avoidance of social situations, but differs from avoidance typically experienced in schizophrenia because a fear of judgment of others rests at the foundation. Despite these differences, increasing evidence suggests that a specific subgroup of patients do in fact meet the diagnostic criteria for both schizophrenia and SAD. This comorbid subgroup (SZ+) tends to have worse outcomes than patients with schizophrenia without social anxiety disorder (SZ-); this includes greater impairment of social functioning (Pallanti et al., 2004; Voges and Addington, 2005; Romm et al., 2012) and even heightened risk for suicide (Pallanti et al., 2004). Conversely, recent data from Achim et al (2013) has found that individuals with SZ+ show *less* encompassing deficits in social cognition than patients with only SZ-, suggesting that the presentation of SAD may not necessarily mean greater overall impairment. Taken together, these results highlight the importance of further understanding the clinical profiles of SZ+ and SZ-.

The expression of social anxiety in schizophrenia has been examined by many previous studies (for a review, see Michail, 2013). While several studies have reported a relation with levels of positive symptoms in patients with schizophrenia and social anxiety (Penn et al., 1994; Lysaker and Hammersley, 2006; Lysaker and Salyers, 2007; Mazeh et al., 2009), others have failed to find such a relation (Pallanti et al, 2004; Voges and Addington, 2005; Birchwood et al, 2006; Michail and Birchwood, 2009; Romm et al, 2012). Additionally, an association between social anxiety in schizophrenia and negative symptoms has been reported by some (Penn et al., 1994; Mazeh et al., 2009), but not all studies (Birchwood et al., 2006). One potential factor underlying these varying results is that these studies use different methods for determining the presence of social anxiety, with some researchers utilizing social anxiety symptom ratings and others employing full or partial diagnostic criteria for SAD (Achim et al., 2011). Typically the studies looking at SAD symptom ratings did not distinguish anxiety symptoms arising from sources related to schizophrenia (e.g. paranoid delusions) from those arising from fear of judgment of others, as in SAD. Additionally, previous studies have tended to classify all psychotic symptoms into only three categories of positive, negative, and general psychopathology, which may not be the best factor structure for schizophrenia symptoms (Lehoux et al., 2009) and cannot account for underlying differences in specific symptoms. It may be that SZ+ and SZ- display different patterns of symptom severity that are cancelled out by such a broad categorization, calling for a more careful examination of the symptom profile of these patients.

In creating a model of the clinical presentations of these two patient groups, another critical aspect to examine is the perception of the self, as SAD is characterized by both negative self-perceptions and low self-esteem (Stopa and Clark, 1993; Clark and Wells, 1995; Smith et al., 2006; Taylor et al., 2013). In individuals with SAD, social anxiety negatively correlates with self-esteem (Clark and Wells, 1995), but this relationship is mediated by patient's perceptions regarding how they are viewed by others (Clark and Wells, 1995). Persons with SAD tend to analyze their worth based upon how they rank in comparison with others (i.e. social rank) (Gilbert, 2000; Trower et al., 1998), resulting in a view of the self which is highly linked to the views of others. For individuals with schizophrenia and SAD, this relationship is further complicated by feelings of shame, social rejection, and entrapment associated with the stigma of schizophrenia (Birchwood et al., 2006; Michail and Birchwood, 2013). These individuals not only have lower self-esteem (Gumley et al., 2004; Karatzias et al., 2007) but also have a lower perception of their social rank, as compared to those with schizophrenia without social anxiety (Birchwood et al., 2006; Michail and Birchwood, 2013). Furthermore, a study by Barrowclough et al. (2003) found that negative self-perceptions were associated with positive symptoms in schizophrenia and suggested that negative self-concept was involved in both the development and maintenance of positive symptoms. If symptomology differs in the SZ+ and SZ- groups, then it may be that negative self-perceptions are differentially related to symptomology in SZ+ and SZ-. Yet, the relation of perception of social rank and symptomology in schizophrenia in these populations has yet to be examined.

The first objective of this study was to further examine the symptom profiles and the perception of social rank in people with a diagnosis of SZ+ in comparison to SZ-. Specifically, our primary goal was to pinpoint differences in symptom severity between SZ+ and SZ- groups using a five-factor model which breaks down symptoms into Positive, Negative, Cognitive/Disorganization, Depression/Anxiety, and Hostility/Aggression components. We also aimed to examine group differences in social anxiety (via a well-recognized symptom scale) and social rank in SZ+ and SZ- and to explore the relationship between symptom severity and social anxiety as well as social rank separately in SZ+ and SZ- patients. While testing differences in social anxiety ratings may seem tautological, we previously observed that high ratings on the LSAS are sometimes observed in paranoid patients, which could also potentially lead to high ratings in SZ- patients (Achim et al., 2013).

Due to their comorbid anxiety, we nonetheless expected that the SZ+ group compared to the SZ- would display more severe symptoms in the Depression/Anxiety symptom factor, more severe social anxiety ratings, and lower levels of perceived social rank than the SZ- group studies (the last of which would replicate previous findings of Birchwood et al., 2006; Michail and Birchwood, 2013). Furthermore, in the SZ- group, we hypothesized that social anxiety ratings would be related to the Depression/Anxiety factor and the Positive symptom factor from the PANSS, whereas the SZ+ would show social anxiety ratings related only to Depression/Anxiety symptoms of schizophrenia. Finally, we expected a differing pattern of association between social rank ratings and symptomology, such that the SZ+ would show a greater association of social rank with symptoms. Exploring these relations in the two subgroups could further highlight the clinical factors linked to high levels of social anxiety and low perception of social rank in people with schizophrenia.

2.4 Methods

2.4.1 Diagnosis of SAD comorbidity and social anxiety ranking

Based upon recent meta-analytical data that anxiety is more commonly diagnosed when the

Structured Clinical Interview for the DSM-IV (SCID) is supplemented with other assessments (Achim et al., 2011), participants were assessed with a comprehensive semi-structured interview based on the SCID but which also included questions from other instruments to provide a more detailed assessment of symptoms (Roy et al., 2011; Achim et al. 2013; Roy et al, in revision). Importantly, one of the scales added to the interview was the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987), a 24-item measure assessing anxiety and avoidance in specific social situations (i.e. eating in a public place). For each of the social situations presented, participants' fear/anxiety and avoidance behavior were reported on scales from 0-3, with higher total LSAS ratings indicating more severe social anxiety and avoidance. This measure of anxiety has shown strong construct validity in both SAD and non-anxious controls (Fresco et al., 2001).

As social anxiety can stem from other sources in schizophrenia (i.e. positive psychotic symptoms), we utilized all available information to make a diagnosis of SAD in these patients. The tools for diagnosis thus included, the LSAS, the SCID, a comprehensive evaluation of patients' symptoms, the patients' clinical files, and information from the clinical team. Only patients who met all of the DSM-IV criteria for current SAD and who displayed social anxiety stemming specifically from a fear of judgment of others were included in the group with comorbid SAD, while patients with no history of SAD were included the group without comorbid SAD. All interviews were conducted by a trained research assistant and reviewed by an experienced psychiatrist (MAR).

2.4.2 Assessment of symptoms and social rank

Schizophrenia symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1986). The PANSS assesses presentation of psychotic symptoms using 30-items. For each item, symptoms are scored on a scale from 1-7, with higher scores indicating more severe symptom presentation.

The PANSS was completed by the treating psychiatrist, another member of the clinical team or a trained research assistant, and all assessments were reviewed by one of the authors (MAR), a senior psychiatrist with an extensive experience with this measure. These ratings were based on all available sources of information, including clinical interviews, information from family, friends, and information from other treatment staff at the Clinique

Notre-Dame-des-Victoires.

Social rank was measured via the Social Comparison Scale (SCS; Allan and Gilbert, 1995). The self-report scale asked participants to assess how they see themselves in comparison to others. The scale consisted of 11 desirable features (i.e. superior) and 11 undesirable opposites (i.e. inferior) separated by a 10-point scale; participants had to report where on the scale they ranked, with higher SCS scores indicating more positive view of their social rank in comparison to others. The SCS has shown good psychometric properties in persons with schizophrenia, with an internal reliability of 0.80 and a re-test reliability of 0.77 (Birchwood et al., 2000).

2.4.3 Data analysis

Patients were divided based on whether they met all the DSM-IV diagnostic criteria for current SAD; this resulted in two groups, SZ+ and SZ- for analysis. Three patients with a history of SAD but that no longer met the diagnostic criteria at the time of the assessment were excluded from this study.

For analysis of symptomology, we utilized a five-factor model based upon a recent review by Lehoux et al. (2009) that examined results of studies employing various five-factor models and found that 26 psychotic symptoms from the PANSS could consistently be classified into five factors. The resulting model, including factors and their component symptoms, utilized in the present study is as follows: (1) Positive (delusions, hallucinatory behavior, grandiosity, suspiciousness/persecution, unusual thought content, lack of judgment/insight); (2) Negative (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity, motor retardation, active social avoidance); (3) Cognitive/Disorganization (conceptual disorganization, difficulty in abstract thinking, mannerisms and posturing, disorientation, poor attention); (4) Depression/Anxiety (somatic concern, anxiety, guilt feelings, depression); and (5) Excitability/Hostility (excitement, hostility, uncooperativeness, poor impulse control). Individual symptom scores comprising each factor were summed, and the resulting scores for each of the five factors were compared between SZ+ and SZ- using t-tests.

For further exploration of our primary results, subsequent analyses were performed using t-tests to compare between-groups scores for the individual symptoms that composed each of the five factors of the PANSS.

The SCS scores and social anxiety ratings on the LSAS were also compared between groups using t-tests. To examine the relationship between anxiety and symptomology, as well as social rank and symptomology, LSAS scores and SCS scores were correlated to PANSS symptom scores using the five-factor model. These analyses were performed separately for the SZ+ group and the SZ- group.

Bonferroni correction was applied for multiple t-tests and correlations with each of the five factors from the PANSS. For exploratory analysis of individual symptoms comprising the five factors, Bonferroni correction was applied per factor to correct for multiple testing, but due to the exploratory nature of this analysis, results were also examined and displayed at a threshold of $p<0.05$.

2.5 Results

2.5.1 Participants

The forty-two outpatients with recent-onset schizophrenia spectrum disorders (34 male; mean age = 25.4) in this study were recruited from Clinique Notre-Dame-des-Victoires of the Institut Universitaire en Santé Mentale de Québec, a clinic specialized in the treatment of first-episode psychoses. Patient diagnoses included schizophrenia (n=31), schizoaffective disorder (n=6), delusional disorder/paranoia (n=3), and psychosis not otherwise specified (n=2). At the time of testing, 18 participants (43%) also met the diagnostic criteria for current SAD and were included in the SZ+ group for analysis; 24 participants (57%) did not meet all diagnostic criteria for current or past SAD and were included in the SZ- group. All participants were taking second-generation antipsychotics; 12 were taking antidepressants, and 5 were also taking benzodiazepines. The first antipsychotic medication had been initiated a mean of 24.9 months before our assessment (range 1-78 months). Only 3 patients had been treated with antipsychotic treatment over 60 months (5 years); 47% of the patients had less than 24 months (2 years) of antipsychotic treatment.

Education level and profession of participants' parents were assessed via the Hollingshead two-factor index of social position (Miller, 1991) to provide a measure of socioeconomic status. To measure participants' general intelligence, the WAIS-III (vocabulary and block design; Ringe et al., 2002) was utilized. Participants were excluded if they presented with an estimated IQ of less than 70, a neurological disorder, or if their treating psychiatrist determined that they were not stable enough to provide informed consent. All participants provided written, informed consent. The study was approved by the ethics committee of the Centre de recherche de l'Institut Universitaire en Santé mentale de Québec.

Participant demographics and clinical assessment scores for the SZ+ and SZ- groups are displayed in Table 2.1. Between the two groups, there were no significant differences in age, gender, socioeconomic status, or estimated IQ scores.

2.5.2 Symptom severity

Group differences in PANSS scores using the five-factor model are displayed in Table 2.2. Results did not reveal a significant between-groups difference in Depression/Anxiety; however, there was a significant difference in the Cognitive/Disorganization factor ($t(40)=3.12$, $p=0.003$), with greater symptom severity scores in the SZ- group. These unexpected results prompted further analysis exploring group differences in the component symptoms of each factor that may have been driving the group differences in Cognitive/Disorganization and similarly, the lack of differences in Anxiety/Depression. For completeness, we also explored the group differences for the symptoms in the other three dimensions of the PANSS, though these results should be interpreted with caution. The results of these between-group analyses are listed under their corresponding factor in Table 2.3. For the Cognitive/Disorganization factor, these analyses revealed significantly higher scores (reflecting greater severity) in the SZ- group compared to the SZ+ group in conceptual disorganization ($t(40)=2.11$, $p=0.041$), difficulty in abstract thinking ($t(40)=2.51$, $p=0.016$), and poor attention ($t(40)=2.82$, $p=0.007$). In contrast, the SZ+ group displayed significantly higher scores than the SZ- group in aanxiety ($t(40)=-3.46$, $p=0.001$) from the Depression/Anxiety factor, and also in suspiciousness/persecution ($t(40)=-2.92$, $p=0.006$) from the Positive factor and in active social avoidance ($t(40)=-2.63$, $p=0.012$) from the Negative factor.

2.5.3 Social anxiety scores and correlations with symptom severity

As expected, the SZ+ group displayed significantly higher anxiety scores on the LSAS ($t=-2.88$; $p=0.006$), with a mean of 59.5, which is considered as moderate social anxiety (see

Table 2.1). In the SZ- group, the mean of 38.0 fell below the threshold that is typically considered as clinically significant social anxiety (Mennin et al., 2002; Rytwinski et al., 2009).

According to the five-factor model, no significant correlations were found between LSAS scores and the symptom factors in either the SZ+ or SZ- group in the Positive, Negative, Cognitive/Disorganization, or Excitement/Hostility components (see Table 2.4). However, there was a significant correlation between anxiety ratings on the LSAS and severity of the Depression/Anxiety factor (r=0.58, p=0.003), but only in the SZ- group.

2.2.3.4. Social rank scores and correlations with symptom severity

Results from the SCS show that the SZ+ group has significantly lower self-rank scores (t=2.90; p=0.006) as compared to the SZ- group (see Table 2.1). According to the five-factor model, no significant correlations were found between social rank and symptom severity but a trend was observed for a correlation with the Positive factor in the SZ- group, with a r=0.40, p=0.054 (see Table 2.4).

2.6 Discussion

2.6.1 Comorbidity diagnosis and characteristics

The present study sought to examine patients presenting with comorbid schizophrenia and SAD and to further assess the ways they are affected in symptomology, social anxiety, and social rank ratings. In our sample of patients with recent-onset schizophrenia spectrum disorders, 43% of participants revealed social anxiety symptoms related to the fear of judgment of others that met all diagnostic criteria for comorbid SAD. According to recent meta-analytical data, prevalence rates of social anxiety disorder in schizophrenia range from 3.6-39.5% (Achim et al., 2011), rendering the rates in this study elevated in comparison to the reported range. This is likely related to our comprehensive diagnostic approach which supplemented the SCID with additional assessments and to the decision to target outpatients, which may lead to increased detection rates according to our meta-analysis (Achim et al., 2011).

Consistent with our original hypothesis, group differences were observed on the LSAS, with SZ+ displaying higher anxiety ratings. Although this may seem intuitive, some

SZ- patients displayed scores on the LSAS indicative of moderate social anxiety (i.e. 25% of the SZ- sample scored 60 or higher, with a maximum score of 81), but based on our comprehensive clinical interview, it was determined that their anxiety was linked to psychosis. Thus, these patients displayed significantly different levels of social anxiety based specifically on the classification of anxiety that either is consistent with (SZ+) or is not consistent with (SZ-) SAD diagnostic criteria. Additionally, SZ+ and SZ- displayed significant differences in SCS scores, with SZ+ displaying a lower perception of social rank. Taken together, these results further support the idea that a characteristic feature of SAD is both anxiety and negative self-evaluation (Clark and Wells, 1995) and that these characteristics appear to be similarly present in a comorbid diagnosis of SZ+ (Birchwood et al., 2006; Michail and Birchwood, 2013).

2.6.2 Symptom severity

Results of the five-factor analysis demonstrated only one significant group difference, in the Cognitive/Disorganization factor. This group difference is one of the most interesting observations of the current study given that patients with SZ- showed more severe cognitive symptoms than those with comorbid SZ+. Specifically, as compared to the SZ- group, the SZ+ group demonstrates lower levels of symptoms in areas of attention, abstract thinking, and conceptual disorganization (although only attention was significant after correction when taking these symptoms separately). Attention is thought to play a crucial role in social anxiety, and in particular, hyper-attention in threatening situations or with regard to (negative) attention to oneself has been a consistent finding in those with primary SAD (Hope et al., 1990; Spur and Stopa, 2002; Bogels and Mansell, 2004). Additionally, a key component of psychological models of SAD is the propensity to attend to and reflect upon how one is perceived by others, and this focus may similarly exist in the SZ+ group and compensate for the attention deficits often observed in people with schizophrenia. Recently, research has highlighted the importance of cognition in schizophrenia, finding that not only is cognition affected in the premorbid phase (Fuller et al., 2002; van Oel et al., 2002; Reichenberg et al., 2010) but also that cognitive symptoms are among the best predictors of social and community functioning in schizophrenia (Tyson et al., 2010; Fett et al., 2011; Fervaha et al, 2014;). In fact, some have even called for a shift of focus to schizophrenia as a cognitive illness (Kahn and Keefe, 2013). However, in studies of the SZ+ and SZ- populations, such cognitive symptom differences have often been neglected, as previous studies examined mainly positive, negative, or specific anxiety-related symptoms (i.e. anxiety and/or suspiciousness) (Birchwood et al., 2006; Michail and Birchwood, 2009; Michail and Birchwood, 2013). Our study suggests that despite showing more important difficulties in some areas of their clinical profiles (Birchwood et al., 2006; Michail and Birchwood, 2013), SZ+ patients also have some aspects in which they are less affected, and this may include cognition. This could have implications for further studies of affected cognition in schizophrenia. However, additional studies are warranted in order to confirm this group difference. Objective neuropsychological tests should also be used to examine the cognitive deficits between these two groups, as this could have consequences for treatment and outcome of these individuals.

As for the Depression/Anxiety factor, despite clear differences in social anxiety ratings between the two groups as judged by the LSAS, we did not observe a significant group difference between the SZ+ and SZ- groups when considering the overall PANSS's factor. However, as this factor combines anxiety with other symptoms such as guilt and depression, it seems to have clouded differences specific to anxiety. In exploring the individual symptom differences in the model, the SZ+ group appears to have more severe anxiety on the PANSS, but displayed no other significant differences as compared to SZ- in the other symptoms comprising the Depression/Anxiety component.

When considering symptoms composing the other factors, the SZ+ group displayed an increased tendency to actively avoid social situations, a finding which has also been replicated by Birchwood et al. (2006) in a population of socially anxious individuals with schizophrenia. Active social avoidance is a hallmark of primary SAD (i.e. without schizophrenia) (Clark and Wells, 1995), and is also fitting with the popular model of SAD, stating that these individuals may avoid social situations as a way to minimize the perceived threat resulting from their hyper-attention in social situations (Mogg and Bradley, 1998; Bogels and Mansell, 2004). The increased avoidance, along with less severe Cognitive/Disorganization symptoms of SZ+ compared to SZ-, suggests a differing clinical presentation among these patient groups and may specifically help to identify a symptom profile specific to the SZ+ population.

However, it should be noted that the present study also found heightened levels of suspiciousness and persecution in SZ+ versus SZ- which were not found in the study by Birchwood et al. (2006). This observation is consistent with the idea that the method of classification of social anxiety may be an important factor leading to observed differences in previous research. Our study utilized a comprehensive diagnostic approach to classify SZ+ and this led to increased detection of SAD relative to other diagnostic methods. Determining consistent and sensitive tools and methods of classifying social anxiety in patients with schizophrenia could be useful in the future for both research and clinical purposes.

2.6.3 Social anxiety scores and correlations with symptom severity

Correlations between PANSS symptom severity and social anxiety ratings were only found in the Depression/Anxiety factor for the SZ- group. Unexpectedly, we did not find an association between the Depression/Anxiety factor and LSAS social anxiety ratings in the SZ+ group. Given that the Depression/Anxiety factor includes a general anxiety symptoms (rather than social anxiety symptoms, per se), we expected an association to be present in both subgroups; however, this Depression/Anxiety factor also includes symptoms such as somatic concern, guilt, and depression, and it may be that these symptoms would be associated with social anxiety ratings in the SZ- group but in the SZ+ group, given the specific nature of anxiety manifested in SZ+.

Contrary to our initial expectations, we also did not observe any significant association between LSAS scores and PANSS symptom scores on the Positive factor. It is possible that our study lacked the power to detect such an association, or that considering symptoms factors may have masked some associations with more specific symptoms. Future studies with greater power would be required to address this question while taking multiple comparisons into account.

2.6.4 Social rank scores and correlations with symptom severity

The positive relation of perceived social rank with the PANSS positive symptom factor, which was at trend level in the SZ- group, is another interesting observation that would deserve replication in a larger sample. The PANSS Positive symptom factor includes common psychotic symptoms, such as delusions, hallucinations, and grandiosity which could be differentially related to social rank in the SZ- group, given the absence of social anxiety. Although we did not examine delusional content or beliefs in the present study, previous research by Smith et al. (Smith et al., 2006) determined that more negative beliefs about the self were associated with more severe persecutory delusions, whereas grandiose delusions were inversely related to negative beliefs about the self. Although only a trend level, our results may support this theory of an association of positive symptoms to views of the self which has been previously reported (Barrowclough et al., 2003; Smith et al., 2006), particularly in the SZ- population; such an association may be important to examine in future studies with these populations.

This study also builds upon work by Birchwood et al (2006) who examined shame and stigma associated with perceptions of social status in social anxiety and schizophrenia; particularly, our results may suggest that individuals with SZ- not only perceive a less inferior social rank than those with SZ+, but that this could also be related to the presentation of psychotic symptomology in schizophrenia. However, these results should be interpreted carefully given the trend level association of these findings.

2.6.5 Limitations

This study has limitations that must be noted. Firstly, our study had a small sample size, which resulted in reduced power. The effects observed for the main analyses with the five-factor model met statistical significance even after applying a correction for multiple comparisons, but this was not always the case for our additional exploratory analyses with the individual symptoms. However, these exploratory analyses allowed us to see subtle differences between the two groups that may have otherwise gone unreported. These findings certainly deserve replication in larger sample sizes with a greater power.

Additionally, we observed group differences in cognitive symptoms based on the PANSS assessment. While these methods allowed for a general assessment of cognition in the patient sample, the group differences in Cognitive/Disorganization should be further examined with more detailed, with objective neuropsychological assessments, which were not included in the current study.

Finally, the present study would have benefited from a group of individuals with a primary diagnosis of SAD to assess whether social anxiety scores and perception of social rank within the comorbid SZ+ subgroup is similar to that displayed in those with a sole diagnosis of SAD.

2.6.6 Conclusions

The present study sought to examine questions remaining in the literature regarding a common comorbidity in schizophrenia. Overall, the results support the idea that the five-factor model, like the typical grouping of symptoms into three categories (positive, negative, and general psychopathology), may not be ideally suited to assess the full range of differences between SZ+ and SZ-. Rather, a specific breakdown of features in these two groups may be necessary to determine how these populations are differentially affected. Interestingly, our analyses showed that neither SZ+ nor SZ- is necessarily more affected in terms of overall symptoms, but instead, within broad categories of symptoms, each group is more affected in different but specific ways. When considering the symptom severity and correlation analyses together, the present study suggests that these two populations may present with distinct clinical profiles, such that the SZ+ population presents with higher levels of social anxiety and active social avoidance and suspiciousness/persecution, as well as lower levels of perceived social rank, but importantly, the SZ+ profile may also include less affected cognition. On the other hand, the SZ- population may present with less severe social anxiety and social avoidance, but may be more affected in cognitive symptoms. While the groups did not differ in terms of levels of many psychotic symptoms, the way in which their perceived social rank is related to positive symptoms may differ.

Although our results are preliminary and should be replicated in larger sample sizes, they nonetheless provide new insight into characteristics of schizophrenia patients who also present with a social anxiety disorder. Future studies may benefit from classifying subgroups based on diagnostic criteria for SAD, rather than severity of social anxiety symptoms assessed with symptom scales, as social anxiety symptoms in schizophrenia vary greatly and may not always be linked to a fear of the judgment of others. Continued research in this line can provide relevant information to develop more directed clinical treatments targeting the specific affected areas in these populations.

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Table 0.1. Demographic and clinical assessment scores (mean and standard deviation) of patient groups

	SZ+	SZ-	SZ+ *vs.* SZ-	
N(%)	18(43%)	24(57%)		
Age	26.3(4.4)	24.6(4.7)	t=-1.20	p=0.239
Gender (male; female)	13;5	21;3	x^2=1.56	p=0.212
Socioeconomic Status†	3.7(1.1)	3.7(1.2)	t=-0.16	p=0.875
IQ estimate	99.7(13.3)	97.6(14.3)	t=-0.46	p=0.649
LSAS total	59.5(25)	38.0(22.9)	t=-2.88	p=0.006**
SCS total	57.6(12.8)	69.6(13.7)	t=2.90	p=0.006**

** p<0.01

† Socioeconomic Status was measured via the Hollingshead Measure; scores ranged from 1 to 5, with higher scores indicating advanced education/professional occupation.

SZ+ = patients with schizophrenia and social anxiety disorder; SZ- = patients with schizophrenia without social anxiety disorder; LSAS = Liebowitz Social Anxiety Scale; SCS = Social Comparison Scale.

Table 0.2 Symptom severity for patient groups, PANSS's five-factor model (mean and standard deviation)

			SZ+ *vs.* SZ-	
	SZ+	SZ-	*t*	*p*
Positive	14.9(4.2)	16.3(5.8)	0.85	0.400
Negative	16.4(5.6)	15.3(6.9)	-0.53	0.600
Cognitive/Disorganization	8.1(2.4)	11.0(3.4)	3.12	0.003**
Depression/Anxiety	8.6(1.7)	7.6(2.9)	-1.31	0.197
Excitement/Hostility	6.6(2.7)	6.5(2.4)	-0.12	0.903

**Bonferonni correction
SZ+ = patients with schizophrenia and social anxiety disorder; SZ- = patients with schizophrenia without social anxiety disorder

Table 0.3 ***Symptom severity for patient groups, PANSS's individual symptoms (mean and standard deviation)***

	SZ+	SZ-	SZ+ vs. SZ- t	p
Positive				
Delusions	3.2(1.1)	3.3(1.3)	0.18	0.857
Hallucinatory behavior	1.7(1.1)	2.3(1.5)	1.36	0.183
Grandiosity	1.7(1.4)	2.3(1.6)	1.21	0.232
Suspiciousness/ persecution	3.3(1.0)	2.3(1.0)	-2.92	0.006**
Unusual thought content	2.4(1.2)	2.7(1.3)	0.65	0.518
Lack of judgment/insight	2.5(1.4)	3.3(1.5)	1.85	0.072
Negative				
Blunted affect	2.3(1.1)	2.4(1.2)	0.27	0.792
Emotional withdrawal	2.5(1.0)	2.5(1.4)	0.00	1.000
Poor rapport	2.5(1.2)	2.2(1.2)	-0.77	0.444
Passive/apathetic social withdrawal	2.4(1.2)	2.5(1.4)	0.37	0.714
Lack of spontaneity	2.0(1.1)	1.8(1.2)	-0.46	0.646
Motor retardation	1.7(1.0)	1.7(0.9)	-0.05	0.963
Active social avoidance	3.0(1.1)	2.2(1.0)	-2.63	0.012*
Cognitive/Disorganization				
Conceptual disorganization	1.6(1.1)	2.4(1.3)	2.11	0.041*
Difficulty in abstract thinking	2.6(1.0)	3.5(1.3)	2.51	0.016*
Mannerism and posturing	1.3(0.6)	1.6(1.0)	1.27	0.212
Disorientation	1.0(0.0)	1.0(0.2)	0.86	0.393
Poor attention	1.7(0.8)	2.5(1.1)	2.82	0.007**
Depression/Anxiety				
Somatic concern	1.6(1.3)	1.8(1.0)	0.39	0.700
Anxiety	3.5(0.6)	2.6(1.0)	-3.46	0.001**
Guilt feelings	1.6(0.6)	1.7(1.0)	0.35	0.726
Depression	1.8(1.0)	1.5(1.0)	-0.91	0.369
Excitability/Hostility				
Excitement	1.3(0.6)	1.4(0.7)	0.40	0.691
Hostility	1.7(0.9)	1.4(0.7)	-1.40	0.169
Uncooperativeness	1.3(0.8)	1.5(0.8)	0.69	0.494
Poor impulse control	2.2(1.3)	2.2(1.3)	0.00	1.000

*p<0.05

**Bonferonni correction

SZ+ = patients with schizophrenia and social anxiety disorder; SZ- = patients with schizophrenia without social anxiety disorder

Table 0.4 Correlations of social anxiety and social rank scores to patients' symptom severity, PANSS's five-factor model

	LSAS				SCS			
	SZ+		SZ-		SZ+		SZ-	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Positive	0.07	0.779	-0.22	0.293	-0.26	0.299	0.40	0.054
Negative	-0.30	0.225	0.24	0.268	0.10	0.685	0.26	0.222
Cognitive/Disorganization	-0.32	0.199	0.21	0.325	0.38	0.125	0.25	0.232
Depression/Anxiety	-0.24	0.331	0.58	0.003**	-0.28	0.255	-0.33	0.112
Excitement/Hostility	0.12	0.623	0.10	0.646	-0.17	0.507	0.02	0.925

**Bonferonni correction

SZ+ = patients with schizophrenia and social anxiety disorder; SZ- = patients with schizophrenia without social anxiety disorder

Chapter 2: Deficits on ToM tasks in individuals with schizophrenia: More than just errors in social information processing

3.1. **Résumé**

Les déficits de théorie de l'esprit (ToM; la capacité à inférer les états mentaux des autres) sont des obstacles au fonctionnement dans la SZ. Pour traiter les facteurs sous-jacents aux déficits en ToM dans la SZ, 25 patients atteints de SZ et 20 témoins contrôles (HC) ont été évalués avec l'échelle de l'anxiété sociale Liebowitz (LSAS), la tâche Histoires combinées (COST; ToM) et la tâche REMICS-fMRI (une tâche verbale qui manipule orthogonalement les scénarios et le contexte social et physique qui sont incongrus ou cohérents avec les attentes normatives lors des jugements sur la cause d'un événement). Aucune corrélation significative n'a été constatée entre les scores ToM réduits et les scores LSAS, mais les scores ToM étaient corrélés avec la condition non congruente de contexte social de la tâche IRMf. Les analyses IRMf ont mis en évidence que les anomalies neuronales dans la SZ étaient principalement observées avant de porter des jugements sociaux, fondés sur le contexte, au cours de la phase de présentation du contexte. Ceci souligne que les déficits en théorie de l'esprit dans la SZ n'étaient pas uniquement dus à des déficits de traitement social, mais aussi au contexte de traitement.

3.2. Abstract

Deficits in Theory of Mind (ToM; i.e., the ability to infer the mental states of others) are an obstacle to functioning in SZ. The present study aimed to address factors that may underlie ToM deficits in SZ. Twenty-five patients with SZ (illness duration mean = 7.88 years) and 20 healthy control (HC) participants were assessed with the Liebowitz Social Anxiety Scale (LSAS), the Social Knowledge Test, the Faces task (emotion recognition), the Combined stories task (COST; ToM), and the REMICS-fMRI task (a verbal task that orthogonally manipulated the social vs. physical scenarios and context that was incongruent or congruent with the normative expectation during judgments about the cause of an event). No significant correlations were found between reduced ToM scores in SZ and clinical measures, but patients' ToM scores correlated with scores on the Social Knowledge test ($r= .524$, $p= 0.007$), the Faces task ($r= 0.474$, $p= 0.017$), and the social, incongruent context condition of the fMRI task ($r= .67$, $p <0.001$), signifying an important role of context in classic ToM judgments in SZ. Main fMRI analyses highlighted that patients did *not* show differences in brain activation in a ventral network of brain regions for social vs. physical judgments, including the ventral medial prefrontal cortex (mPFC), ventral temperoparietal junction (TPJ), and temporal poles. For context-incongruent vs. context-congruent judgments, patients showed significant differences compared to healthy participants in the right transverse temporal gyrus, but similar activation to healthy controls in a dorsal brain network including the dorsal mPFC, dorsal TPJ, and dorsolateral PFC. Neural abnormalities in SZ were primarily observed prior to making social and context-based judgments, during the context presentation phase, where patients showed alterations related to context-processing in the supplementary motor area/dorsal anterior cingulate, right insula, posterior cingulate cortex, and right TPJ. Overall, the study highlights that deficits in ToM abilities in SZ are not purely due to deficits in social processing but also related to processing complex contextual information.

3.3. **Introduction**

Theory of Mind (ToM), which is classically defined as the ability to infer the mental states of others (i.e., intentions, beliefs, and emotions), is an integral aspect of social interactions. In the general population, daily actions are guided both by one's own mental state and how he or she perceives the mental states of others. In schizophrenia (SZ), however, patients experience robust deficits in ToM abilities, and these deficits are negatively tied to their functioning in social and community environments (Brüne, Abdel-Hamid, Lehmkämper, & Sonntag, 2007; Fett et al., 2011; Pinkham & Penn, 2006). Notably, ToM deficits in SZ are present prior to onset of SZ, throughout the course of the disorder, and persist even after the classic symptoms of schizophrenia have abated (Bora, Yucel, & Pantelis, 2009; Green et al., 2012; Ventura et al., 2015). As pharmaceutical treatments have little effect on improving this ability, ToM deficits in SZ remain a significant obstacle to functioning and recovery in SZ (Green & Harvey, 2014). Therefore, there is an important need to better understand the social and cognitive processes underlying ToM impairments in individuals with SZ to develop better targets for treatment interventions.

Individuals with SZ often also present with general deficits in non-social cognitive domains, such as attention and executive functioning (Bechi et al., 2015; Couture et al., 2011; Martínez-Domínguez, Penadés, Segura, González-Rodríguez, & Catalán, 2015; Joseph Ventura, Wood, & Hellemann, 2013). Such general cognitive deficits associated with SZ could therefore play a role in ToM abilities in SZ. In fact, a recent case study of four individuals with SZ reported that their ToM scores improved following cognitive remediation therapy that targeted non-social cognitive abilities only (Thibaudeau et al., 2017). Such findings may arise because the classic, story-based ToM tasks by which we measure patients' ToM abilities typically require both a judgment based on a social stimulus (i.e., a character), as well as attending to and integrating surrounding context (i.e., what else is happening or has previously happened that could help understand the character; Achim et al., 2013; Lavoie, Vistoli, Sutliff, Jackson, & Achim, 2016). For instance, in the classic ToM task known as the False-belief task, a participant is presented with a scenario involving two characters and an object. In the scenario, one character moves an object without the knowledge of the other, and the participant must judge where the unknowing character will search for the object based on this context and considering the knowledge of the character.

Without incorporating the presented context (that the object had been moved while the first character was not looking), the participant would not correctly solve the ToM task.

Classic behavioral tasks have been adapted for use in functional magnetic brain imaging (fMRI) to identify the brain regions supporting ToM processes. In healthy individuals, these fMRI investigations have highlighted the recruitment of a widespread group of brain regions supporting ToM processing, including the medial prefrontal cortex (mPFC), the lateral prefrontal cortices, the temporoparietal junction (TPJ), the precuneus, and the temporal poles (Frith & Frith, 2007; Mar, 2011; Schurz et al., 2014; van Overwalle & Baetens, 2009). Although this group of brain regions is often referred to as the 'ToM network,' a meta-analysis of 73 studies of ToM suggests that ToM is supported by specific brain regions depending on the ToM task utilized (Schurz et al., 2014). Schurz and colleagues (2014) showed that when the analyses were separated by type of task, the classic False-belief task was the only type of task to show activation of this full 'ToM network' (referred to in the rest of the paper as the reported ToM network). The brain regions within this reported ToM network may therefore not activate entirely in response to processing mental states (as all tasks in the meta-analysis fulfilled this criterion) but may also be sensitive to other aspects involved in completing the task.

Elaborating on this study by Schurz et al (2014), a recent study by our team (Lavoie et al., 2016) used a novel fMRI task to dissociate social and context processing in healthy participants. The task asked participants to identify the cause of an event after being presented with a scenario that was either social or physical in nature (i.e., referring to a character or to a physical object), as well as context that was either congruent or incongruent with what one would expect given the initial scenario. Results of this task showed that brain activation of the reported ToM network could be divided into at least two subnetworks: (1) a dorsal subnetwork (i.e. dorsal TPJ, dorsal mPFC, and dorsolateral PFC) that was activated during context-incongruent vs. context-congruent judgments, regardless of whether it included a social or physical scenario, and (2) a ventral subnetwork (ventral TPJ, ventral mPFC, and temporal poles) that was activated during judgements for social vs. physical scenarios, regardless of whether the added context was incongruent or congruent. Overall, the ToM literature in healthy controls thus suggests an important role for context in ToM tasks.

In patients with SZ, some neuroimaging studies have reported reduced activation in the reported ToM network, while others have reported enhanced activation or a combination of reduced and enhanced activation among these brain regions (Andreasen et al., 2008; Benedetti et al., 2009; Brüne, 2008; Ciaramidaro et al., 2015; Das, Lagopoulos, Coulston, Henderson, & Malhi, 2012; Dodell-Feder et al., 2014; J. Lee et al., 2011; Pedersen et al., 2012; Russell et al., 2000). Abnormal functioning within the mPFC and TPJ are the most frequently reported results among these studies (Kronbichler et al., 2017). However, the methods assessing ToM-related brain activation have varied substantially between tasks, with some tasks relying very little on surrounding context (e.g. the Reading the Mind in the Eyes Task assessed in Russell et al., 2000) and others relying heavily on surrounding context (e.g. the False-belief task in Dodell-Feder, 2014). To date, a systematic fMRI manipulation to dissociate social and contextual components of ToM judgments has yet to be conducted in patients with SZ. Such an investigation may be of relevance in SZ given the evidence for behavioral impairments in context processing in these individuals (Cohen, Barch, Carter, & Servan-Schreiber, 1999; Elvevag, Duncan, & McKenna, 2000; Servan-Schreiber, Cohen, & Steingard, 1996).

For patients with SZ, certain clinical features of the illness could also play an important role in ToM deficits, as SZ is a heterogeneous disorder that can include varying positive, negative, and cognitive symptoms, as well as comorbid conditions. For instance, a recent study by Roy et al., (2015) showed that 47.5% of individuals in their sample of patients with SZ met the diagnostic criteria for social anxiety disorder, a disorder marked by an intense fear of judgment and the desire to project a positive impression of oneself to others (Clark & Wells, 1995). Importantly, individuals with SZ who also express prominent social anxiety may process social situations differently than individuals with SZ who do not. Specifically, research shows that these individuals tend to exhibit protected social knowledge abilities (i.e. the understanding of social norms and rules; Achim et al., 2013) and reduced levels of cognitive symptoms (e.g., poor attention, difficulty in abstract thinking; Sutliff, Roy, & Achim, 2015) compared to individuals with SZ without social anxiety disorder. While primary social anxiety disorder has been associated with reduced abilities on ToM tasks in individuals without SZ (Cui et al., 2017; Hezel & McNally, 2014; Washburn, Wilson, Roes, Rnic, & Harkness, 2016), little evidence has examined ToM in relation to the levels of social anxiety in patients with SZ.

The overarching goal of the present study was to pinpoint important mechanisms underlying ToM deficits in SZ. Specifically, the first objective was to explore the relation of patients' classic ToM task performance with levels of symptoms and social anxiety, as well as with scores on social cognition and general cognition measures. The second objective was to address whether patients' ToM deficits were due to purely social impairments, to the level of context involved in a judgment, or to both social and context components. We therefore assessed whether patients' classic ToM performance was linked to performance on social and/or context-based judgments using a task that orthogonally manipulates the Type of Scenario (social vs. physical) and the Type of Context (incongruent vs. congruent; Lavoie et al., 2016). Lastly, we examined functional brain activation associated with the Type of Scenario and Type of Context manipulations in patients with SZ and healthy participants. We hypothesized that results would highlight correlations between patients' reduced ToM scores and levels of social anxiety, symptom severity, and cognitive deficits. We also hypothesized that patients' ToM scores would be related to their accuracy on social judgments that include incongruent context. For fMRI analyses, we hypothesized that patients with SZ would exhibit altered brain activation compared to controls during context-incongruent judgments (regardless of the social or physical nature of the scenario), particularly in those brain regions previously associated with contextual processing, i.e. the dorsal TPJ, dorsal mPFC, and dorsolateral PFC.

3.4. **Method**

3.4.1 Participants

Twenty-five right-handed patients diagnosed with SZ (n=16) or schizoaffective disorder (n=9) based on DSM-IV criteria were recruited from outpatient clinics of the Centre Intégré universitaire de santé et de services sociaux de la Capitale-National (CIUSS-CN) in Québec City, Canada. At the time of testing, all patients were taking a second-generation antipsychotic. All patients were deemed stable enough to participate in the study by their treating psychiatrist.

Twenty right-handed healthy control (HC) participants were recruited from Université Laval and the local community (19 also reported in Lavoie et al., 2016). HC participants were matched to the patients with SZ on gender, age, and parental socioeconomic status. The two groups were not matched on IQ (Matrix and Vocabulary subscales of the Wechsler Adult Intelligence Scale-IV, mean HC = 113.0 ±12.52, SZ = 100.2 ±15.2; Wechsler, 2008), given that this may result in overcorrected or counterintuitive findings on cognitive function (Dennis et al., 2009). Participant characteristics are presented in Table 3.1.

Exclusion criteria for all participants included a history of neurological disorder, a contraindication for MRI or an estimated IQ below 70. For HC participants, exclusion criteria also included a history of psychotic disorder, a first-degree relative with a psychotic disorder, and current use of psychoactive medication. All participants were native French-speakers. All participants gave their informed consent to participate in the study. The local Research Ethics Committee of the Centre de recherche CERVO, formerly the Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec, approved this study (Project 305).

3.4.2 Assessments

All participants completed three separate testing sessions, including a clinical, a cognitive, and an fMRI assessment. Each session took approximately two-hours to complete.

3.4.2.1 Clinical assessment

3.4.2.1.1 Schizophrenia symptoms

Patients' symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay, Opler, & Fiszbein, 1986), completed by our research team based on results of a comprehensive clinical interview derived from the Structured Clinical Interview for Diagnostic Disorders (SCID-IV). Patients' PANSS scores were assessed using the 5-factor model proposed by Lehoux et al., (2009), which has previously been used in patients with SZ (Sutliff et al., 2015). The model includes the following factors and component symptoms: (1) Positive (delusions, hallucinatory behavior, grandiosity, suspiciousness/persecution, unusual thought content, lack of judgment/insight); (2) Negative (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity, motor retardation, active social avoidance); (3) Cognitive/Disorganization (conceptual disorganization, difficulty in abstract thinking, mannerisms and posturing, disorientation, poor attention); (4) Depression/Anxiety (somatic concern, anxiety, guilt feelings, depression); and (5) Excitement/Hostility (excitement, hostility, uncooperativeness, poor impulse control).

3.4.2.1.2 Social anxiety

Social anxiety symptoms in patients with SZ and HC participants were measured with the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987), a 24-item measure assessing anxiety and avoidance in specific social situations (e.g., eating in a public place). For each of the social situations presented, participants reported their fear/anxiety and avoidance behavior on scales from 0 to 3, with higher total LSAS ratings indicating more severe social anxiety and avoidance (clinically significant social anxiety is typically defined as scores reaching 30-32 or above; Mennin et al., 2002; Rytwinski et al., 2009; Santos, Loureiro, Crippa, & Osório, 2015). LSAS has good psychometric properties, including internal consistency and convergent and discriminant validity (Fresco et al., 2001).

3.4.2.2 Social cognitive assessment

3.4.2.2.1 Combined Stories Test (COST; Achim, Ouellet, Roy, & Jackson, 2012)

This task consisted of 20 short stories and a total of 26 corresponding ToM questions. Participants were presented with one written story at a time and instructed to read it aloud. After each story, participants were asked 1 or 2 open questions about the mental states of the characters in the story and were encouraged to refer to the written text if needed. All answers were scored with a validated correction grid (Achim et al., 2012). This test has good psychometric properties (Achim, Sutliff, Samson, Montreuil, & Lecomte, 2016; Achim et al., 2012; Thibaudeau et al., 2018) and has been used in previous studies with different clinical populations (Achim et al., 2013; Gaudreau et al., 2015; Lavoie et al., 2014; Thibaudeau et al., 2017; Tousignant et al., 2016).

3.4.2.2.2 Situations task (Achim et al., 2012)

The Situations task is a test of social knowledge abilities that consisted of 14 short hypothetical situations which were read to participants. After each situation, participants were asked to respond with the emotion that best described how people would feel in this situation. This social knowledge task did not include an action or reaction by a character but instead, required the participant to reflect on the mental state of the character in a general sense (rather than in a given context, making it distinct from the ToM task; Thibaudeau et al., 2018). The Situations task shows good psychometric properties (Thibaudeau et al., 2018).

3.4.2.2.3 Faces task (Ekman & Friesen, 1976)

This Faces task is an emotion recognition task that consisted of 28 standardized emotional facial stimuli. Participants were asked to select the label that best corresponded to the image (i.e., happy, surprised, angry, disgusted, afraid, or neutral). The presented stimuli have been adapted to present emotions corresponding to the French language, while the images remained the same. This version of the task has been used in other studies to assess emotion recognition in clinical populations (Achim et al., 2013; Lavoie et al., 2014)

3.4.2.3 General cognitive assessment

To assess the relation of ToM abilities with general cognition in SZ, measures of attention, flexibility, processing speed, and working memory were selected. Specifically, subscores from the following measures were utilized: Digit Span test from the WAIS (Wechsler, 1997), the Wisconsin Card Sorting test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), and the Trail-making test (Delis, Kaplan, & Kramar, 2001). The forward and backward measures from the Digit Span subtest have been shown to be predictive of attention and working memory abilities, respectively (Hale, Hoeppner, & Fiorello, 2002), while perseverative errors and categories completed from the WCST task are used as measures of set-shifting and cognitive flexibility (Strauss, Sherman, & Spreen, 2006). Lastly, the Numbers only subtests from the TMT number was used as a measure of processing speed and the Number-letter switch (minus Numbers) from the TMT was used as a measure of working memory (while controlling for processing speed; Mahurin et al., 2006).

3.4.2.4 fMRI assessment

Participants were scanned using a Philips Achieva 3T MRI scanner and an 8-channel SENSE head coil. Structural images were acquired with an MPRAGE sequence (TR = 8.2 ms, TE = 3.7 ms, FoV= 250 mm, flip angle = 8°, 256×256 matrix, 180 slices/volume, slice thickness =

1mm, no gap). Changes in blood oxygenation level-dependent (BOLD) signal (T2* weighted) were then assessed using a gradient echo-planar imaging (EPI) sequence (repetition time TR = 3000 ms, echo time TE = 35 ms, FoV= 230 mm, flip angle = 90°, 128×128 matrix, 45 slices of 3mm covering the whole brain and most of the cerebellum, no gap, voxel size = 1.8×1.8×3 mm). Two runs were acquired, each including 230 EPI volumes acquired along the AC–PC plane.

3.4.2.4.1 REMICS fMRI task (Lavoie et al., 2016)

The fMRI-REMICS task included 64 verbal scenarios and surrounding context, from which participants were to infer the most likely cause of the event. Each trial was divided into three phases: A Scenario phase, a Context phase, and a Judgment phase. First, during the Scenario phase, a sentence was presented visually on screen to describe the main event. Then, in the Context phase, a second sentence appeared under the first and added the context relevant to the cause of the event. Lastly, in the Judgment phase, two potential causes of the event were presented on the screen, and participants were to select the most likely cause of the event. Thus, the goal of the task was for participants to judge the cause, taking into consideration both the scenario and context.

Scenarios presented on screen either described a situation involving a person (Social condition) or a physical object (Physical condition). Furthermore, the context either added information that was congruent with the prototypical inference about the cause of the event (Congruent condition) or added information that was incongruent with the prototypical inference and required an adjustment of the inference about the cause of the event (Incongruent condition). Thus, the task fit a 2 x 2 design leading to 4 task conditions: Social inferences with incongruent context [**SocInc**], Social inferences with congruent context [**SocCon**], Physical inferences with incongruent context [**PhyInc**], and Physical inferences with congruent context [**PhyCon**]. The sentences have been validated to trigger spontaneous judgments of the cause of the social event (i.e. the intention of the character; *Social* conditions) or of the physical event (*Physical* conditions; see Lavoie et al., 2016 for validation details). The timing of task events and examples of each condition are presented in Figure 3.1.

All participants first completed 8 practice trials outside the scanner. The fMRI task then included 2 runs of 32 trials each (8 trials of each of the 4 conditions per run) and lasted around 10 minutes per run.

3.4.3 Analyses

3.4.3.1 Clinical and cognitive assessments

All clinical and cognitive measures were tested for group differences to determine if patients were impaired in various aspects of social processing and general cognition. T-tests were used for all measures except the WCST, which was assessed with Mann-Whitney U tests due to its non-parametric distribution. Additionally, performance scores from the REMICS-fMRI task were entered into an ANOVA (Within-subject factors = Type of Scenario and Type of Context; Between-subject factor = Group).

Correlations were conducted between the COST and the PANSS 5-factor scores and LSAS scores in patients with SZ in order to address the relation of ToM scores to the clinical presentation of SZ. Correlation analyses were also conducted between the COST and social cognition and general cognition measures in patients with SZ. Finally, patients' ToM scores on the COST were assessed for correlations with their performance on the four REMICS task conditions.

3.4.3.2 fMRI preprocessing

Functional MRI data were preprocessed using Statistical Parametric Mapping, version 8 (SPM8; Wellcome Department of Cognitive Neurology, London, UK). Data were first corrected for different slice timing within a volume (reference = middle slice) and functional images of both runs were realigned to the mean functional image. To account for excess movement artifacts associated with imaging clinical populations, the Artrepair toolbox was used (Mazaika, Hoeft, Glover, Glover, & Reiss, 2009; Mazaika, Whitfield, & Cooper, 2005). Volumes with head movements greater than 1 mm/TR were corrected via interpolation of adjacent slices. Runs that required correction for more than 10% of the volumes were excluded from the analyses (4 runs total, 1 run for 3 participants with SZ; 1 run for 1 HC) to reduce potential for interpolation errors due to excessive motion (Mazaika et al., 2005).

Participants' structural images were then co-registered with their mean functional image. For most participants, structural images were segmented based on the ICBM-152 Montreal Neurological Institute (MNI) template. These segmentation parameters were used to normalize their functional data (2 mm isometric voxel) into a standard anatomical space. The functional images of four SZ participants showed distortions when applying this procedure and were thus normalized directly to MNI template. Finally, data were smoothed using a 6mm Gaussian kernel.

3.4.3.3 fMRI analysis

The Scenario phase, Context phase, and Judgment phase of the REMICS task were modeled as separate regressors in a General Linear Model, for a total of 10 covariates of interest: 2 for the Scenario phase (Soc, Phy); 4 for the Context phase (SocInc, SocCon, PhyInc, PhyCon); and 4 for the Judgment (SocInc, SocCon, PhyInc, PhyCon). Six additional regressors were added for movement. A 456s high-pass filter was used, which was determined based on the length between the start of a trial and the next trial of the same condition.

For whole-brain analysis of our repeated measures, between-groups design, we implemented a hypothesis-driven method of targeted t-tests, in keeping with recent studies with similar designs (Brüne, 2008; Das, Lagopoulos, et al., 2012; Lavoie et al., 2016; Pedersen et al., 2012; Vistoli, Lavoie, Sutliff, Jackson, & Achim, 2017). Particularly, we examined brain regions which showed greater recruitment for social vs. physical situations and incongruent vs. congruent context, based on the two subnetworks shown using this contrast in healthy participants (Lavoie et al., 2016). The main fMRI analysis focused on group differences in activation during the Judgment phase of the task, as this is the moment where participants must make an explicit judgment as to the cause of the event and is also the phase where healthy participants showed activation of the full reported ToM network using the same design (Lavoie et al., 2016). However, to account for potential abnormalities in social and contextual processing prior to the judgment in patients with SZ, additional analyses were performed for the social and context manipulations during the Context and Scenario phases of the task.

First-level analysis thus included the following contrasts at the Judgment phase and at the Context phase: (1) Type of Scenario (Soc > Phy) implemented as (SocInc + SocCon) > (PhyInc + PhyCon) and (2) Type of Context (Inc > Con), implemented as (SocInc +

PhyInc) > (SocCon + PhyCon). For the Scenario phase, only the Type of Scenario contrast was performed, as the context was not yet presented. For the second-level analyses, two-sample t-tests (SZ < HC and HC > SZ) were used to assess group differences in the Type of Scenario and Type of Context manipulations. The Marsbar toolbox was then used to extract the mean beta values associated with the significant clusters for each of the four task conditions (SocInc, SocCon, PhyInc, PhyCon) and ANOVAs were performed to test for significant interactions. Lastly, conjunction analyses were used to assess the regions of common activation in SZ and HC. All contrasts were analyzed with a voxel threshold of $p < 0.005$ along with a cluster threshold of $k > 105$, corresponding to a whole-brain corrected probability of 0.05 based on Monte Carlo simulations (using 3dClustSim in AFNI 16.2.13[7]).

3.5. **Results**

3.5.1 Clinical and cognitive assessments (Tables 3.2 and 3.3)

Patients with SZ presented with a total score of 63.17 (13.11) on the PANSS, indicating that they were mildly to moderately symptomatic (Leucht et al., 2005; see Table 3.2 for scores on 5 symptom factors). Patients also presented with clinically important levels of social anxiety on the LSAS (mean = 46.44 ±21.43), which was significantly greater than levels observed in HC participants ($t=-2.96$, $p=0.005$). Additionally, as expected, patients showed significantly lower scores than HC participants on the classic ToM measure, the COST ($t=4.1$, $p<0.001$). No significant group differences were observed, however, for performance on the Situations task ($t=1.16$, $p=0.112$), Faces task ($t=0.84$, $p=0.405$), Digit Span forward or backward ($t=0.468$, $p=0.642$ and $t=1.65$, $p=0.106$, respectively), or the WCST perseverative errors or categories completed ($U=148.0$, $p=0.237$ and $U=158.5$, $p=0.335$, respectively). For the Trail-making test, there was a trend towards a group difference on the Number-Letter switch subscore ($t=-2.00$, $p=0.052$), and a significant group difference on the Numbers subscore ($t=3.85$, $p<0.001$). While not significant, all results were in the expected direction for patients vs. controls.

For the REMICS-fMRI task performance, there was a main effect of Group ($F= 11.30$, $p=0.002$) and a main effect of Type of Context ($F= 22.40$, $p<0.001$). There was no

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[7] This version of AFNI has been updated to account for non-gaussian smoothing using autocorrelation function of neighboring voxels (Cox, Chen, Glen, Reynolds, & Taylor, 2017).

significant effect of Type of Scenario (F< 1, due to equal mean differences between conditions), and no interactions emerged (all p's > .1).[8]

Patients' scores on the COST correlated with their scores on the Situations task (r=0.57, p=0.003) and the Faces task (r=0.47, p=0.017); both remained significant after Bonferroni correction for the social cognition tasks (i.e. p<0.025). No significant correlations were observed in patients with SZ between the COST and clinical measures (PANSS or LSAS scores). However, patients' scores on the COST significantly correlated with performance scores in the SocInc condition of the REMICS-fMRI task (Pearson's r= 0.67, p <0.001), but not with performance scores on the other conditions (SocCon r=0.33, PhyCon r=0.18, PhyInc r=0.22).

3.5.2 Main fMRI analyses: REMICS task results at the Judgment phase

3.5.2.1 Type of Scenario contrast (Soc > Phy; Table 3.4 and Figure 3.3, purple)

For the Type of Scenario contrast, there were no between-groups differences in activation during the Judgment phase (HC > SZ or SZ > HC). Subsequent conjunction analysis (SZ ∩ HC) for this contrast, however, revealed activation in several brain areas of the reported ToM network, including the ventral mPFC, PCC, bilateral temporal poles, and bilateral ventral TPJ.

3.5.2.2 Type of Context contrast (Inc > Con; Table 3.4 and Figure 3.3, green)

For the Type of Context contrast, the between-groups comparison for HC > SZ showed no differences in brain activation during the Judgment phase. However, the inverse comparison, SZ > HC, showed a significant group difference in the right transverse temporal gyrus (TTG). A Type of Context x Group interaction was confirmed with an ANOVA (F=16.34; p<0.001; Table 3.4) and no other interactions were found. Subsequent t-tests showed that both groups modulated their activation of this region based on the Type of Context but in opposite directions: HC showed *less* activation in the right TTG for Inc context than Con context (t=3.16, p=0.005), while SZ showed *greater* activation in the right TTG for Inc context than

[8] The sample was not normally distributed and could not be transformed due to a mode at ceiling effect, as also observed in healthy participants (Lavoie et al., 2016). However, given the robustness of ANOVA tests to non-extreme, skewed data (Norman, 2010; Pearson, 1931), we proceeded with reporting parametric tests.

Con context (t=-2.53, p=0.018).

Subsequent conjunction analysis (SZ ∩ HC) again revealed several regions of significant activation in the reported ToM network. These regions included the dorsal mPFC, right dorsolateral PFC, PCC, and bilateral dorsal TPJ, further suggesting that SZ and HC groups recruit a largely similar network during social and context-based judgments.

3.5.3 Additional fMRI analyses: REMICS task results at earlier task phases

3.5.3.1 Scenario presentation

At the Scenario presentation phase, between group comparisons (HC > SZ or SZ > HC) and conjunction analysis (SZ ∩ HC) revealed no significant regions of activation.

3.5.3.2 Context phase

3.5.3.2.1 Type of Scenario contrast (Soc > Phy; Table 3.5 and Figure 3.4, purple)

The between-groups comparison for the Type of Scenario contrast during the Context phase showed significant differences in activation in the right parahippocampal gyrus for HC > SZ. In this region, patients with SZ exhibited negative modulation of activation for Soc vs. Phy scenarios, but HC participants did not (t=-4.27, t=0.73, respectively). A Type of Scenario x Group interaction was confirmed with an ANOVA (F=16.21; p<0.001; Table 3.4), and no other interactions were observed. The inverse group comparison (SZ > HC) showed a significant difference in a cluster within the left frontopolar PFC (FP-PFC), and again, the Type of Scenario x Group interaction was confirmed with an ANOVA (F=18.42; p<0.001; Table 3.6), and no other interactions were found. In this region, HC participants showed reduced activation in Soc scenarios compared to Phy scenarios, while patients failed to show significant modulation of activation of this region based on Soc vs. Phy scenarios (t=5.74, t=-0.25, respectively).

Conjunction analysis (SZ ∩ HC) of the Type of Scenario manipulation during the Context phase showed significant activation in the PCC/precuneus, left temporal pole, and bilateral TPJ.

3.5.3.2.2 Type of Context contrast (Inc > Con; Table 3.5 and Figure 3.4, green)

For the Type of Context manipulation during the Context phase of the task, the between-groups comparison showed no significant differences for HC > SZ. However, for SZ > HC, several regions showed significant differences between patients with SZ and HC participants for the Type of Context contrast, including the left premotor cortex, SMA/dorsal anterior cingulate (ACC), right middle insula, PCC, and right TPJ. In all of these brain regions, HC participants showed negative modulation of brain activation for Inc > Con context, while patients showed positive modulation for the Inc > Con comparison. The Type of Context x Group interaction was confirmed for all brain regions (see Table 3.6).

The conjunction analysis (SZ ∩ HC) of the Type of Context contrast during this phase showed significant activation within the left inferior frontal gyrus.

3.6. Discussion

The present study examined task- and illness-related factors that may underlie ToM deficits in SZ. Importantly, this study used both clinical and cognitive assessments, as well as a novel fMRI task that manipulated the Type of Scenario (social vs. physical) and Type of Context (incongruent vs. congruent) to determine whether ToM impairments in SZ are linked to the social nature of a judgment, to the level of context involved, or to both. In addition to presenting with impairments on the classic ToM task, patients with SZ also presented with clinically significant social anxiety on the LSAS and reduced processing speed compared to HC participants (as measured by the Trail-making test Numbers score). In accordance with our hypothesis, behavioral results showed a correlation between patients' reduced performance on the classic ToM task and their performance on the social, context-incongruent condition of the REMICS-fMRI task. Brain imaging results, however, did not reveal that patients with schizophrenia had abnormalities in brain activation within the reported ToM network for either the Type of Scenario or Type of Context manipulation, but instead highlighted similar activation in patients and HC participants in several regions within this network, including the ventral mPFC, ventral TPJ, and bilateral temporal poles in relation to social vs. physical scenarios. A similar pattern was witnessed for incongruent vs. congruent context, such that patients and HC participants activated the dorsal mPFC, dorsolateral PFC, and dorsal TPJ for these judgments, regardless of whether the scenario was social or physical in nature. The mPFC and TPJ are some of the most common brain regions showing altered activation in previous neuroimaging studies of ToM in SZ (e.g. Andreasen et al., 2008; Brune et al., 2008; Lee et al., 2011; Walter et al., 2009); however, the present results suggest that activation of these brain regions in ToM tasks may be related to processing context rather than the social nature of a situation, thereby suggesting the importance of controlling for context in ToM tasks. Results of earlier phases of the REMICS-fMRI task also support this finding, with patients displaying abnormalities in brain activation during the presentation of written context *prior* to making a social or nonsocial judgment. Overall, the study highlights that deficits in ToM abilities in schizophrenia are not purely due to deficits in social processing but may be importantly related to processing incongruent contextual information in ToM tasks.

3.6.1 Correlational analyses do not suggest a relation between ToM deficits and clinical measures or general cognition

In keeping with previous studies suggesting prominent social anxiety in SZ (ex: Achim et al., 2013; Michail & Birchwood, 2009; Roy et al., 2015), the present patient sample displayed clinically significant levels of social anxiety on the LSAS. However, contrary to our expectation, given previous studies showing a relation of social anxiety with ToM scores in primary social anxiety disorder (Cui et al., 2017; Hezel & McNally, 2014; Washburn et al., 2016), the results did not suggest an association between their social anxiety and ToM abilities. Yet, one explanation for this lack of a relationship may be that we did not examine if these individuals met the full diagnostic criteria of social anxiety disorder. Instead, we examined social anxiety in all patients to encapsulate the full range of social anxiety present in the group, which was determined to be the favorable approach given our small sample size. However, this approach likely resulted in the inclusion of patients whose social anxiety was related to the presentation of psychotic symptoms, rather than social anxiety of a primary nature, which may have affected our findings. Given that the exploration of social anxiety in SZ is recent, the best methods for identifying and diagnosing these patients remain unknown (Pallanti, Cantisani, & Grassi, 2013). Future studies should explore this concept further by assessing the relation of social anxiety in patients meeting the diagnostic criteria for a comorbid social anxiety disorder in SZ to further probe a potential relationship.

Patients with SZ did not display impaired performance on social knowledge, emotion recognition, or cognitive flexibility measures, but did display reduced processing speed and a trend towards significantly reduced working memory as assessed with subsections of the Trail-making test. Importantly, a meta-analysis by Dickinson and colleagues (2007) showed that reduced processing speed is one of the most robust cognitive deficits in SZ), suggesting that the present study was able to replicate an important cognitive impairment in the patient sample. This reduced processing speed in SZ, however, did not relate to patients' reduced behavioral ToM abilities. The ToM assessment (the COST) did not include a time-constraint, and therefore, it is likely that this measure was not affected by patients' processing speed. In fact, only social knowledge and emotion recognition scores were associated with patients' ToM abilities on the story-based COST. Although ToM is a unique construct, literature does suggest that ToM is a higher-order social cognitive function that relies on lower-level social processing abilities including concepts of social knowledge and emotion processing (Yang, Rosenblau, Keifer, & Pelphrey, 2015). However, the lack of correlation between other cognition measures and ToM in this study may also be related to the fact that our patient sample did not display some very well-replicated cognitive deficits such as in executive functions (Fioravanti, Bianchi, & Cinti, 2012). Future studies will therefore be needed to further address this relation between ToM and social and non-social cognition in schizophrenia.

3.6.2 Correlational analyses highlight that ToM deficits in SZ are strongly correlated to task performance for social judgments that involve incongruent context

Although the typical definition of ToM (i.e. the ability to infer the mental states of others) does not include the ability to integrate context in mental state inferences, the social, context-incongruent condition was the only condition of the REMICS-fMRI task in which patients' behavioral scores correlated with their performance on a classic ToM task. Importantly, patients' scores on the ToM task did not show a relationship with scores on the social, context-congruent condition of the REMICS-fMRI task. While the congruent condition required participants to read context, this congruent context was validated to be in line with a spontaneous inference elicited by reading the initial scenario (Lavoie et al., 2016). Therefore, the association between patients' ToM abilities and their performance on the social, incongruent context condition is likely linked specifically to the incongruent, or unexpected, nature of the social context. This may then be related to processes of attending to unexpected information, inhibiting one's previously held view, or integrating this new information to update an inference or to form a new inference entirely. Indeed, patients with SZ may be impaired in later, higher-cognitive processes associated with processing context, such as context integration and cognitive flexibility (Champagne-Lavau, Charest, Anselmo, Rodriguez, & Blouin, 2012). Overall, more research is needed to pinpoint the underlying aspects of social, incongruent context processing that is specifically related to ToM in schizophrenia. However, it is clear from the results that context is an important aspect of ToM that needs to be addressed by future studies.

3.6.3 fMRI results reveal brain activation associated with social and context-based judgments is relatively intact in patients with schizophrenia

For the fMRI analysis, we examined brain activation related to the Type of Scenario and Type of Context manipulations at both the Context phase of the task (i.e. during the presentation of context prior to making a judgment as to the cause of the event) and at the Judgment Phase (i.e. the phase of the task where participants must explicitly make a judgment as to the cause of the event). Our analyses represent an important addition to the ToM literature in SZ, given that the majority of studies to date have utilized fMRI tasks with block designs that take into account brain activation during the entire ToM task, from processing the initial scenario and its context to explicitly making a mental state judgment.

Our main fMRI analysis for this study examined the Judgment phase of the task, given our initial hypothesis that patients would exhibit differences in brain activation during this phase, based on results of healthy controls showing the recruitment of distinct social and context-related networks during this task phase (Lavoie et al., 2016). Specifically, we hypothesized that patients would exhibit altered activation within the ventral regions of the reported ToM network during social vs. physical judgments and in the dorsal portion of this network for context-incongruent vs. congruent-congruent judgments, as seen in healthy participants (Lavoie et al., 2016). However, for the Type of scenario contrast, results did not show any regions that differed based on the group, suggesting that patients with SZ do not have specific deficits at the neural level associated with making social judgments. On the other hand, for the Type of Context contrast, patients with SZ showed a significant difference in activation of the right transverse temporal gyrus (TTG), with HC participants activating the right TTG less during the context-incongruent condition vs. context-congruent conditions and patients activating this region more for context-incongruent vs. context-congruent conditions.

Although altered activation of the TTG, the primary auditory processing center of the brain, was not expected for the present study, evidence suggests that the TTG is involved in phonological processing of written words (Hickok & Poeppel, 2007). This region may then have been recruited in order to process the verbal stimuli associated with the context-based judgments. The TTG has close connections with areas of the frontal and temporal lobe and is involved in verbal working memory tasks (Johnson et al., 2006; Peters et al., 2009; Wager, Spicer, Insler, & Smith, 2014). For instance, Wagner et al. (2014) showed that the less participants activated the TTG, the better they performed on a working memory task, highlighting that *inhibition* of this region may be required for more complex tasks that involve working memory. This pattern of activation is consistent with the results of the current study: HC participants showed less activation in the right TTG for judgments based on incongruent context (which would require a greater demand on working memory processes) vs. the congruent context condition. While the opposite pattern was observed in the TTG for patients with SZ, several studies have reported reduced structural integrity in the temporal lobe throughout the course of schizophrenia (Benedetti et al., 2009; Buckley, 2005; Gaser, Nenadic, Volz, Büchel, & Sauer, 2004; Sigmundsson et al., 2001; Wright et al., 2000). These disorder-related structural abnormalities have previously shown a correlation with ToM-related functional abnormalities (Benedetti et al., 2009), and therefore, it could be that structural abnormalities are also involved in the differences in patients in the present study.

Follow-up conjunction analyses addressed the areas of activation in patients with SZ during the Type of Scenario and Type of Context manipulations and revealed significant activation in the reported ToM network. Specifically, for social scenarios (vs. physical scenarios), activation was located in the ventral mPFC, ventral bilateral TPJ, and bilateral temporal pole, regardless of the contextual nature of the judgment. On the contrary, for judgments that added incongruent context (vs. those that added congruent context), activation was located in the dorsal mPFC, bilateral dorsal TPJ, and dlPFC, regardless of the social nature of the judgment. This ventral/dorsal association observed in the present study is also fitting with previous reports showing functional distinctions between the dorsal and ventral subregions of the mPFC and TPJ. For instance, the dorsal mPFC has been associated with cognitively demanding tasks, such as conflict monitoring (Van Overwalle, 2011), error detection (Modirrousta & Fellows, 2008; Nee, Kastner, & Brown, 2011), and executive control (Posner, Rothbart, Sheese, & Tang, 2007; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004), while the ventral mPFC has been associated with processing mental states of the self and others (D'Argembeau et al., 2007; Van Overwalle, 2009, 2011) and emotionally salient stimuli (Bzdok et al., 2013; J. P. Mitchell et al., 2005). The TPJ may also be divided into dorsal and ventral regions that serve different cognition functions (Carter & Huettel, 2013; Krall et al., 2014; Scholz, Triantafyllou, Whitfield-Gabrieli, Brown, & Saxe, 2009). For instance, a study by Scholz et al., (2009) showed that the ventral portion of the TPJ was activated in mental state processing, while the dorsal part was involved in reorienting attention from an unexpected stimulus.

Furthermore, the spatial gradients within these regions likely reflect differing connectivity, as a recent functional parcellation of the TPJ showed that the ventral TPJ showed resting state connectivity with the vmPFC and the anterior insula (Mars et al., 2012). Together, activation of the ventral portions of the mPFC and TPJ in the present study may thus reflect recruitment of a ventral attention brain network, as described by Corbetta & Shulman, (2002) & Corbetta, Patel, & Shulman (2008), which is responsible for bottom-up, or stimulus-driven, orientation of attention in response to salient stimuli. Although our social condition was designed to be emotionally neutral, it is possible that the social nature of a mental state inference itself may be salient from an evolutionary perspective (Adolphs, 2001) and therefore the recruitment of the vmPFC and vTPJ in response to social stimuli may indeed be a salient or 'stimulus-driven' response.

The dTPJ, on the other hand, has been identified as a 'circuit-breaker' within the dorsal attention system that is involved in top-down control to orient attention to important stimuli (Astafiev, Shulman, & Corbetta, 2006). The dmPFC, FEF and dorsolateral PFC are also part of this dorsal attention system (Corbetta et al., 2008; Ptak, 2012), and therefore, activation of these regions during the Type of context manipulation may signify that both groups were able to recruit this network to perform goal-directed action, in this case, making social and context-based judgments. Specifically, the FEF may be involved in abstract representations of actions (Ptak, 2012; Trageser, Monosov, Zhou, & Thompson, 2008), while the dorsolateral PFC is involved in maintaining and manipulating those representations in working memory (Barbey, Koenigs, & Grafman, 2013; Curtis & D'Esposito, 2003; Smith et al., 2011; Veltman, Rombouts, & Dolan, 2003; Wagner, Maril, Bjork, & Schacter, 2001).

Other regions of the reported ToM network that were activated in the conjunction analysis for the Type of Scenario manipulation include the temporal poles and the PCC. The temporal poles are hypothesized to be vital to the use of personal memories to understand the mental states of others (Moriguchi et al., 2006). The PCC, on the other hand, is associated with mental imagery and internally directed attention as part of the default mode network (Greicius, Supekar, Menon, & Dougherty, 2009; Leech, Kamourieh, Beckmann, & Sharp, 2011; Margulies et al., 2009). The REMICS-fMRI task, being a verbal task of social scenarios, would likely require participants to actively utilize mental imagery associated with the social situation, as well as recall their own self-experiences in order to judge others' mental states.

Overall, the results of the Judgment phase highlight that patients with SZ, like HC participants, are able to recruit both stimulus-driven and top-down attentional resources, as well as brain regions important for self-other processing, in order to make social and context-based judgments.

3.6.4 Abnormalities in brain activation in schizophrenia specific to the context phase: Evidence for ToM as a multidimensional process

Exploratory analysis of the social and context task manipulations at earlier task phases highlighted group differences during the Context phase of the task when participants were presented contextual information related to the initial scenario. Results showed a between-groups difference during the Type of Scenario contrast in the FP-PFC, a region previously associated with relational processing such as maintaining old items and integrating new rules

(Boschin, Piekema, & Buckley, 2015; Kroger et al., 2002; Raposo, Vicens, Clithero, Dobbins, & Huettel, 2011). Particularly, in the FP-PFC, HC participants modulated their activation based on the Type of Scenario, deactivating the FP-PFC during social scenarios but not during physical scenarios, while patients with SZ did not significantly adapt their activation. A study by Raposo et al. (2011) showed a dissociation of the FP-PFC and the mPFC, such that the FP-PFC was activated in response to relational components of a task regardless of the social or physical nature of the task, whereas the mPFC was activated in response to judgments of the other vs. the self. In the present study, although it was not an explicit goal of the REMICS task, the physical condition may rely more on concrete relations between objects, while the social conditions rely on dynamic, abstract processing. Particularly, given the role of the FP-PFC, HC participants may deactivate the FP-PFC during presentation of context associated with social scenarios, in favor of recruiting activation of the mPFC, while activating the FP-PFC for physical scenarios.

Patients also showed abnormal activation during the Type of Scenario within the right parahippocampal gyrus. The parahippocampal gyrus is an important part of the limbic system that has been associated with contextual associative processing (Aminoff, Kveraga, & Bar, 2013; Zhou et al., 2016). In the present study, HC participants showed greater activation in the parahippocampal gyrus for social vs. physical scenarios, while patients showed the opposite relation, inhibiting this region during social scenarios. At the Context phase of the task, participants are not asked to make a judgement at this point, but they are aware that they will soon have to judge the cause of the event and are thus likely processing this new context in their mental model of the event. Patients may then inefficiently recruit this region for social processing, which is in line with results of other studies of altered parahippocampal activation (Garrity et al., 2007; Surguladze et al., 2006).

For the Type of Context manipulation at the Context phase, regions showing differences in activation in patients with SZ compared to HC participants included the right middle insula, the premotor cortex, SMA, and PCC, and occipital areas. This portion of the insula falls within the sensorimotor region, as indicated by the meta-analysis by Kurth and colleagues (2010), which is intrinsically connected to the motor and occipital regions to regulate skeletomotor orientation and response selection (Cauda et al., 2011; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). Results of the present study suggest that while HC may modulate brain networks differently for getting ready to choose a response to contextually difficult tasks, patients with SZ do not appear to make this distinction. This Type of context contrast also shows reduced modulation in activation in patients in the right TPJ (SMG)/TTG. Given that this activation also includes altered activity within the right TTG observed in the Judgment phase may actually begin earlier in the task. This interesting result further supports information processing deficits in schizophrenia that occur at the phase of collecting and integrating information to be used for a response/judgment. However, it is important to note that during the Context phase, the initial sentence describing the scenario was still on screen (above the sentence describing context), and participants were aware that they would soon be asked to make a judgment on the next screen. Therefore, although the timing of this activation coincides with the presentation of contextual information, it is possible that participants may have still been focusing on the initial scenario or alternatively, preparing for their upcoming judgment, rather than specifically processing context.

To our knowledge, only one other study has used an event-related fMRI design that allowed for the examination specifically of the context presentation in a ToM task. This study by Varga et al., (2013) used a task similar to the REMICS task but designed specifically to examine ironic statement (vs. literal statement) comprehension. In this task, context was presented first, followed by an ironic statement requiring a forced-choice judgment. Interestingly, in line with results from the present study, Varga et al., (2013) showed that patients with SZ had significantly different brain activation only during context presentation but not during the ironic statement/judgment phase. However, Varga and colleagues (2013) found greater activation between patients vs. controls in the left inferior frontal gyrus, while the present study observed healthy activation in patients with SZ in the left inferior frontal gyrus during the conjunction analysis of the Context phase. Our task, however, was designed to present clear, simple statements which would likely not require as in-depth language processing involved in the irony task, and patients may have therefore been able to recruit this brain region as healthy controls.

Overall, although it was hypothesized that greater differences would be observed in patients with SZ during the Judgment phase of the task, the present results are in line with results of Varga et al (2013) as well as reviews suggesting that ToM is a multi-dimensional process made up of several component processes, from basic sensory to social context processing (Brunet-Gouet & Decety, 2006; Schaafsma et al., 2015). Results of the REMICS task thus add to this previous work suggested that deficits in ToM may occur earlier at earlier phases of stimuli processing.

3.6.5 Considerations and limitations

The present study has limitations that should be considered. First of all, the present study did not observe impaired performance across cognitive domains as would be expected based on previous meta-analyses (e.g. Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014; Fioravanti, Bianchi, & Cinti, 2012). We did, however, observe a typical difference in IQ in patients with SZ. The sub-scores of the WCST, Digit-Span, and Trail-making test used in this study were chosen specifically to target attention, flexibility, and working memory. The measure of IQ, however, may have targeted different domains, such as problem-solving and language abilities (as part of the Matrix and Vocabulary WAIS tests, respectively), which could explain this dissociation between IQ and neurocognitive abilities in the patient sample.

Given the lack of observed neurocognitive deficits in patients with SZ, we cannot exclude that this sample may have been well-functioning and this is why we did not observe group difference at the judgment phase of the task. Furthermore, our sample size may have limited these affects. Although our sample size of 25 patients is one of the largest samples used in fMRI studies of ToM in this population, it is quite small compared to previous behavioral studies showing neurocognitive impairments in SZ (e.g. Bechi et al., 2015; Couture et al., 2011). However, we did not perform a comprehensive assessment of cognition and therefore, it is possible that the patients would have been impaired on other aspects of cognitive function that could be related to ToM deficits. Particularly, a basic measure of context processing, such as the AX-Continuous Performance Test (Cohen & Servan-Schreiber, 1992), would be a useful tool to determine if the patient sample indeed displayed deficits in perceptual context processing, given that this is the moment of the task when the patients showed altered brain activation.

Additionally, the study was not able to determine deficits specifically on the social, incongruent condition of the REMICS-fMRI, despite showing a correlation of impaired ToM abilities on the classic ToM task and the social, incongruent condition of the fMRI task. However, contrary to the COST, the REMICS-fMRI task was not designed to be sensitive to specific behavioral differences. Instead, the REMICS-fMRI task was developed to systematically activate the process of interest, which in this case is representing social scenarios and integrating complex context. The social conditions of the REMICS-fMRI task specifically targeted understanding the intentions of others and were designed to be emotionally neutral. Therefore, the associated brain activation addresses a more cognitive aspect of ToM and cannot speak to social processes related to emotional processing in SZ during ToM judgments. This remains to be addressed in future studies, as context also likely plays an important role in understanding the emotions of others.

Lastly, the study did not assess the relation of ToM-related brain activation to schizophrenia symptoms, duration of illness, or other illness-related factors that may be related to altered brain activation in SZ. As SZ is a heterogeneous disorder, such differences in clinical presentation may also be involved in heterogeneous results among fMRI studies in SZ and should be investigated in future studies with larger sample sizes.

3.6.6 Conclusions

Overall, the study finds little evidence for affected social processing in SZ. Instead, results highlight that patients may be affected in processing context and integrating this information into an inference, as evidenced by altered brain activation at the Context presentation phase of the fMRI task. However, during social- and context-based judgments, patients with SZ showed largely intact brain activation, including the ventral and dorsal portions of the mPFC, PCC, and TPJ, core regions of the reported ToM network. To better clarify the cognitive processes involved in ToM and how they can go awry in SZ, future studies should thus further examine the effect of timing in recruitment of brain regions in ToM tasks.

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Table 0.1 Participant characteristics and assessment scores

	HC	SZ	HC vs. SZ
N	20	25	
Gender (male:female)	16:4	19:6	$X^2 = 0.008$; $p = 0.927$
Age	28.55 (7.9)	29.96 (9.0)	$t = -0.55$; $p = 0.670$
Parental SES†	3.10 (0.85)	3.43 (0.94)	$t = -1.12$; $p = 0.232$
Estimated IQ	113.0 (12.5)	100.2 (15.2)	$t = 3.03$; $p = 0.004$*
Diagnoses (N)			
Schizophrenia		16	
Schizoaffective disorder		9	
Illness duration (years)		7.88 (8.12) Range = 0.68 – 39.40 years	

*Between-groups differences significant at $p < 0.05$.

† Parental SES was measured via the Hollingshead Measure; scores ranged from 1 to 5, with higher scores indicating advanced education/professional occupation.

HC = healthy control; SZ = schizophrenia; SES = socioeconomic status.

Table 0.2 Performance scores on clinical assessments, social cognition, and general cognitive measures.

	HC	SZ	T-statistic, p value
PANSS symptoms			
Positive	--	14.38 (6.44)	--
Negative	--	15.83 (6.49)	--
Cognitive/Disorganization	--	9.79 (3.01)	--
Depression/Anxiety	--	8.50 (2.89)	--
Excitement/Hostility	--	6.83 (2.96)	--
TOTAL		63.17 (13.11)	
Social anxiety			
LSAS	28.08 (19.84)	46.44 (21.43)	$t = -2.955, p = 0.005^*$
Social cognition			
COST	45.15 (3.88)	37.2 (7.94)	$t = 4.10, p < 0.001^*$
Situations task	11.58 (1.35)	10.8 (1.73)	$t = 1.62, p = 0.112$
Faces task	22.74 (2.18)	22.16 (2.30)	$t = 0.842, p = 0.405$
Non-social cognition			
Digit span forward	10.89 (2.49)	10.6 (1.63)	$t = 468, p = 0.642$
Digit span backward	9.16 (2.87)	8.00 (1.76)	$t = 1.653, p = 0.106$
WCST categories completed	4.84 (1.86)	4.05 (2.26)	$U =158.5, p = 0.335$
WCST perseverative errors	0.149 (0.01)	0.175 (0.09)	$U = 148.0, p = 0.237$
TMT Numbers	11.65 (1.90)	8.68 (2.10)	$t = 3.852, p < 0.001^*$
TMT Number-letter switch (minus Numbers)	10.44 (4.12)	8.25 (2.97)	$t = 2.00, p = 0.052$
REMICS accuracy[†]			
SocInc	14.75 (1.25)	13.52 (2.04)	--
SocCon	15.40 (0.94)	14.48 (1.48)	--
PhyInc	15.10 (1.21)	13.32 (1.75)	--
PhyCon	15.45 (1.00)	14.28 (1.82)	--

[*]Between-groups differences significant at $p < 0.05$;

[†]Analyses performed ANOVA (see Section 3.5.1 for Type of Scenario, Type of Context, and Group effects).

HC = healthy control; SZ = schizophrenia; LSAS = Liebowitz Social Anxiety Scale; COST = Combined Stories Test; WCST = Wisconsin Card Sorting Test; TMT = Trail-making Test.

Table 0.3 Correlations of patients' COST scores with clinical assessment, social cognition, and general cognition scores

	COST	
	r	p
PANSS symptoms		
Positive	0.27	0.196
Negative	0.20	0.345
Cognitive/Disorganization	-0.20	0.346
Depression/Anxiety	0.29	0.173
Excitement/Hostility	0.14	0.530
Social anxiety		
LSAS	-0.06	0.782
Social cognition		
Situations task	0.52	0.007*
Faces task	0.47	0.017*
Non-social cognition		
Digit span forward	0.20	0.339
Digit span backward	0.28	0.174
WCST categories completed	0.25	0.282
WCST perseverative errors	0.02	0.252
TMT Numbers	0.09	0.674
TMT Number Letter- Letter	0.39	0.086

*Between-groups differences significant at $p < 0.05$.

LSAS = Liebowitz Social Anxiety Scale; COST = Combined Stories Test; WCST = Wisconsin Card Sorting Test; TMT = Trail-making Test.

Table 0.4 Brain activation during REMICS task Judgment phase: Social and context manipulations

Type of scenario contrast (Soc > Phy)							
Brain region	**BA**	**k**	**x**	**y**	**z**	**T-value SZ**	**T-value HC**
Between-groups: HC > SZ							
None	--	--	--	--	--	--	--
Between-groups: SZ > HC							
None	--	--	--	--	--	--	--
Conjunction: SZ ∩ HC							
R ventral mPFC	10	115	2	56	-10	3.78	5.53
L PCC	31, 23	1603	-2	-60	18	6.43	6.55
R temporal pole	38	574	42	14	-30	8.35	5.99
L temporal pole	38	217	-42	10	-34	4.09	8.28
R ventral TPJ (Angular gyrus)/R fusiform	39, 37	620	52	-60	22	4.80	5.59
L ventral TPJ (Angular gyrus)	39	106	-50	-66	22	3.47	3.57
Type of context contrast (Inc > Con)							
Between-groups: HC > SZ							
None	--	--	--	--	--	--	--
Between-groups: SZ > HC							
R TTG	41	157	54	-10	8	2.86	-2.37
Conjunction: SZ ∩ HC							
L frontal eye field	8	271	-40	22	42	4.61	4.88
R,L frontal eye field/R,L dorsal mPFC	8,9,10	1104	20	30	56	4.53	4.21
R dorsolateral PFC	9	161	48	24	40	3.86	4.10
R FP-PFC	10	277	34	54	0	5.28	4.17
L FP-PFC	10	384	-36	56	4	5.21	5.54
L dorsal FP-PFC	10	168	-20	58	28	4.55	5.52
R,L PCC/R,L precuneus	31, 23, 7	402	0	-62	30	5.21	3.46
R dorsal TPJ (Angular gyrus)	39	550	58	-56	36	5.57	4.59
L dorsal TPJ (Angular gyrus)	39	1038	-54	-58	32	5.50	5.63
R cerebellum	NA	268	20	-78	-32	4.58	3.77

Brain regions showing significant activation in the Judgment phase for between-groups two-sample t-tests and conjunction analyses. Above results are significant at $p < 0.005$ and $k > 105$, corresponding to a cluster-corrected threshold of $p < 0.05$.

Soc = social condition; Phy = physical condition; BA = Brodmann area; Inc = incongruent context condition; Con = congruent context condition; SZ = schizophrenia; HC = healthy controls; TTG= transverse temporal gyrus; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; FP-PFC = frontopolar prefrontal cortex; TPJ = temperoparietal junction.

Table 0.5. Brain activation during REMICS task Context phase: Social and context manipulations

Brain region	BA	k	x	y	z	T-value SZ	T-value HC
Type of scenario contrast (Soc > Phy)							
<u>Between-groups: HC > SZ</u>							
R parahippocampal gyrus	36	150	8	-30	-4	-4.27	0.73
<u>Between-groups: SZ > HC</u>							
L FP-PFC	10	190	-34	50	18	.85	-0.25
<u>Conjunction: SZ ∩ HC</u>							
R,L PCC/R,L precuneus	31, 7	858	2	-56	24	5.26	7.37
L temporal pole	38	148	-40	16	-34	4.40	3.88
R TPJ (Angular gyrus)	39	210	48	-64	18	4.18	3.07
L TPJ (Angular gyrus)	39	250	-48	-64	20	5.95	3.08
Type of context contrast (Inc > Con)							
<u>Between-groups: HC > SZ</u>							
None	--	--	--	--	--	--	--
<u>Between-groups: SZ > HC</u>							
L dorsal premotor cortex	6	110	-18	-2	70	1.94	-3.93
L ventral premotor cortex/L STG	6, 22	212	-46	-2	6	-0.18	-5.21
R SMA / R dorsal ACC	6, 32	415	4	8	50	2.01	-4.65
R middle insula	13	270	40	-8	-4	0.83	-5.68
L middle/superior occipital gyrus	18, 19	331	-16	-78	24	4.70	-2.90
R superior/middle occipital cortex	19, 18	240	20	-84	34	1.34	-4.73
L inferior occipital cortex	19	209	-44	-70	-2	2.55	-2.98
L PCC	31	135	-6	-60	36	4.41	-1.53
R TPJ (SMG)/R TTG	40, 41	493	50	-26	22	0.44	-5.66
R cerebellum	NA	2007	28	-48	-34	4.13	-3.12
<u>Conjunction: SZ ∩ HC</u>							
Left inferior frontal gyrus	44	198	-48	18	16	4.92	3.43

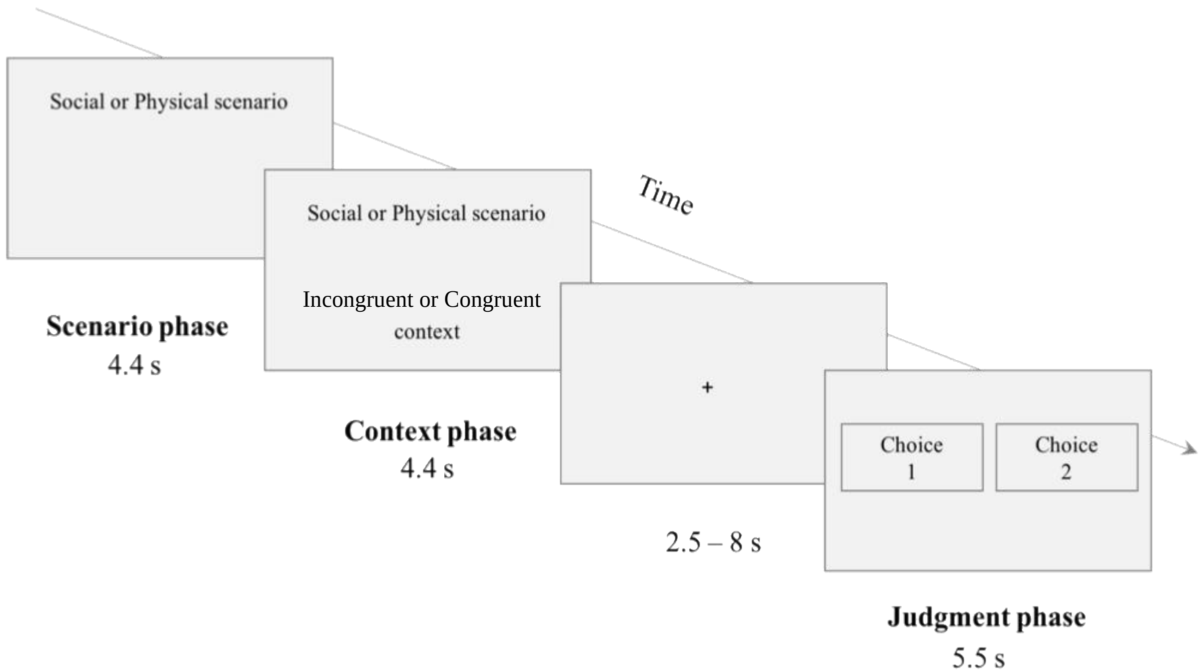
Brain regions showing significant activation in the Conext phase for between-groups two-sample t-tests and conjunction analyses. Above results are significant at $p < 0.005$ and $k > 105$, corresponding to a cluster-corrected threshold of $p < 0.05$.
Soc = Social condition; Phy = Physical condition; BA = Brodmann area; Inc = Incongruent context condition; Con = Congruent context condition; SZ = schizophrenia; HC = healthy controls; R = right; L = left; FP-PFC = frontopolar prefrontal cortex; PCC = posterior cingulate cortex; STG = superior temporal gyrus; SMA = supplementary motor area; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; TPJ = temperoparietal junction; SMG = supramarginal gyrus; TTG= transverse temporal gyrus.

Table 0.6 ANOVA results of ROI analyses

	Type of Scenario	Type of Scenario x Group	Type of Context	Type of Context x Group	Type of Scenario x Type of Context	Type of Scenario x Type of Context x Group	Group
R TTG	1.19	0.44	0.44	16.34*	2.60	0.65	< 0.01
R Parahippocampal	1.56	16.21*	0.07	0.09	2.46	1.80	0.09
L FP-PFC	15.63*	18.42*	3.54	2.22	1.63	2.58	1.70
L dorsal premotor	0.82	0.18	4.51	18.95*	0.05	2.72	0.18
R SMA/R dorsal ACC	0.80	0.65	3.36	22.30*	0.02	3.70	0.12
R middle insula	8.22	2.10	28.50*	27.07*	0.60	3.74	0.82
L middle/superior occipital gyrus	2.87	0.14	0.84	23.25*	1.12	0.14	0.43
R superior/middle occipital cortex	9.40*	0.30	5.70*	15.93*	2.54	0.32	< 0.01
L inferior occipital	3.94	0.82	0.82	16.30*	0.10	0.61	0.30
L PCC	50.64*	3.55	0.51	15.43*	< 0.01	0.05	0.01
R TPJ (SMG)/ R transverse temporal gyrus	1.66	< 0.01	25.82*	23.32*	0.12	0.81	5.63*
R cerebellum	0.86	0.36	1.34	31.45*	1.35	0.04	0.35

*Between-groups difference significant at $p < 0.05$.

STG = superior temporal gyrus; SMA = supplementary motor area; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; TPJ = temperoparietal junction; SMG = supramarginal gyrus; TTG= transverse temporal gyrus.



Examples of REMICS task conditions

Condition	Scenario	Context	+	Judgment phase	
SocInc	You observe a friend getting an orange from the fridge	Someone tells you that they learned a new circus trick		He wants to eat the oranges	He wants to juggle the oranges
SocCon	You observe a man climbing on the diving board of the pool	Someone tells you that he checked the water temperature		He wants to jump in the pool	He wants to clean the pool
PhyInc	You observe that the gas motor of a boat stops suddenly	Someone tells you that the lake is full of algae at this spot		The gas tank of the boat is empty	The propeller is trapped in the algae
PhyCon	You observe a deflated tire in the front of a vehicle	Someone tells you that the road is filled with potholes		The tire got a hole	The tire burst because of the heat

Figure 0.1 REMICS-fMRI task outline and examples of conditions.

SocInc = Social incongruent context; SocCon = Social congruent context; PhyInc = Physical incongruent context; PhyCon = Physical congruent context.

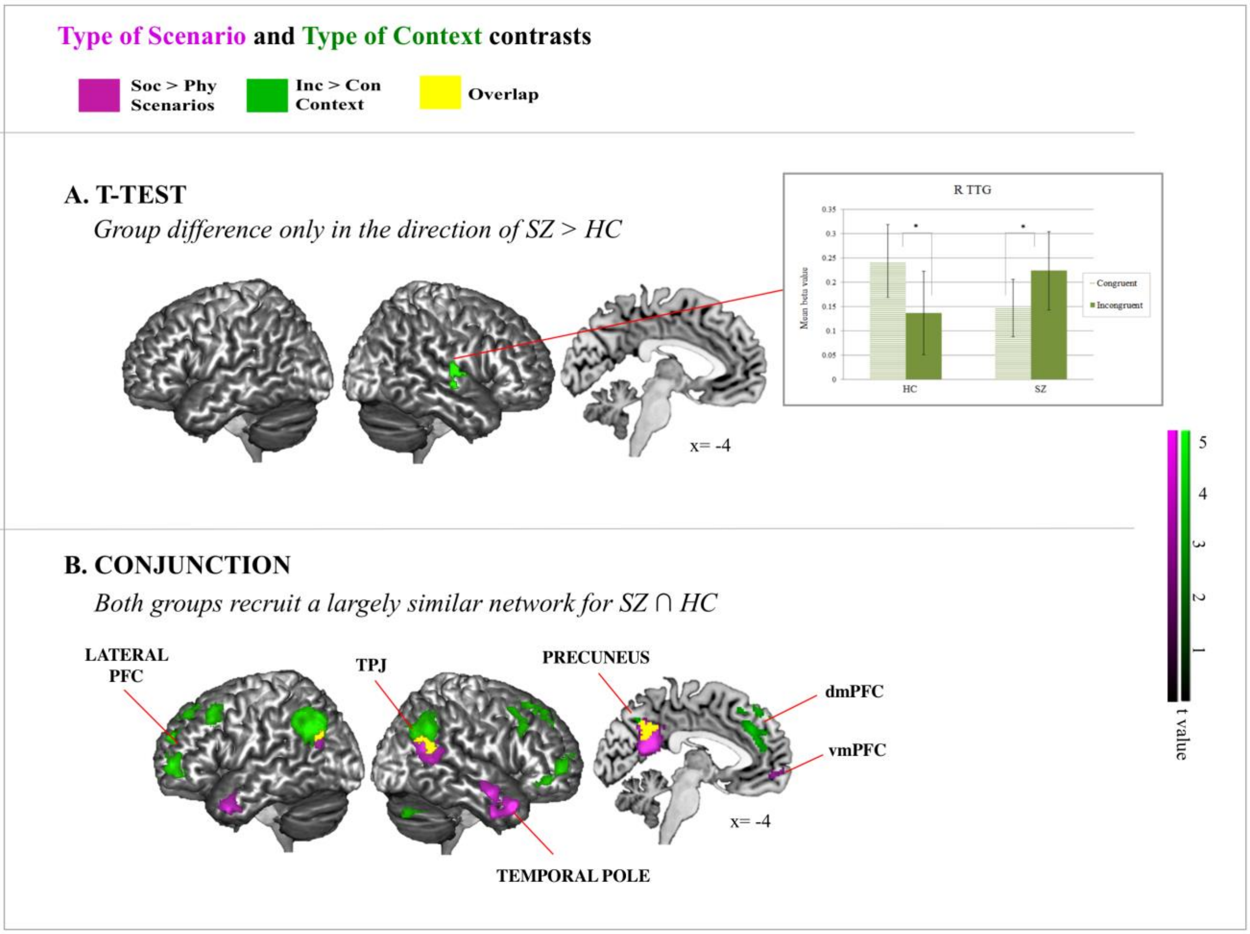


Figure 0.2 Brain activation during REMICS task** Judgment phase**: Social and context contrasts

(A) Two-sample t-tests for SZ > HC for Soc > Phy (no significant results) and Inc > Con (green)**; (B)** Conjunction analysis Soc > Phy (purple) and Inc > Con (green). Overlap between two contrasts shown in yellow. Results are shown at $p < 0.005$ and $k > 105$, corresponding to a cluster-corrected threshold of $p < 0.05$.
SZ = schizophrenia, HC = healthy controls; Soc = Social condition; Phy = Physical condition; Inc = Incongruent context condition; Con = Congruent context condition; R = Right; TTG = transverse temporal gyrus; PFC = prefrontal cortex; TPJ = temporo-parietal junction; dmPFC = dorsal medial prefrontal cortex; vmPFC = ventromedial prefrontal cortex.

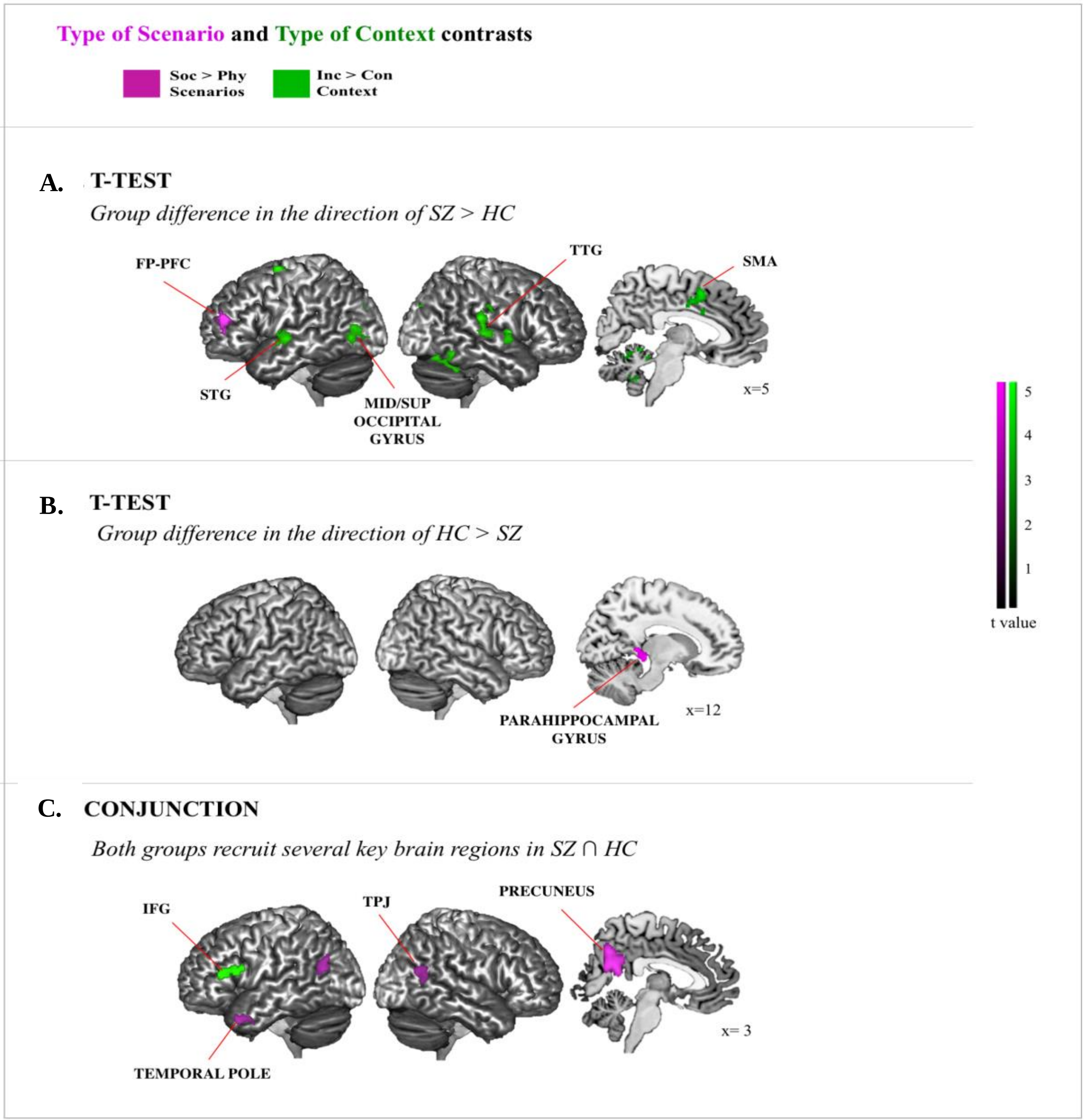


Figure 0.3 Brain activation during REMICS task Context phase: Social and context contrasts

(A) Two-sample t-tests for SZ > HC for Soc > Phy (purple) and for Inc > Con (green); **(B)** Two-sample t t-tests for HC > SZ for Soc > Phy (purple) and for Inc > Con (no significant results) **(C)** Conjunction analysis Soc > Phy (purple) and Inc > Con (green). Results are shown at $p < .005$ and $k > 105$, corresponding to a cluster-corrected threshold of $p < .05$. SZ = schizophrenia, HC = healthy controls; Soc = Social condition; Phy = Physical condition; Inc = Incongruent context condition; Con = Congruent context condition; IFG = inferior frontal gyrus; TPJ = temporo-parietal junction.

Chapter 3: Functional connectivity analysis reveals disruption of large-scale networks during a ToM task in patients with schizophrenia

4.1 Résumé

Les réseaux cérébraux impliqués dans les déficits de traitement de la théorie de l'esprit (ToM) en schizophrénie (SZ) restent incertains. Cette étude a examiné l'activation cérébrale lors de jugements sociaux et contextuels en SZ. Vingt contrôles (HC) et 25 patients atteints de SZ ont participé à une tâche IRMf dans laquelle on leur avait demandé de juger de la cause d'un événement social ou physique (type de facteur de scénario) dans un contexte qui est incongru ou cohérent (type de facteur de contexte) avec les attentes normatives lors des jugements sur la cause d'un événement. Les fluctuations BOLD dans l'ensemble du cerveau ont été limitées à la variance prévisible à partir des stimuli de tâche avec une analyse contrainte des composantes principales (CPCA). Les patients ne présentaient pas d'activation altérée dans les composantes en fonction du type de scénario, mais une activation cérébrale altérée liée au facteur de type de contexte. Plus précisément, les patients atteints de SZ ne modulaient pas l'activité cérébrale de régions clés en fonction du contexte, alors que le patron de connectivité cérébrale des HC montrait des différences.

4.2 Abstract

Recent evidence has highlighted the importance of context processing in Theory of Mind (ToM) deficits in patients with schizophrenia (SZ), but the underlying brain networks involved in ToM processing deficits in SZ remain unclear. The present study examined coordinated brain activation during social and contextual-related judgements in SZ. Twenty healthy controls (HCs) and 25 patients with SZ completed an fMRI task in which they were asked to make a judgment about the cause of a social or physical event (Type of Scenario factor) given congruent or incongruent context (Type of Context factor). Whole-brain BOLD fluctuations were constrained to the variance that was predictable from the task stimuli using Constrained Principal Component Analysis (CPCA). Four components accounting for a total of 34.63% of the task-related variance in the two groups were extracted. Two components contained sustained task activation/deactivation: (1) the Task-positive component consisted of sustained activation in the posterior occipital and superior parietal lobe (areas responsible for visual and attentional control); (2) the Task-negative component consisted of sustained deactivation in the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC)/precuneus (areas of the Default-Mode Network). Conversely, two components contained activation associated with specific phases of the task: (1) the Early-task network included activation in visual regions (calcarine fissure, lateral occipital); (2) the Late-task network included activation near the end of the task, in the bilateral precentral and postcentral gyrus, temporo-parietal junction (TPJ) and dorsolateral PFC. Patients did not exhibit altered activation in the components based on the Type of Scenario, but showed altered brain activation related to the Type of Context factor. Specifically, in the Task-positive component, Early-task component, and Late-task component, patients with SZ did not modulate their brain activation in these regions based on whether the context associated with a scenario was incongruent or congruent, while the pattern of brain connectivity of HCs did show such difference. These results highlight that context processing in ToM tasks may be associated with altered recruitment of functional brain networks in SZ. Lastly, patients showed reduced deactivation compared to HCs in the Task-negative network throughout the task, suggesting that this may be a core illness-related feature.

4.3 Introduction

Social deficits are a hallmark of schizophrenia (SZ) and are associated with reduced functioning and community integration (Fett et al., 2011; Hooker & Park, 2002; Roncone et al., 2002). Among the social disturbances associated with the illness are impairments in Theory of Mind (ToM) -- i.e. the higher-order social cognitive process of inferring the intentions, emotions, and beliefs of others (M. Green et al., 2008). In healthy participants, completing ToM tasks has been associated with activation of a wide-spanning group of brain regions, including the medial prefrontal cortex [mPFC], the precuneus/posterior cingulate cortex [PCC], the bilateral tempero-parietal junction [TPJ], and the temporal poles) (Frith & Frith, 2007; Mar, 2011; Schurz et al., 2014; van Overwalle & Baetens, 2009). In patients with SZ, however, the specific neural correlates of ToM deficits remain unclear. For instance, while several studies have examined differences in ToM-related brain activation for patients with SZ compared to healthy controls (e.g., Brüne, 2003; Brune et al., 2011; Brunet, Sarfati, Hardy-baylé, & Decety, 2003; Das, Lagopoulos, Coulston, Henderson, & Malhi, 2012; Dodell-Feder, Tully, Lincoln, & Hooker, 2014; Lee, Quintana, Nori, & Green, 2011; Pedersen et al., 2012; Russell et al., 2000), results have been largely heterogeneous among studies, including both over- and under-activation of brain regions typically associated with ToM activation (Bosia, Riccaboni, & Poletti, 2012; M. Green et al., 2015).

Although ToM is defined as a social process, the way in which ToM is operationalized in ToM tasks typically involves processing both a social character, as well as the context surrounding that character (Achim, Guitton, et al., 2013; Lavoie et al., 2016). Accordingly, a recent fMRI study of patients with SZ (Sutliff, Chapter 2) manipulated social and context components of judgments to assess whether patients experienced deficits in purely social processing (i.e., processing social events vs. physical events, regardless of the level of context), whether they exhibited impairments in context processing (i.e., processing incongruent or unexpected context vs. congruent or expected context, regardless of whether the corresponding event was social or physical), or both. Importantly, this study used an event-related fMRI design that allowed for the analysis of different phases of ToM judgments (i.e., scenario presentation, context presentation, and judgment phases), in contrast to previous studies that used block designs to assess activation throughout the entire task (e.g., Brüne, 2003; Das et al., 2012; Dodell-Feder et al., 2014; Lee et al., 2011). Results highlighted that patients with SZ did *not* exhibit significantly different brain activation from healthy participants specifically associated with social judgments. Instead, patients showed altered brain activation during the presentation of context associated with those scenarios, and these alterations were present regardless of whether the scenario detailed a social character or a physical object. ToM deficits observed in SZ may therefore be linked to context processing, rather than being related solely to deficits in making a social judgment. Notably, given the group differences observed during context presentation in this task, heterogeneous findings in the literature could stem from different methods of analysis, such as combining context presentation and mental state judgments in a single time point for the analyses. Investigations of ToM in patients with SZ could therefore benefit from utilizing tasks or methods of analyses that allow for the dissection of the component processes involved throughout ToM tasks -- from stimulus processing to actively attributing a mental state.

Functional connectivity approaches may thus be an important next step in the study of ToM, particularly given that these methods allow both for the examination of activation across time, as well as the interconnectedness/coordinated recruitment of brain regions (Friston & Frith, 1995; Friston, 2011). These approaches hold particular relevance in the schizophrenic population, given that altered connectivity may underlie some of the main clinical and cognitive symptoms of SZ, including social deficits (Bullmore, Frangou, & Murray, 1997; Friston & Frith, 1995; Stephan, Baldeweg, & Friston, 2006). To date, studies have identified altered connectivity of several brain networks in SZ. A recent review of resting-state functional connectivity in SZ (Sheffield & Barch, 2016) highlighted two affected networks: (1) a task-negative network, consisting of the mPFC and PCC, the TPJ and temporal poles (typically referred to as the Default Mode Network or DMN; (Buckner et al., 2008; Raichle et al., 2001), and (2) a task-positive network consisting of frontal and parietal brain regions associated with the dorsal attention network (e.g., frontal eye fields (FEF) and intraparietal sulcus, and performance on a wide variety of cognitive tasks (e.g. dorsal and ventral lateral prefrontal cortices (dlPFC, vlPFC), insula, supplementary motor area (SMA); Fox et al., 2005; Power et al., 2011). Importantly, the task-negative DMN is activated at rest and during self-reflective thought but *deactivated* during cognitively-demanding tasks, while the task-positive network is deactivated at rest but *activated* during cognitively demanding tasks.

In addition to resting-state studies, the task-negative and task-positive networks have been found to be altered in SZ in a variety of non-social cognitive tasks (Godwin, Ji, Kandala, & Mamah, 2017; Haatveit et al., 2016; Lavigne & Woodward, 2018; Paul D. Metzak et al., 2012). However, few studies have investigated functional connectivity associated with social cognition. One such study by Das et al (2012) investigated functional connectivity in patients with SZ and healthy controls during an implicit ToM paradigm, the Moving Shapes task, in which participants viewed animated shapes engaged in goal-driven interactions (e.g., bluffing, persuading, or mocking one another). In this study, patients with SZ exhibited reduced connectivity between task-negative and task-positive networks in the ToM conditions correlated with ToM performance outside the scanner, suggesting that these networks may play an important role in ToM deficits in SZ. Important to the study of ToM, the task-negative DMN consists of brain regions that are also associated with those of the reported ToM network: the major hubs of the DMN are located in the mPFC and PCC, as well as the TPJ and temporal poles (Mars et al., 2012; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008; Spreng, Mar, & Kim, 2009). Given that humans may in fact construct mental models of others based on our own mental states (Davies & Stone, 1995; Shanton & Goldman, 2010), the self-reflective nature of the DMN may be a crucial component of social cognition. The task-positive network, on the other hand, has been found to increase in activation in association with the cognitive demand required by a task (Paul D. Metzak et al., 2012). Therefore, this network may be associated with the more complex aspects of ToM tasks, such as integration of contextual information.

The present study aimed to identify the brain networks involved in completing a ToM task (including three successive task events: scenario presentation, addition of context, and judgment prompt) in patients with SZ and healthy controls and to determine whether affected networks in SZ were related to social and/or context processing. Specifically, we employed a multivariate connectivity analysis (Constrained Principal Component Analysis; CPCA) to determine the task- and group-related components (i.e., networks of coordinated brain activation) recruited during social and context task manipulation. We expected that the results would highlight reduced connectivity of task-negative and task-positive networks in patients with SZ. Given the theoretical overlap between self-reflective thought and social cognition (e.g., Davies & Stone, 1995), we expected that the task-negative network would be linked to the social task conditions. Furthermore, given the relation between cognitive load and task-positive activation, we expected that the task-positive network would be an important component affected in SZ, which would be involved specifically in the context task manipulations. Overall, we expected that results would support previous findings that patients with SZ display impairments in their ability to process context in social and physical scenarios.

4.4 Method

4.4.1 Participants

Participants are the same as those used in Chapter 2 (see Section 3.4 for full details)

4.4.2 fMRI assessment

Participants were scanned using a Philips Achieva 3T MRI scanner and an 8 channel SENSE head coil. Structural images were acquired with an MPRAGE sequence (TR = 8.2 ms, TE = 3.7 ms, FoV= 250 mm, flip angle = 8◦, 256×256 matrix, 180 slices/volume, slice thickness = 1mm, no gap). Changes in blood oxygenation level-dependent (BOLD) signal (T2* weighted) were then assessed using a gradient echo-planar imaging (EPI) sequence (repetition time TR = 3000 ms, echo time TE = 35 ms, FoV= 230 mm, flip angle = 90◦, 128×128 matrix, 45 slices of 3mm covering the whole brain and most of the cerebellum, no gap, voxel size = 1.8×1.8×3 mm). Two runs were acquired, each including 230 EPI volumes acquired along the AC–PC plane.

4.4.2.1 REMICS fMRI task (Lavoie et al., 2016)

The fMRI-REMICS task included 64 verbal scenarios and surrounding context, from which participants were to infer the most likely cause of the event. Each trial was divided into three phases: A Scenario phase, a Context phase, and a Judgment phase. First, during the Scenario phase, a sentence was presented visually on screen to describe the main event. Then, in the Context phase, a second sentence appeared under the first and added the context relevant to the cause of the event. Lastly, in the Judgment phase, two potential causes of the event were presented on the screen, and participants were to select the most likely cause of the event.

Thus, the goal of the task was for participants to judge the cause, taking into consideration both the scenario and context.

Scenarios presented on screen either described a situation involving a person (Social condition) or a physical object (Physical condition). Furthermore, the context either added information that is congruent with the prototypical inference about the cause of the event (Congruent condition), or added information that was incongruent with the prototypical inference and required an adjustment of the inference about the cause of the event (Incongruent condition). Thus, the task fit a 2 x 2 design leading to 4 task conditions: Social inferences with incongruent context [SocInc], Social inferences with congruent context [SocCon], Physical inferences with incongruent context [PhyInc], and Physical inferences with congruent context [PhyCon]. The sentences have been validated to trigger spontaneous judgments of the cause of the social event (i.e. the intention of the character; Social conditions) or of the physical event (Physical conditions; see Lavoie et al., 2016 for validation details). The timing of task events and examples of each condition are presented in Figure 4.1.

All participants first completed 8 practice trials outside the scanner. The fMRI task then included 2 runs of 32 trials each (8 trials of each of the 4 conditions per run) and lasted around 20 minutes.

4.4.3 fMRI preprocessing

Functional MRI data were preprocessed using Statistical Parametric Mapping, version 8 (SPM8; Wellcome Department of Cognitive Neurology, London, UK). Data were first corrected for different slice timing within a volume (reference = middle slice) and functional images of both runs were realigned to the mean functional image. To account for excess movement artifacts associated with imaging clinical populations, the Artrepair toolbox was used (Mazaika et al., 2009, 2005). Volumes with head movements greater than 1 mm/TR were corrected via interpolation of adjacent slices. Runs that required correction for more than 10% of the volumes were excluded from the analyses (4 runs total, 1 run for 3 participants with SZ; 1 run for 1 HC) to reduce potential for interpolation errors due to excessive motion (Mazaika et al., 2009).

Participants' structural images were then co-registered with their mean functional image. For most participants, structural images were segmented based on the ICBM-152 Montreal Neurological Institute (MNI) template. These segmentation parameters were used to normalize their functional data (2 mm isometric voxel) into a standard anatomical space. The functional images of four SZ participants showed distortions when applying this procedure and were thus normalized directly to MNI template. Finally, data were smoothed using a 6mm Gaussian kernel.

4.4.4 Task-based functional connectivity analysis (fMRI-CPCA)

Functional connectivity associated with the full time-course of the task was examined via constrained principal component analysis for fMRI (fMRI-CPCA; open-source software available online at www.nitrc.org/projects/fmricpca). CPCA combines regression and principal component analysis (Hunter & Takane, 2002; Takane & Hunter, 2001; Takane & Shibayama, 1991). In fMRI-CPCA, the whole-brain BOLD fluctuations are constrained to the variance in BOLD signal (using multivariate multiple regression) that is predictable from the sequence of stimuli presentation during the task. fMRI-CPCA has been employed in several previous works (Lavigne, Metzak, & Woodward, 2015; P. Metzak et al., 2011; Paul D. Metzak et al., 2012; Whitman, Metzak, Lavigne, & Woodward, 2013). Figure 4.2 provides an overview of the fMRI-CPCA pipeline, including input, analysis, and output.

In this task, we estimated 10 Time-bins (TR=3s), which allowed us to analyze a 30 second time-window, from the trial onset (time = 0s) until 15 seconds after the start of the Judgment phase (to capture the full hemodynamic response curve associated with the Judgment phase; see Figure 4.1A, right side, for Judgment phase timing). For this time window, we analyzed the associated hemodynamic response function (HRF) curve for the 4 task conditions (SocCon, SocInc, PhyCon, PhyInc) for each subject (10 Time-bins x 4 conditions x 45 subjects). After combining the pre-processed EPI data of all subjects and regressing this subject specific data with the design matrix, components were then extracted using data from all participants (SZ and HC). Extraction was accomplished through singular value decomposition on the variability that is predictable from the contrast (see Figure 4.2 for overview of CPCA analysis). The retained components then underwent a HRF rotation (Metzak et al., 2011). The HRF rotation used a total of 5 curves and were modeled on our task event durations: (1) Event [0 – 4.4s] (2) Context phase [4.4 – 8.8s] (3) Response phase

[10.8 – 16.3s] (4) Event + Context phase [0 – 8.8s], (5) Event + Context phase + Response phase [0 – 16.3s].

For each component, the results provide (1) an activation map of functionally coordinated voxels and (2) an estimated HRF curve based on the predictor weights of the associated functional network at each Time-bin and in each condition. Activation maps for each component were examined using the dominant 10% of component loadings as in previous cognitive studies using this type of analysis (Lavigne & Woodward, 2018; Metzak, Lavigne, & Woodward, 2015). The predictor weights were entered into a repeated-measures ANOVA with the within-subject variables Time-bin (1 to 10), Type of Scenario (Soc, Phy), and Type of Context (Inc, Con) and the between-subject variable of Group (SZ, HC). This allowed us to examine the effects of the task manipulations (Type of Scenario and Type of Context) in each component, as well as determine which components are related to differences in activation between SZ and HC. Tests for normality and sphericity were carried out. Skewness and kurtosis were within acceptable levels (±2) and Greenhouse-Geisser adjustment in degrees of freedom for any analyses in which the sphericity assumption was violated did not affect interpretation of the results. ANOVAs were therefore used, with a significance level of $p < .05$.

4.5 Results

Inspection of the scree plot of singular values indicated that 4 components should be extracted (see Cattell, 1966 and Cattell & Vogelmann, 1977 for further details on the scree test). The task-related variance accounted for by each of the four rotated components was 10.64%, 10.15%, 8.82%, and 5.02% (1-4, respectively). Two components were associated with sustained task activity, including a Task-positive component (Component 3) and a Task-negative component (Component 2; results for both displayed in Table 4.1 and Figure 4.3). Conversely, two components showed HRF peaks related to specific phases of the task: an Early-task component (Component 4) and a Late-task component (Component 1; results for both displayed in Table 4.2 and Figure 4.4). All components displayed a significant main effect of Time-Bin that followed a biologically plausible shape (i.e., expected HRF shape) throughout the course of the task. Of note is that changes in brain activity, due to the BOLD response are typically expected to begin around 8 seconds after an event and takes around 20 seconds to return to baseline (Huettel, Song, & McCarthy, 2009). Additionally, all components displayed an interaction of Type of Context x Time-bin, and all but the Early-task component displayed an interaction of Type of Scenario x Time-bin, indicating that the task manipulations did affect brain activation across time. Furthermore, all components displayed one main effect or interaction related to the effect of Group. Results of ANOVA for all four components are presented in Table 4.3. For this paper, we will focus on the main effects and interactions effects of these components that pertain to Group differences between SZ and HC.

4.5.1 Sustained task activity (Table 4.1 and Figure 4.3)

The Task-positive component was associated with a sustained BOLD response from task onset until the end of the Judgment phase, with its highest levels of activation from 12-24s. Overall, this component consisted of positive loadings[9] in a cluster of 9860 voxels, which encompassed the posterior bilateral occipital lobes (i.e. the cortex surrounding the calcarine fissure, inferior and middle occipital gyrus, and fusiform gyrus) and extended dorsally to the superior parietal lobe. Additionally, this component consisted of clusters in brain regions associated with motor control (precentral gyrus, supplementary motor [SMA]), and both social and non-social cognitive functions (TPJ, dlPFC). Predictor weights of the sustained Task-positive component showed a significant interaction between Group, Type of Context, and Time-bin ($F=2.412$, $p=.030$), reflecting a significant Group x Type of Context effect at Time-bin 8 only (24s after task onset; $F=6.63$, $p=.014$). Dissecting this result further showed that HC modulated their brain activation based on the Type of Context at Time-bin 8, with reduced activation in the congruent versus incongruent conditions ($t=4.27$, $p<.001$). Patients with SZ patients, however, did not show a significant difference between context conditions ($t=1.25$, $p=.223$).

The Task-negative component showed consistent deactivation throughout the task, with greatest points of deactivation between 9 and 21s, suggesting sustained task-related

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[9] The output of the CPCA components are referred to in terms of their positive and/or negative loadings but these results imply activations and/or deactivations, respectively (Goghari, Sanford, Spilka, & Woodward, 2017; Woodward et al., 2006)

deactivation throughout the scenario, context, and early judgment phases. This component included regions corresponding to the DMN (Buckner et al., 2008; Raichle et al., 2001), including clusters of negative loadings within the mPFC/vACC, posterior cingulate cortex (PCC)/precuneus, and bilateral TPJ. Additional regions showing deactivation in this component included the bilateral superior temporal gyrus, left anterior insula, and right anterior inferior frontal gyrus. The ANOVA revealed a significant main effect of Group for this Task-negative network (F= 4.80, p=.034), with *lesser* deactivation in SZ compared to HC.

4.5.2 Early- and Late-task activity (Table 4.2; Figure 4.4)

The Early-task component included an HRF curve that peaked during Time-bins 2-4 (3-12s), suggesting an association with the scenario presentation. The Early-task component recruited a large cluster of positive loadings in visual processing areas (calcarine fissure, visual association area, lateral occipital, and lingual gyrus), as well as motor (precentral gyrus, SMA) and somatosensory areas (postcentral gyrus). This component was further associated with negative loadings in frontal regions (dorsal mPFC, frontopolar cortex (FP-PFC)/orbital PFC, FEF inferior frontal gyrus), as well as the TPJ and anterior insula. This component showed a Group x Type of Context interaction (F=7.75, p=.008) throughout the task, which reflected that HC modulated brain activation between incongruent and congruent conditions (t=5.27, p<.001), while patients with SZ did not (t=1.17, p=.254).

The Late-task component showed an HRF curve that peaked at Time-bin 7 (21s), suggesting a relation to the end of the Context phase and the preparation for making a judgment. The Late-task component included positive loadings in motor and somatosensory, as well as parietal brain regions, including the bilateral precentral gyrus and postcentral gyrus extending into the superior parietal lobule and TPJ, as well as the dlPFC. Given the timing of activation of motor and sensory brain areas, this component likely reflected brain activation associated with using the response box to make a choice during the task. This component showed an interaction of Group x Type of Context (F=9.70, p=.003), again reflecting a difference between incongruent and congruent context conditions in the HC group (t=-1.56, p=.001), but not in patients with SZ (t=0.29, p=.778).

4.6 Discussion

The present study used a multivariate connectivity analysis in patients with SZ and HC participants to address the coordinated brain activation involved in an fMRI task manipulating social and context-based judgments. Four components were identified that accounted for the greatest task-related variance: (1) a Task-positive network that was associated with activation of visual, motor, and social and non-social cognitive regions throughout the task; (2) a Task-negative network associated with suppression of brain activation throughout the task in regions of the DMN; (3) an Early-task network comprised of activation in primary and secondary visual regions associated with the stimuli presentation phases of the task (4) a Late-task network comprised of activation in motor and parietal regions associated with the judgment phase of the task. For all four components, patients with SZ did not exhibit altered activation based on the Type of Scenario (i.e. whether the scenario was social or physical). However, in three of the four components (excluding only the Task-negative network), patients showed altered brain activation compared to controls that was related to the Type of Context (i.e. whether the context was incongruent or congruent). Specifically, in the Task-positive component, Early-task component, and Late-task component, patients with SZ did not modulate their brain activation in these regions based on the whether the context associated with a scenario was incongruent or congruent, while the pattern of brain connectivity of healthy participants did show such difference. These results highlight the importance of altered context processing, rather than altered social processing, as a feature that is associated with altered brain activation during ToM tasks. Lastly, regardless of the task manipulations, patients showed less deactivation compared to controls in the Task-negative network, suggesting that this may be a core illness-related feature.

4.6.1 Patients with SZ show less suppression of the Task-negative DMN, regardless of the social and contextual task manipulations

The Task-negative component observed in this study notably consisted of large clusters of deactivation within the mPFC/ACC and PCC/precuneus. These cortical midline structures have been hypothesized to be essential in self-reflective thought (G Northoff & Bermpohl, 2004), which must be suppressed in order to focus on externally-oriented stimuli. Indeed, in the present study, healthy individuals did show greater suppression of this network across the task conditions. In patients with SZ, this reduced suppression during the task may suggest that individuals with SZ had difficulty disengaging self-focused thoughts in favor of engaging in the task. This was in contrast to our expectation that the task-negative network would be related to the social conditions in patients, given that several brain areas of this network are involved in processing mental states of others (e.g., the mPFC, precuneus, and lateral prefrontal cortex; Mars et al., 2012). Completing this task required individuals to read and understand written scenarios, which may have introduced a 'cognitive load' that required DMN suppression for participants to engage in the task, regardless of the task condition. Indeed, in patients with SZ, connectivity analysis has previously shown reduced suppression of the DMN associated with a non-social language based semantic priming task (Jeong & Kubicki, 2010), suggesting that in SZ, this altered activation may not be specific to social tasks). Therefore, because the DMN is deactivated in response to cognitively-demanding tasks, it is possible that, our results stem from the use of a verbal stimuli in this task.

However, a perhaps more likely hypothesis is that these results indeed reflect a core illness-related feature of SZ that is present regardless of the condition, given that several studies in SZ have highlighted a generally reduced suppression of DMN brain regions (Das, Calhoun, & Malhi, 2012; Jeong & Kubicki, 2010; Zhou et al., 2016). For instance, Das et al (2012) showed reduced DMN suppression in both ToM- and non-ToM related conditions in SZ, notably, using a paradigm consisting of goal-directed (ToM) and random (non-ToM) visual animations. This observation in a non-verbal paradigm provides further support that sustained deactivation in the present study was no purely due to cognitively-demanding verbal conditions but rather a component of SZ. Furthermore, during cognitive tasks recent studies have further found alterations in regions of the DMN in first-degree relatives of individuals with SZ (Whitfield-Gabrieli et al., 2009) and individuals at high-risk for developing SZ (Fryer et al., 2013), further suggesting DMN alterations are an underlying feature of the disorder itself.

4.6.2 Patients do not modulate Task-positive network based on the Type of Context during task disengagement

Based on previous studies highlighting an important role for a task-positive network in SZ in addition to a task-negative network (Sheffield & Barch, 2016), we expected to observe group effects in the Task-positive component, in addition to the Task-negative component. While results did uncover that the Task-positive network is important in ToM tasks, a significant Group x Type of Context interaction was only observed in this network at one time-bin (7 seconds after the Judgment phase). After the HRF peak during the Judgment phase, there was a steeper decline for congruent conditions than incongruent conditions in HCs but not in patients with SZ. Thus, this result likely reflected group differences in task-disengagement. This finding is supported by previous studies suggesting that individuals with SZ do display abnormalities in executive attentional processes, such as task-disengagement (Fuggetta, Bennett, & Duke, 2015; Luck & Gold, 2008; Nestor et al., 1992).

Notably, this Task-positive component was associated with activation in the dlPFC and the TPJ, regions which have been associated with top-down attentional control (Corbetta & Shulman, 2002; Corbetta, Patel, & Shulman, 2008). These brain regions have been frequently implicated in ToM processing (Lavoie et al., 2016; Schurz et al., 2014), but this is likely linked to attentional processing associated with ToM judgments (Geng & Vossel, 2013). As the incongruent condition would likely require participants to devote greater attentional resources to the stimuli, it may also be slower to disengage those resources. Indeed, data in healthy individuals has shown that the effortful cognition is associated with altered connectivity that continue after the immediate demands of the task are met (Gordon, Breeden, Bean, & Vaidya, 2014). Accordingly, the steeper decline following judgments for congruent context conditions in HC participants may reflect a quick deactivation for congruent conditions in order to preserve cognitive resources. Patients then differed from controls in their ability to distinguish between incongruent and congruent context. However, given that the observed interaction effect was significant only at one Time-bin, the results of differences in SZ in this network should be interpreted with caution.

4.6.3 Patients with SZ do not modulate coordinated activation in Early-task and Late-task components based on the Type of Context

In addition to sustained task activity, CPCA analysis highlighted two components that displayed peaks of coordinated activation at specific time points in the task: one early in the task and one late in the task. The Early-task network was composed of basic visual and motor regions, which were recruited from the first moments of the task, peaking at 9 seconds into the task. This component, therefore, likely reflected brain activation associated with basic visual processing. The Late-task component, on the other hand, was comprised of a group of brain regions, which have been shown to be recruited by various cognitive demands (Duncan & Owen, 2000; Fedorenko, Duncan, & Kanwisher, 2013). For instance, Fedorenko, Duncan, & Kanwisher (2013) used a single-subject analysis to test seven different cognitive tasks; they found that the precentral gyrus, dlPFC, and anterior insula were involved in all tasks, examining processes from arithmetic to storing information in working memory. This network consisting of 'domain-general' regions was in fact the component that predicted the greatest amount of task-related variance (10.64%), suggesting that general cognitive processes play an important role in ToM task-related activation in both healthy participants and patients with SZ.

Importantly, for both early- and late-task networks, the results again suggest that HC participants modulated the activation of these brain regions in response to the context manipulations, while patients did not make this distinction. The activation of both sensory and motor-related networks is frequently overlooked in ToM studies, perhaps with the idea that the control condition should remove this element in subtraction-based studies. However, given these results, such functions may actually be important to the study of ToM, particularly if context is not properly controlled for between ToM and control conditions. Indeed, given that social situations may be more dynamic and context-dependent than physical scenarios, it may be necessary to take the level of context into account in comparing social and non-social scenarios.

4.6.4 Rethinking the concept of a 'ToM network' in SZ

Despite evidence that ToM performance is related to social judgments with incongruent context (i.e., Lavoie et al., 2016 and Sutliff, Chapter 2), the present study did not find evidence that patients with SZ were affected in a component specifically related to social processing or contextual processing. Instead, the findings highlight the recruitment of brain networks that are involved in general cognitive functions, self-focused thought, and visual perception of stimuli.

These findings are particularly timely to add to the literature, as ToM deficits have recently been investigated as an endophenotype of SZ based both on evidence that ToM impairments are present throughout the course of the disorder and that individuals with SZ show altered neural processing during ToM tasks in SZ (Martin et al., 2014; Mohnke et al., 2015). Although recent meta-analytic data using a variety of ToM tasks suggests that patients with SZ show alterations in the mPFC and TPJ (Kronbichler et al., 2017), the present results highlight the importance of further dissecting the specific neurobiological underpinnings of ToM, rather than examining regional brain activation of areas typically associated with a 'ToM network.' In the present study, we observed alterations in both the mPFC and TPJ, but their recruitment was associated with different components at different phases in the task. For instance, the mPFC showed reduced coordinated task-suppression across all conditions as part of the DMN, while in the Early-task component, altered mPFC activity in SZ was specifically related to the Type of Context. Accordingly, the investigation of ToM as an endophenotype in SZ may be considered premature (R. L. Mitchell & Young, 2016). However, continuing to understand the component processes involved in ToM abilities in SZ may help to identify the processes underlying robust social cognitive and functional impairments throughout the disorder.

4.6.5 Study Limitations

The present study has some limitations that must be considered in interpreting the results. Given that this is the same group of participants that was used in our previous study (Chapter 2) in which we did not observe important group effects on the Type of Scenario manipulation, it is possible that the patient sample presented with intact social processing. In fact, while the patients were impaired on behavioral ToM, the group did not show differences from healthy controls in other aspects of social cognition (see Chapter 2). Additionally, it is also possible that the rigorous testing protocol which may have unintentionally selected high-functioning patients. However, the included participants were mildly symptomatic as judged by the PANSS and represented various stages of the illness, with durations ranging from 6 months to 40 years (see Chapter 2 for further details).

4.6.6 Conclusions

This is the first study to our knowledge to examine functional connectivity during social and contextual task manipulations in patients with SZ. Importantly, results highlight the involvement of multiple large-scale brain networks for completing the task, rather than a solitary ToM network. The present study also provides further evidence that patients with SZ do not show differences in brain activation related strictly to social processing, but instead, provides evidence that patients with SZ fail to modulate coordinated brain activation in response to different types of context. Overall, this research supports the list of growing studies that suggest an importance of context processing in SZ and also shows that ToM tasks rely on multiple processes, from basic perception to task judgment.

4.7 References

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Table 0.1 CPCA components with sustained task activation/deactivation

	Brain regions	BA	k	x	y	z	Load -ings
Task-positive component							
R, L	Middle occipital gyrus/ Superior parietal lobule/ Calcarine/ Lingual gyrus/ Inferior occipital gyrus/ Fusiform gyrus	18, 7, 17, **19**, **37**	986 0	-12	-82	-10	0.33
L	Precentral gyrus/ FEF/ Inferior frontal gyrus/ DlPFC	**6**, 8, 44, 45, **46**	308 1	-44	4	50	0.32
L	Middle temporal gyrus/ Temporal pole/ TPJ	21, 38, 39	176 2	-56	-34	-2	0.28
R, L	SMA/ MPFC	**6**, 8	762	-2	8	58	0.29
R, L	Cerebellum	--	18	0	-58	-38	0.17
R	DlPFC	9	11	54	26	22	0.17
R	Middle temporal gyrus	21	2	52	-6	-18	0.17
R	Superior parietal lobule	**7**	1	28	-60	50	0.16
Task-negative component							
L	Visual association area	18	11	-12	-84	-8	.17
R, L	MPFC/ DlPFC/ FP-PFC/ ACC	10, 9, 32, 24	707 3	0	56	2	-0.30
R, L	PCC/ Precuneus	**31**, 7, 23	478 8	2	-24	38	-0.28
R	TPJ/ Transverse temporal	40, **39**, 41	218 7	58	-46	42	-0.26
L	DlPFC/ FEF/ FP-FPC	9, **8, 10**	796	-22	46	36	-0.23
L	TPJ/ Transverse temporal	40, 41	181	-56	-24	10	-0.19
R	Superior temporal/ Posterior insula	22, 13	127	40	-8	-12	-0.20
L	TPJ	39	107	-50	-66	36	-0.19
L	Superior temporal/ posterior insula	22, 13	85	-40	-18	-4	-0.19
L	Anterior insula	13	59	28	18	-16	-0.19
R	Fusiform gyrus	37	41	62	-48	-4	-0.18
R	Inferior frontal gyrus	44	19	56	12	2	-0.18
R	Lateral occipital	19	10	56	-62	8	-0.17
R	Inferior orbital cortex	11	6	18	10	-16	-0.17
R	Thalamus	50	4	10	0	8	-0.17
L	Inferior orbital cortex	11	2	-16	10	-18	-0.17

Brain regions and loadings values (positive = red, negative = blue) for gray matter in the Task-Positive component (Component 2) and the Task-Negative component (Component 3); BA= Brodmann area; R= Right; L= Left; FEF= Frontal eye field; DlPFC = Dorsolateral prefrontal cortex; TPJ= Tempero-parietal junction; SMA= Supplementary motor area; MPFC= medial prefrontal cortex; FP-PFC= Frontopolar prefrontal cortex; ACC= Anterior cingulate cortex; PCC= posterior cingulate cortex;

Table 0.2 CPCA components related to task events

	Brain regions	BA	k	x	y	z	Load -ings
Early-task component							
R, L	Calcarine/ Visual association area/ Lateral occipital/ Lingual gyrus	17, 18, 19	11331	-2	-78	8	0.26
L	Precentral gyrus	6, 4	774	-52	-4	46	0.25
R, L	SMA	6	112	-4	2	60	0.16
R	Precentral gyrus	6	62	56	-4	42	0.14
L	Precentral gyrus	6	24	-60	0	18	0.13
R	Postcentral gyrus	5	24	2	-40	56	0.12
L	Posterior superior temporal gyrus	22	14	-52	-36	16	0.12
L	Anterior superior temporal gyrus	22	6	-58	-8	-6	0.12
R, L	MPFC	8	892	-2	32	42	-0.19
L	TPJ	39	749	-44	-56	46	-0.18
L	FEF	8	668	-48	18	40	-0.16
L	FP-PFC/ orbital PFC	10, 47	304	-44	44	-6	-0.19
L	Anterior insula	13	209	-30	24	-6	-0.17
R	Anterior insula	13	88	34	24	-6	-0.16
R	Inferior frontal gyrus	44	68	54	20	10	-0.14
L	Inferior frontal gyrus	45	67	-52	18	6	-0.14
R	Orbital PFC	47	45	48	40	-10	-0.15
R	DlPFC	9	4	48	24	34	-0.12
L	DmPFC	8	1	-12	28	54	-0.12
Late-task component							
R	Precentral gyrus / SMA/ Postcentral gyrus/ Precuneus/ TPJ	4, 6, 1, 7, 39	6970	42	-18	52	0.39
L	Postcentral gyrus /Superior parietal lobule/ TPJ	1, 7, 39, 40	2801	-46	-32	46	0.30
R	Precentral gyrus/ inferior frontal gyrus	6, 44	1474	58	10	30	0.24
L	Cerebellum	--	1048	-24	-54	-22	0.27
L	Anterior insula	13	1041	-30	22	4	0.26
R	Fusiform gyrus	37	734	28	-56	-16	0.23
L	dlPFC	9	468	-46	30	26	0.19
L	Precentral gyrus	6	421	-30	-4	62	0.24
R	Thalamus	50	234	12	-16	6	0.25
R	dlPFC	9	115	46	32	28	0.20
L	Middle insula	13	74	-40	-2	10	0.19
R	Posterior insula	13	46	34	-20	4	0.19
L	Thalamus	50	44	-10	-16	8	0.19
R	Cerebellum	--	15	28	-66	-30	0.17
L	Precuneus	7	12	-10	-72	46	0.17

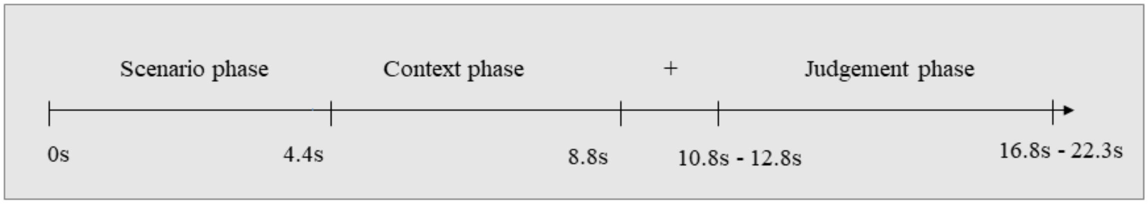
Brain regions and loadings values (positive = red, negative = blue) for gray matter in the Early task component (Component 4) and the Late task component (Component 1); BA= Brodmann area; R= Right; L= Left; SMA= Supplementary motor area; ACC= Anterior cingulate cortex; WM= white matter; MPFC= medial prefrontal cortex; TPJ= Tempero-parietal junction; FEF= Frontal eye field; FP-FPC= Frontopolar cortex; DlPFC= dorsolateral prefrontal cortex; DmPFC= dorsomedial prefrontal cortex.

Table 0.3 CPCA Predictor Weight ANOVA of Effects

Effect	**F statistic**			
	Task-positive Component 3	**Task-negative Component 2**	**Early-task Component 4**	**Late-task Component 1**
4-way interactions				
Type of Scenario x Type of Context x Time-Bin x Group	0.87	0.74	1.85	1.73
3 way interactions				
Type of Scenario x Type of Context x Time-Bin	0.69	0.62	**2.28**	1.68
Type of Scenario x Type of Context x Group	0.04	0.10	1.72	0.00
Type of Scenario x Time-Bin x Group	0.96	1.14	0.87	0.84
Type of Context x Time- Bin x Group	**2.41**	0.70	2.04	1.71
2- way interactions				
Type of Scenario x Type of Context	1.06	0.17	0.20	0.08
Type of Scenario x Group	0.05	0.10	0.92	0.98
Type of Context x Group	0.04	0.41	**7.75**	**9.70**
Time-Bin x Group	1.41	0.91	1.18	1.22
Type of Scenario x Time-Bin	**4.88**	**3.15**	1.75	**3.65**
Type of Context x Time- Bin	**7.72**	**4.61**	**5.36**	**3.64**
Main effects				
Type of Scenario	0.09	**4.69**	3.16	**15.73**
Type of Context	**13.87**	2.84	**19.67**	**7.38**
Group	1.40	**4.80**	0.01	2.40
Time-Bin	**32.68**	**43.22**	**26.87**	**30.68**

Bold font indicates F is significant results at $p < .05$

A. REMICS task timeline



B. REMICS task conditions and examples

Condition	Scenario	Context	+	Judgment phase	
SocInc	You observe a friend getting an orange from the fridge	Someone tells you that they learned a new circus trick		He wants to eat the oranges	He wants to juggle the oranges
SocCon	You observe a man climbing on the diving board of the pool	Someone tells you that he checked the water temperature		He wants to jump in the pool	He wants to clean the pool
PhyInc	You observe that the gas motor of a boat stops suddenly	Someone tells you that the lake is full of algae at this spot		The gas tank of the boat is empty	The propeller is trapped in the algae
PhyCon	You observe a deflated tire in the front of a vehicle	Someone tells you that the road is filled with potholes		The tire got a hole	The tire burst because of the heat

Figure 0.1REMICS task timeline and examples.

SocInc = Social Incongruent condition; SocCon = Social Congruent context condition; PhyInc = Physical Incongruent condition; PhyCon = Physical congruent condition.

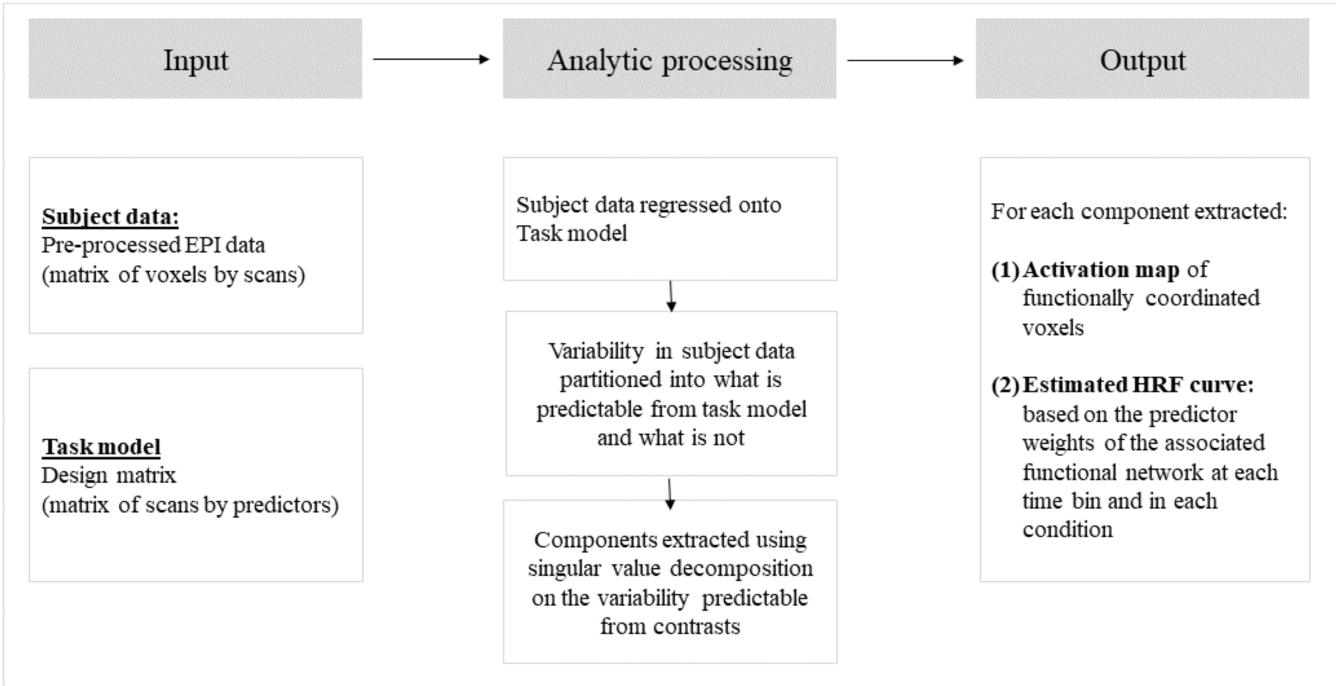


Figure 0.2 CPCA pipeline (adapted from CPCA manual, version 16).

EPI = echo-planar imaging; HRF = Hemodynamic response function.

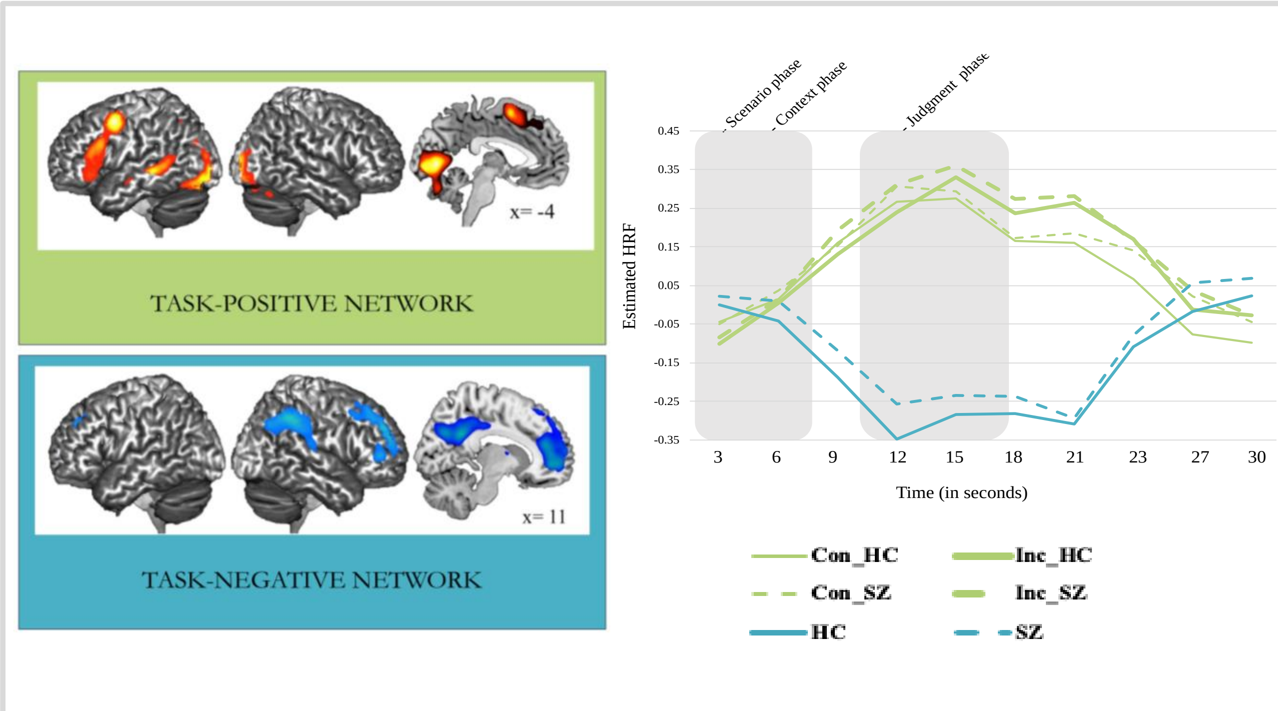


Figure 0.3 Sustained task activity components during REMICS-fMRI task

Left: Top 10% of dominant loadings are displayed for Task-Positive and Task-negative networks. Red/yellow indicates positive loadings and blue/green indicates negative loadings. Task-Positive network threshold for positive loadings, min = 0.16, max = 0.33; no negative loadings. Task-Negative network: threshold for positive loadings, min = 0.16, max = 0.30; threshold for negative loadings, min = -0.30, max = -0.16. **The Task-Positive Network (Top Left)** includes consistent activation throughout the task in brain regions associated with visual processing (posterior bilateral occipital lobes), motor control (precentral gyrus and supplementary motor area), and social and non-social cognition (temporo-parietal junction and dorsolateral prefrontal cortex). **The Task-Negative Network (Bottom Left)** shows consistent deactivation throughout the task in brain regions corresponding to the Default Mode Network, including the medial prefrontal cortex/ anterior cingulate cortex, precuneus, and temporo-parietal junction. **Right**: The graph show predictor weights from ANOVA (i.e. estimated HRF) across the time course of the REMICS task. Green line shows the Task-Positive network; Blue line shows the Task-Negative network;

HRF = Hemodynamic response function; Con = Congruent conditions; Inc = Incongruent conditions; HC = healthy controls; SZ = schizophrenia.

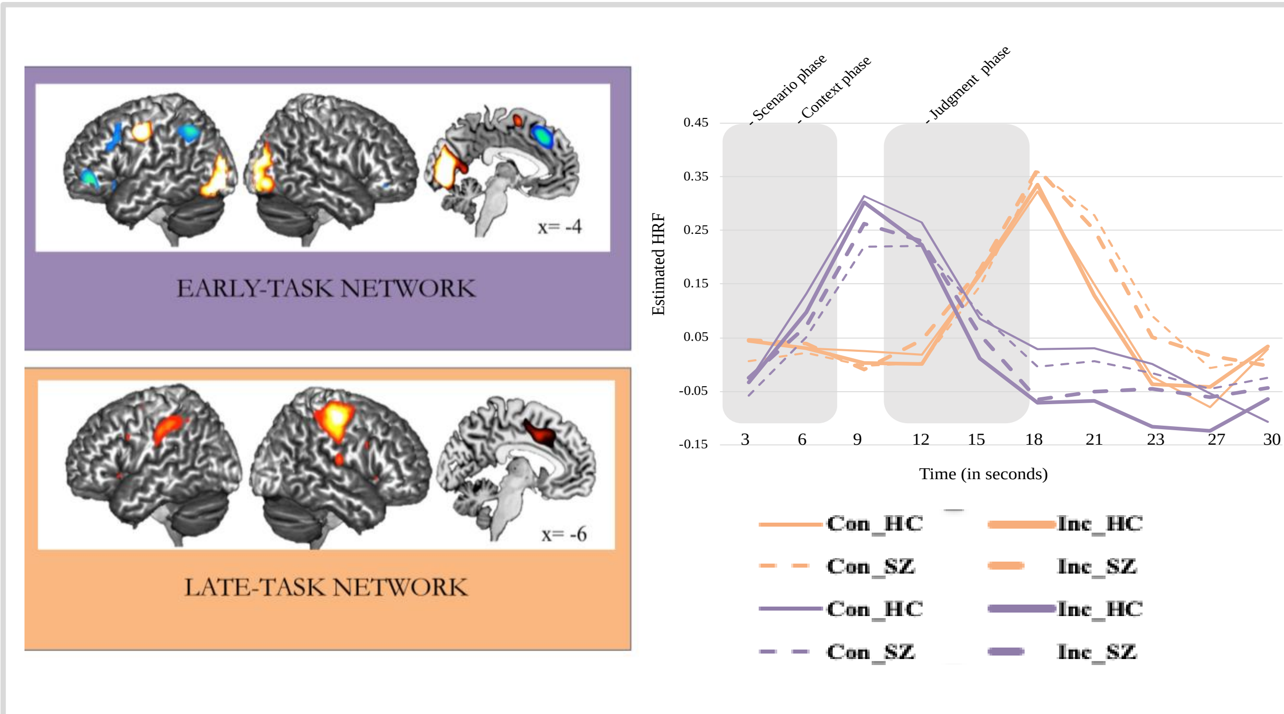


Figure 0.4 Early-Task and Late-Task network activity components during REMICS-fMRI task

<u>Left</u>: Top 10% of dominant loadings are displayed for both networks. Red/yellow indicates positive loadings and blue/green indicates negative loadings. Early-Task network: threshold for positive loadings, min = 0.12, max = 0.19; threshold for negative loadings, min = -0.19, max = -0.12. Late-Task network: threshold for positive loadings, min = 0.17, max = 0.39; no negative loadings. **<u>The Early-Task Network</u> (Top Left)** includes early activation in brain regions responsible for visual (bilateral lateral occipital lobe), motor (precentral gyrus, supplementary motor area), and somatosensory (postcentral gyrus) processing but deactivation in regions associated with social and non-social cognitive processing, including the dorsal medial prefrontal cortex (dmPFC), frontopolar cortex (FP-PFC), inferior frontal gyrus, and temporo-parietal junction (TPJ). **<u>The Late-Task Network</u> (Bottom Left)** includes late activation in brain regions involved in motor and somatosensory processing (precentral and postcentral gyrus). **<u>Right</u>**: Graph shows predictor weights from ANOVA (i.e. estimated HRF) across the time course of the REMICS task. Purple line shows Early-Task network; Orange line shows Late-Task network;

HRF = Hemodynamic response function; Con = Congruent conditions; Inc = Incongruent conditions; HC = healthy controls; SZ = schizophrenia.

General Discussion

A defining characteristic of schizophrenia (SZ) is impairment in navigating the complex social world. As a result, individuals with SZ tend to have fewer meaningful social relationships as well as generally reduced long-term functional outcomes (C. A. Harvey, Jeffreys, McNaught, Blizard, & King, 2007; Stevens et al., 2009). Given that antipsychotic treatments show little effect on improving these deficits (Addington & Addington, 2000; Pinkham et al., 2003), recent initiatives, such as the SCOPE (Pinkham et al., 2014), have been developed to improve understanding of the underpinnings of these deficits in order to develop more targeted treatment approaches. The present thesis aimed to add to this important research field by providing data on mechanisms linked to social deficits in SZ. Particularly, given the heterogeneity in illness presentation among individuals with SZ, as well as the heterogeneity among tasks used to measure social deficits in SZ, this thesis examined illness- and task-related factors that could be linked to observed social deficits. The three studies presented in this thesis provide both behavioral and brain imaging evidence for important factors linked to social deficits in schizophrenia. The following discussion seeks to provide an overview of the major findings of this research, as well as discuss the implications of this research for the field and future research directions.

5.1 Major findings

5.1.1 Illness-related factors linked to social deficits in SZ

5.1.1.1 Social anxiety is related to disturbances of the social self in SZ

Chapter 1 presented an empirical study of individuals with SZ that aimed to identify the role of comorbid social anxiety disorder (SAD) in SZ on the perception of self (Objective 1). Forty-three percent of the patients with SZ included in this study also met the diagnostic criteria for SAD, supporting previous studies identifying high prevalence rates of social anxiety in SZ (Achim et al., 2011; Roy et al., 2015). Furthermore, Chapter 1 showed that patients with SZ who met the diagnostic criteria for comorbid SAD had a lower perception of their social rank (i.e., they rated themselves as inferior compared to healthy controls for a variety of personal attributes such as intelligence) than individuals who did not meet the SAD diagnostic criteria. These results suggest that comorbid SAD may be related to disturbances in processing one's view of himself or herself in SZ.

In Chapter 1, the relation of social anxiety to symptomatology in SZ was also examined, and results importantly highlighted a relation of social anxiety to the cognitive/disorganization factor of symptoms. Specifically, individuals with SZ without comorbid SAD (SZ-SAD), had greater levels of difficulties in abstract thinking and attention compared to those with the comorbid diagnosis (SZ+SAD). Building upon these findings, this study also identified relations between social anxiety, perceived social rank, and certain schizophrenia symptoms. For instance, perceived social rank correlated negatively with delusions in the SZ+SAD group, but positively with delusions in the SZ-SAD group. This result that delusions showed opposite correlations with perceived social rank in patients with SZ only and patients with comorbid SZ+SAD may reflect differing characteristics of delusions in these populations. For instance, in patients with comorbid SZ+SAD, perceptions of social rank may be related to delusions of a persecutory nature in which they perceive threats of others, while in individuals with SZ-SAD, higher perceived social rank may be related to grandiose delusions. However, the study did not examine specific types of delusions patients were experiencing or causal relations among variables, so these hypotheses would have to be further tested in future studies.

By targeting individuals' perceptions of social rank, Chapter 1 focused on understanding the social self, i.e., the outward version of oneself including one's narrative view of the self (Nelson & Raballo, 2015). It is this self that forms the basis of how individuals put themselves forward in social scenarios and engage with others. Particularly, when individuals feel they are inferior to others, they may be less likely to approach others and more likely to interpret negative interactions as being their own fault, which could eventually lead to social withdrawal. Given that individuals with SZ have important impairments in social interactions with others, how social anxiety in SZ could be related to the higher-order social process of attributing mental states (i.e. ToM) was thus an important next step, given the significant relation between ToM and functional outcomes in SZ (Fett et al., 2011).

In Chapter 1, a separate sample of 25 patients with SZ were assessed with the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) to determine their levels of social anxiety. Patients with SZ were also assessed with a classic behavioral measure of ToM (the Combined Stories Task; COST; (Achim et al., 2012) to determine their ToM abilities, and correlational analyses were performed to determine if ToM deficits were related to clinical presentation of social anxiety (Objective 2a). Given that we observed differences in perceptions of social rank in SZ related to social anxiety in Chapter 1, we expected that social anxiety would also be related to alterations in the perception of others' mental states. However, the analysis did not show a significant correlation between social anxiety and ToM performance in patients with SZ.

This finding may be explained by the method that was employed to measure social anxiety in Chapter 2. Given restricted access to diagnostic files, we assessed social anxiety using LSAS scores only, rather than by dividing patients with SZ into two subgroups (i.e., patients with SZ and SAD and patients with SZ without comorbid SAD) as was done in Chapter 1. While recent studies suggest that the LSAS is an important component of identifying social anxiety is SZ (Roy, Demers, & Achim, 2018; Roy et al., 2018), these studies also highlight the importance of taking into account the full DSM-5 diagnostic criteria. Specifically, one of the diagnostic criterion for SAD that was not addressed in Chapter 2 was that the anxiety is not accounted for by another condition. Notably, the other condition could indeed refer to SZ, as social anxiety is often present in SZ but linked to delusions or other psychotic symptoms. In contrast, social anxiety symptoms in SAD are characteristically marked by *a fear of evaluation or judgment* from others. It is therefore, possible that in the present study, different sources of social anxiety contributed to the reported scores on the LSAS in patients with SZ. Given that primary SAD is associated with reduced ToM abilities (Cui et al., 2017; Hezel & McNally, 2014; Washburn et al., 2016), social anxiety may be related to ToM abilities specifically in those individuals whose social anxiety stems from a fear of judgment of others but not in all patients with SZ. Although we were not able to test this in the current thesis, this is certainly an important area of research for future studies, given the reduced functioning that is frequently seen in individuals presenting with SZ and significant social anxiety (Pallanti et al., 2004).

Overall, the studies presented in Chapter 1 and 2 have shed light on illness-related factors in SZ that are involved in social deficits, suggesting that comorbid SAD in SZ is related to alterations in perceived social rank; however, there is no evidence to support a link between social anxiety symptoms in SZ and ToM deficits in SZ.

5.1.2 Task-related factors linked to social deficits in SZ

Given the heterogeneity in ToM tasks that have been used to measure this process in previous studies of SZ (discussed in detail in Section 1.3.4.3), Chapter 2 and 3 aimed to address whether ToM deficits in SZ were related uniquely to social processing, or whether they were also related to context processing (Objective 2b and Objective 3, respectively). To accomplish this goal, a novel fMRI task known as the REMICS task was employed in patients with SZ. For this task, participants were instructed to make judgements about the cause of the event described in presented scenarios. Each of these scenarios had previously been validated to generate a spontaneous inference about the potential cause. Scenarios could be social or physical in nature, and they were followed by the presentation of context, which was validated to be congruent or incongruent with the most likely spontaneous inference. The 2 x 2 orthogonal design thus allowed us to directly assess the impact of the Type of Scenario (social vs. physical) and Type of Context (incongruent vs. congruent) factors on brain activation in SZ at these time points during the task. Additionally, patients were assessed with a classic ToM behavioral task. Correlations between patients' scores on this behavioral task and their performance on the four conditions of the REMICS task were performed. In keeping with results previously observed in healthy participants (Lavoie, Vistoli, Sutliff, Jackson, & Achim, 2016), this study showed that, in patients with SZ, behavioral performance on the ToM task significantly correlated with their performance on the social incongruent, context condition. This finding is important given that the classic definition of ToM (the ability to attribute the mental states of others) would imply that both social conditions on the REMICS task are "ToM conditions." Yet, our results highlight that patients' ToM scores on a classic behavioral ToM task only related to the social, *incongruent context* condition but not the social condition with congruent context. These results thus emphasize that patients' ToM deficits, as operationalized in a classic ToM task, may reflect deficits in social processing, as well as in context processing – but not social processing deficits overall.

These results were supported by fMRI evidence from Chapter 2 which showed that during the presentation of added context, the activation of several brain regions differed in patients with SZ compared to healthy controls. For context that was related to social scenarios (versus physical scenarios), healthy controls deactivated the frontopolar PFC (FP-PFC) during social scenarios compared to non-social scenarios, while patients with SZ did not significantly modulate their brain activation based on the type of scenario. Additionally, in the parahippocampal gyrus patients exhibited greater activation for social compared to non-social scenarios, while healthy controls showed greater activation in this region for non-social compared to social scenarios. Previous studies have highlighted that activation of the FP-PFC and parahippocampal regions are associated with performing tasks of relational and contextual associative processing, therefore, altered activation of these regions in the present study suggest inefficient contextual processing in patients with SZ (Aminoff et al., 2013; M. Li, Lu, & Zhong, 2016; Raposo et al., 2011). In Chapter 2, patients with SZ also showed altered activation in the right TPJ while processing context that was incongruent with (vs context that was congruent with) the initial scenario. Importantly, these differences in brain activation were unique to the phase of the task in which context was presented, further supporting the importance of assessing context processing deficits in SZ.

In healthy participants, the phase of the task where individuals must make a judgment as to the cause of the event activated the majority of classically ToM-related regions. At this phase, patients activated several of the same brain regions as healthy participants during causal judgments, and this pattern was present for both social vs. physical scenarios and incongruent vs. congruent context contrasts. Specifically, for the contrast between social and physical judgments both groups displayed activation of the ventral mPFC, ventral bilateral TPJ, and bilateral temporal pole; for incongruent vs. congruent context-based judgments both groups displayed activation in the dorsal mFPC, bilateral dorsal TPJ, and dlPFC. This ventral/dorsal spatial dissociation is consistent with activation that has been observed in several studies for social and cognitive processing, respectively (Carter & Huettel, 2013; Krall et al., 2014; Scholz et al., 2009; Van Overwalle, 2011). Overall, Chapter 2 highlights that patients with SZ display altered neural activation associated with processing context but not with making causal judgments.

In order to further examine the timing and coordinated activation associated with the REMICS task, the study in Chapter 3 aimed to address ToM using functional connectivity. We used Constrained Principal Component Analysis (CPCA) for the first time to study ToM in SZ. Importantly, CPCA allows for the visualization of the hemodynamic response function (HDR) that can be predicted from the task manipulations (i.e., the Type of Scenario and Type of Context) and the participant group (i.e., patients and controls). Results of this study highlighted that four large-scale networks were involved in the completion of the task. Two of the networks displayed sustained task activation/deactivation throughout the task (i.e., the Task-positive network and the Task-negative network), and two networks showed activation specifically related to the phase of the task (i.e., the Early-task network and the Late-task network). Importantly, none of these networks showed a relation specifically to altered activation associated with social versus physical processing in SZ. Instead, three of the four networks showed altered activation related to the type of context involved in the task. Moreover, CPCA results revealed that in all three of these networks, patients did not modulate their brain activation (as healthy controls did) in response to different levels of context. These results highlight impaired context processing in SZ, while emphasizing the involvement of large-scale brain networks associated with different time-points throughout the task. These results are particularly important given that the majority of fMRI studies of ToM in SZ to date have utilized block design tasks, which focused on altered ToM activation across the entire task (e.g. Benedetti et al., 2009; Brüne, 2008; Dodell-Feder, Tully, Lincoln, & Hooker, 2014). The study in Chapter 3, therefore, adds data to the literature regarding coordinated brain activation associated with specific task phases and supporting previous researchers that ToM is not a monolithic process defined by one brain network (Schaafsma, Pfaff, Spunt, & Adolphs, 2015; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014; discussed further in Section *5.3.2.2*).

Combined, Chapter 2 and Chapter 3 both highlight the role of context in ToM processing in SZ. We observed in Chapter 2 that alterations in brain activation in patients with SZ are observed primarily during the phase in which context is presented. In Chapter 3, we added to this information by showing that altered brain activation in SZ during the fMRI task was related to an inability to modulate the activation of key brain areas in response to different levels of context. Indeed, the behavioral correlations in Chapter 2 also highlight that patients' performance on ToM tasks is also importantly related to their ability to process complex context information as in the social condition with incongruent context. Overall, these chapters add to the literature by presenting novel findings that patients do not show altered brain activation related to social processing overall but show specific impairments related to their ability to recruit coordinated brain activation involved in to processing different types of context.

5.2 Additional findings

5.2.1 Coordinated brain activation of a network supporting self-reflection and stimulus-independent thought is affected in SZ

Chapter 3 also provided insights into brain activation related to the Default Mode Network (DMN) in SZ. The DMN is a well-documented brain network known to support self-perception and self-reflective thoughts. Specifically, we identified a component (referred to in Chapter 3 as the Task-negative component) that was comprised of major nodes of the DMN – the mPFC and PCC – which accounted for a significant amount of task-related variance in brain activation during the REMICS task. Furthermore, contrary to the other components identified in our analysis that showed altered activation related to the type of context, the DMN was not related to the task manipulations. Instead, for both groups, this network showed sustained deactivation throughout all task conditions; however, patients with SZ displayed *reduced* deactivation of DMN regions during the task compared to healthy controls.

Previous studies have highlighted that the DMN is activated at rest and in the absence of cognitively-demanding stimuli (Buckner et al., 2008; Raichle et al., 2001; Whitfield-Gabrieli & Ford, 2012). Accordingly, the DMN has been found to be suppressed during a wide variety of cognitive tasks, and its suppression has been associated with enhanced performance on tasks involving memory encoding/retrieval and working memory (Daselaar et al., 2009, 2004; Zhou et al., 2016). It is therefore hypothesized that activation of this network is related to internally- or self-focused thought, while deactivation of this network suppresses the internally-focused thought in favor of focusing on external stimuli and engaging in cognitively-demanding tasks (Buckner, 2013; Raichle, 2015). The results in Chapter 3 therefore suggest that patients with SZ may inefficiently suppress the DMN throughout the fMRI task. Given that this effect was not associated specifically with the contextual or social nature of the task condition, it may be an inherent disorder-related characteristic of SZ. Such results are indeed supported by previous studies highlighting altered DMN processing in SZ (Jeong & Kubicki, 2010; Zhou et al., 2016).

Although the DMN is described as a Task-negative network, it is important to note that tasks that involve self-focused thoughts, such as remembering one's past or thinking about one's future (Buckner & Carroll, 2007; Spreng, Mar, & Kim, 2009) show increased activation in this network compared to baseline. Indeed, a meta-analysis (Georg Northoff et al., 2006) combined results from 26 studies that used tasks of self-referential processing (e.g. trait judgments of oneself, recognition of one's face, spatial awareness of one's body, remembering one's past, ownership of one's movements, etc.),[10] and identified prominent activation of the mPFC and PCC – two important regions of the DMN – across all tasks included. Dynamic causal modeling has shown that the mPFC and PCC have dense reciprocal connections, whereby the PCC is involved in driving self-related thoughts, which are regulated by the mPFC (Davey, Pujol, & Harrison, 2016; B. Li, Wang, Yao, Hu, & Friston, 2012; Sharaev, Zavyalova, Ushakov, Kartashov, & Velichkovsky, 2016). However, the PCC is a hub that also connects with other large-scale networks, including subcortical structures such as the hippocampus, which are importantly involved in encoding and retrieving episodic and autobiographical memories (Ushakov et al., 2016). These brain regions of the DMN may thus be involved in connecting current thoughts with previous self-experiences and temporally connecting one's own narrative experience of the self.

The findings of Chapter 3 as well as previous research of altered DMN activation in SZ, together suggest that individuals with SZ have inefficient brain networks for processing self-relevant thoughts.

[10] It is worth noting that in this meta-analysis, the concept of self-referential processing included both the basic self and the social self as defined by Nelson & Rabello (2015; see section 5.1.1.1).

5.2.2. Mixed evidence for the role of symptomatology in social deficits in SZ

5.2.2.1 The relationship between symptoms and social anxiety in SZ

In Chapter 1, the severity of SZ symptoms was examined in patients with SZ+SAD and patients with SZ-SAD. Importantly, results showed that individuals with SZ+SAD presented with less severe cognitive/disorganization symptoms. Looking at individual symptoms within that factor, we found that patients with SZ+SAD presented with less severe difficulties in abstract thinking and attention compared to those SZ-SAD. Although we did not expect to observe this relation, these results highlight the importance of examining these patients. It is possible that these patients are able to compensate for deficits in social scenarios by attending more to externally directed details which could aid in their abstract thinking. This is supported by previous studies reporting that individuals with social anxiety exhibit heightened attention to details in threatening situations (Mogg & Bradley, 2002; Pishyar, Harris, & Menzies, 2004).

Previous studies addressing the relation of symptoms and social anxiety in SZ have focused primarily on psychotic symptoms, rather than cognitive symptoms. While some studies have reported a significant correlation between positive symptoms and social anxiety in SZ (Lysaker & Hammersley, 2006; Lysaker & Salyers, 2007; Mazeh et al., 2009; Penn, Hope, Spaulding, & Kucera, 1994) others have reported no association (Birchwood et al., 2007; Pallanti et al., 2004; Romm et al., 2011; Voges & Addington, 2005). Our study in Chapter 1 supported the latter group of studies, finding no relation between social anxiety symptoms and positive symptoms in SZ. In the comorbid SZ+SAD group, this was expected, as the classification into this subgroup was based on the diagnostic criteria for SAD necessitating that their social anxiety stems from fear of judgment of others, rather than from positive symptoms of SZ. However, in the SZ-SAD group, we indeed hypothesized that social anxiety symptoms would be related to positive psychotic symptoms of SZ rather than fear of judgment. Although we did not observe a relation with positive symptoms, we instead observed a relation with the Depression/Anxiety component. This indicated that the social anxiety reported by the SZ-SAD group may be related to general anxiety and depression symptoms rather than positive psychotic symptoms of schizophrenia.

Nonetheless, it is important to consider that SZ is a heterogeneous disorder, and it is unlikely that social anxiety in SZ stems from the same source in all patients. Future studies should consider the distinction between patients whose anxiety meets the diagnostic criteria for SAD and patients who experience social anxiety that may be a part of core symptoms of SZ.

5.2.2.2 The relationship between symptoms and ToM in SZ

In Chapter 2, we addressed whether ToM abilities correlated with severity of SZ symptom factors (Positive, Negative, Cognitive/Disorganization, Depression/Anxiety, and Excitement/Hostility) in a group of individuals with SZ. Given the potential role of context processing in ToM abilities, we expected that cognitive symptoms would be an important factor associated with behavioral ToM performance in SZ. However, we did not find support for this hypothesis in this population, and in fact we did not observe a relation between ToM abilities and symptom severity on any of the five symptom factors in SZ. Our results thus add to the literature suggesting that ToM deficits in SZ are state-dependent rather than trait-dependent (Bora, Yücel, et al., 2009; M. Green et al., 2012; J. Ventura et al., 2015). Notably, some of the strongest findings in support of ToM deficits as a state-dependent phenomenon is that ToM deficts are those studies reporting deficits in unaffected first-degree relatives of individuals with SZ and populations who are at high-risk for developing SZ but do not display clinical symptoms (e.g. Ayesa-Arriola et al., 2016; Bora & Pantelis, 2013; Eltaweel & Ibrahim, 2017; Lavoie et al., 2013).

As discussed in detail in Section 1.2.2.3.2, the literature is mixed on its relation of ToM and symptoms, but this may be due to heterogeneity in ToM tasks. A meta-analysis would be beneficial to determine the aspects of ToM tasks and SZ that are responsible for previously observed correlations.

5.3 Implications of the thesis

5.3.1 On the understanding of SZ

Bridging the gap between observed social deficits and the underlying neurobiology in SZ is one of the greatest barriers to treating and improving functioning in SZ. The present thesis aimed in a general sense to promote this bridge with a focus on improving our understanding of social deficits and social and context-related brain activation in SZ. One of the main findings this thesis -- altered brain activation is associated with context processing in SZ --

is in keeping with the literature dating back to Kraepelin that discusses altered cognitive processing as a core feature of SZ. However, given more recent literature highlighting the link between cognition and social deficits in SZ (e.g. Fett et al., 2011), it is important to begin with the implications of this thesis on the understanding of cognition in SZ.

5.3.1.1 Cognition in SZ: encoding and integration of information

In this thesis, we observe that patients display differences compared to healthy controls during context presentation, rather than making a causal judgment relying on that context. Theoretically, the context presentation phase of our fMRI task would require individuals to engage cognitive resources to encode and integrate the presented context with the initial scenario, as well as update one's mental model about the cause of the event. Therefore, one explanation for the observed differences in activation between the two groups is that patients with SZ are generally impaired in encoding the context. Indeed, if information was not properly encoded into the participants' memory stores, they would not have been able to correctly make a judgment, even if the ability to reason and make a judgment is intact. Although few studies have addressed the issue of context processing using an event-related design, a study by MacDonald et al. (2005) employed such a design and found that patients with SZ showed reduced activation in the dlPFC during encoding of the context (MacDonald et al., 2005). Similarly, in a study of executive control by Schlösser et al., (2008), patients with SZ were impaired compared to controls during the information encoding phase during a task in which participants were to hold letters in memory. In this study, patients with SZ displayed hypoactivation in the dlPFC and the anterior cingulate during the encoding of letters. Although we did not observe differences in dlPFC activation in SZ for the context phase, we did observe group differences in activation in other regions involved in information encoding in healthy participants, including the superior occipital gyrus, TPJ, and dorsal premotor cortex (Cansino, Maquet, Dolan, & Rugg, 2002), which would support this hypothesis.

It is also possible that the observed differences in activation between the two groups could be associated with integration of context, rather than the encoding of context. Particularly for the context-incongruent condition, the context needed to be integrated with the initial scenario to update one's mental model. Therefore, even if information was properly encoded, a deficit in this ability to integrate the new information would still be associated with deficits in the patient group. Researchers have indicated the TPJ as being central in updating one's mental model based on context. Particularly, the right TPJ has been hypothesized to be involved in post-perceptual processing (Geng & Vossel, 2013) and unexpected stimulus processing (Corbetta & Shulman, 2002; Shulman, Astafiev, McAvoy, D'Avossa, & Corbetta, 2007). In our study in Chapter 2, patients do display aberrant activation in the right TPJ in response to incongruent vs. congruent context, during the context presentation phase, which would support this theory. Patients' altered activation during the context phase may be related to a disconfirmatory bias, a commonly reported deficit in patients that refers to the tendency to hold onto an original interpretation and disregard evidence incongruent with one's previously held interpretation (Lavigne et al., 2015; Moritz & Woodward, 2006)[11]. For example, in the study by Moritz & Woodward (2006), participants were presented with fragments of pictures. Each picture initially appeared to take the shape of one object/animal, but as more fragments appeared, the object gradually began to take another shape entirely (e.g., an image that initially appears as a lemon but later presents as an image of a frog). During the task, participants are asked to make plausibility ratings on the definite shape of the object. While healthy participants reduced their plausibility scores for the original interpretation as more image fragments were presented, patients with SZ did not (e.g., they continued to rate the image as highly plausible that it was a lemon rather than a frog). Importantly, this could be relevant to the present REMICS task, as the task was designed for individuals to have an initial interpretation as to the cause of the event simply by reading the scenario.

Context processing may also be viewed as a core feature of SZ itself, rather than as part of a specific cognitive domain. For instance, a model of cognitive deficits in SZ developed by (Cohen & Servan-Schreiber, 1992) asserts that cognitive deficits observed in SZ are all rooted in deficits in context. According to this model, all cognitive deficits observed in SZ, from attention to executive functions, are related to a difficulty in processing

[11] Although bias against disconfirmatory evidence is theoretically linked to executive functions such as perseveration, Woodward, Buchy, Moritz, & Liotti (2007) used a factor analysis to show that perseverative errors on the Wisconsin Card Sorting Test (WCST) did not load onto the factor for scores on a common test assessing disconfirmatory bias, the Bias Against Disconfirmatory Evidence (BADE) task. Perseverative errors on the WCST were instead related to other common neuropsychological tests such as the Trail-making Test A and B, while BADE scores were related to positive symptom scores. This disconfirmatory bias may therefore related delusional ideation, rather than exclusively executive function deficits.

context and maintaining an internal representation of context in a way that it can be manipulated and used later. For instance, deficits in selective attention may be attributed to difficulties in ignoring irrelevant or interfering context. Similarly, difficulties in language processing could be attributed to difficulties in properly using surrounding context in a sentence to infer the meaning.

Overall, results highlighted that alterations associated with context processing in SZ were not restricted to social conditions, which may suggest a generalized information processing deficit, whether it be at the encoding phase or at a later stage of information integration and model updating.

5.3.1.2 Neurobiological alterations in SZ

The mechanism by which context is processed and held in one's mental model is hypothesized to involve a neurobiological gating mechanism that regulates which new contextual inputs will be encoded. Specifically, this would mean that only certain signals would pass through a "gate" and be encoded by the PFC, while others would be blocked and not be encoded. Such a system has been hypothesized to function through neuromodulatory effects of dopaminergic projects on target neurons (Braver & Cohen, 2000; D'Ardenne et al., 2012). In line with this theory, an fMRI study by D'Ardenne et al (2012) found a phasic increase in activation in the ventral tegmental area and the substantial nigra (the dopaminergic nuclei of the brain) in response to context-dependent cues. Furthermore, the timing of this activation correlated with the reaction time for context-dependent signals and this timing was consistent with the timing that would be expected for encoding of new context. Given that this signal from the dopaminergic nuclei of the brain correlated with activation in the dorsolateral PFC, the observed context-dependent signaling may be related to the mesocortical dopaminergic pathway.

This mesocortical dopaminergic pathway is likely crucial in the presentation SZ. Specifically, one of the leading hypotheses of SZ (Howes & Kapur, 2009), states that hypoactivation of dopaminergic D1 activation in the prefrontal cortex is regulated by heightened activation of glutamatergic neurons in the frontal cortex. Reduced dopamine in the prefrontal cortex, particularly in regard to D1, then provides feedback to the dopaminergic nuclei of the midbrain to increase dopaminergic release and hence D2 receptor activation. Notably, this may be related to altered context processing in individuals with SZ, given that altered neurocognition in SZ has been shown to correlate with reduced D1 activation in the dorsolateral PFC(Goldman-Rakic et al., 2004; Williams & Castner, 2006). Accordingly, a recent study of a small sample of patients treated with the antipsychotic aripiprazole showed that higher aripiprazole occupancy of striatal D2 receptors was associated with improved working memory performance (Shin et al., 2018). Given that this medication is a dopaminergic partial agonist (i.e. binds to dopaminergic receptor but with partial efficacy), it could be hypothesized that this medication would act to reduce dopaminergic activation in areas with increased dopamine and to increase dopamine in areas with low dopamine, and the cognitive improvements could indeed be linked to increased dopaminergic input (Shin et al., 2018). An open-label study of 76 patients with SZ (Kern et al., 2006) showed that after 26 weeks of treatment with aripiprazole, individuals had improved cognitive functioning compared to baseline, and notably that patients treated with aripiprazole showed greater improvements in verbal learning compared to patients treated with olanzapine (a dopamine antagonist). These results were echoed by later papers showing promising effects of aripiprazole on improving cognition (Riedel et al., 2010; Suzuki, Gen, & Inoue, 2011).

Importantly, this evidence implicates the dorsolateral PFC in altered dopaminergic transmission, a key mechanism believed to underlie the onset of the disorder. The dlPFC is also implicated in context processing in several studies (e.g. D'Ardenne et al., 2012; Kroger et al., 2002; Lavoie et al., 2016) As stated above, we did not observe dorsolateral PFC activation differences in the context presentation phase of Chapter 2; however, Chapter 3 highlighted alterations in the dorsolateral PFC in the Early-task and Late-task networks, which were associated with aberrant context processing in patients with SZ. Context processing deficits in SZ, as observed in the present thesis, may therefore relate not only to core cognitive deficits but also to altered neurotransmitter systems in SZ.

5.3.1.3 Large-scale network alterations in SZ

Although our results found important differences in patients and controls in regional brain activation, a major component of this thesis also examined large-scale brain networks involved in performing a ToM task. Overall, we replicated previous results highlighting the importance of a Task-positive and a Task-negative network in cognition (Sheffield & Barch, 2016). Previous studies have reported that the more the DMN is suppressed, the better participants perform on cognitive tasks depending on attention to external stimuli (Daselaar et al., 2009). Furthermore, studies have demonstrated a correlation between Task-positive and Task-negative networks, with greater anti-correlation between these networks being indicative of higher cognitive performance (Clare Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Hampson et al., 2010). While the Task-negative network is necessary for self-referential thought, the Task-positive network is involved in cognitive tasks, which may, given the findings of this thesis, include ToM.

Based on the reported functions of these networks, the push and pull between them may be indicative of a delicate balance between attending to internal versus external stimul (i.e., self- and other-processing). Although we did not study the connection between networks in our study, a previous functional connectivity study of ToM in SZ by Das, Calhoun, & Malhi, (2012) found reduced connectivity between Task-positive and Task-negative networks, and the rate of correlation was related to reduced ToM abilities on the Moving shapes paradigm. This provides further evidence of the involvement of alterations in large-scale brain activation in ToM-tasks in SZ.

5.3.2 On the understanding of social processing

It is clear that individuals with SZ exhibit significantly altered social abilities during real-world social interactions. Therefore, an important question raised by our findings is: why did we not observe alterations in brain activation in SZ compared to controls while processing social versus physical events? A likely explanation is the intrinsic context involved in real-world social scenarios that was controlled for in our social versus physical scenario contrast. In the real world, deciphering social scenarios may involve a great deal of context, some of which is necessary to understand a situation and some of which is irrelevant. If individuals with SZ, as observed in the present research, are not able to efficiently identify and adapt their cognitive resources accordingly, then they may not be able to process the appropriate information, which could indeed hinder their ability to comprehend the mental states of others. Importantly, tasks aimed at more closely approximating real-world social interactions may offer data that would be more applicable to real-world social scenarios.

An important distinction between typical cognitive tasks, whether social cognitive or neurocognitive, and real-world processing, is that the flow of context is continuous in the real-world. During the REMICS task, for example, an initial scenario is presented on screen alone, followed by the addition of contextual information. Similarly, in common working memory tasks, there is an encoding phase, followed by a delay period, followed by a manipulation phase. While these tasks have been specifically developed to decompose larger processes into its smaller parts, the processing of social contextual information likely does not function in such discrete pieces which likely affects the findings.[12] An article by Hasson, Chen, & Honey (2015) suggests that in daily life, prior information is continually influencing the processing of current information. According to the authors, a basic example of this can be found in language comprehension: phonemes only have meaning in the greater context of a word, and a word only has meaning in the greater context of a sentence. Therefore, even the simple task of reading a sentence, requires integration of previous contextual information. To extrapolate this to social situations, it is clear that long-term memory would also play an important component, in terms of recalling previous experiences with different contexts and individuals. This would be true within a single conversation, but also would extend to all previous encounters with an individual. In extrapolating this to social situations, it is evident that social processing would require continuously incoming and outgoing information involving not only encoding and perception but also memory.

Virtual reality technology may offer promising new tasks to study ToM by testing patients' abilities while simulating dynamic real-world social processing. For instance, Canty, Neumann, & Shum (2017) recently developed a task known as the Virtual Assessment of Mentalizing Ability (VAMA), in which participants were to navigate a virtual shopping center to complete a list of errands and answer questions each time a social interaction occurs with the participant's virtual ¨friends.¨ Notably, virtual reality technology can also be used for social cognitive training, focusing on improving abilities to understand social scenarios in various contexts, such as the recently reported Dynamic Interactive Social Cognition Virtual Reality Training (DiSCoVR) for people with psychotic disorder (Nijman, Veling, Geraets, Aleman, & Pijenborg, 2017). While virtual reality technology has only recently been applied to ToM in SZ, it will surely provide useful insight into social processing in upcoming years.

[12] This is particularly true in the REMICS task: participants were aware that they would next have to select the cause of the event from two alternative choices and they therefore may have been using the context phase as a preparatory or pre-judgment phase.

5.3.2.1 Relating social processes to the DMN

The DMN, while typically addressed as the self-referential network, has been hypothesized to play a central role in social processing others, as well. From a neuroscience perspective, evidence of this consists of the findings that the same regions that are recruited as part of the DMN, are also recruited during tasks requiring one to attribute mental states of others (e.g. the mPFC, PCC, and TPJ). This finding has led to the hypothesis that social processing is the default function of the brain (Schilbach et al., 2008). According to this idea, in the absence of external stimuli, our brains would be left to thinking about one's concept of the self, such as imagining the future and remembering the past. Yet, an unescapable feature of the 'self' may be that it exists in a world cohabitated by the 'other.' In that sense, the self-reflective nature of thinking about one's self would necessitate applying self-related concepts in the other. This DMN, then, may be the mechanism by which individuals think about both themselves and others (Molnar-Szakacs & Uddin, 2013). DMN could therefore be the link discussed in Simulation Theory, whereby the mental states of others necessitate the self.

The role of context would therefore need to be addressed in this link, given the findings of this study. As briefly discussed above, context is important for internal representations of both the social and physical world; however, it is also possible that internal representations of the self also play a factor in these representations of other individuals. Our internal representations of the self may thus be applied to others for use in planning, decision-making, and general responses to external stimuli/demands. If indeed, the DMN is involved in a physiological baseline of the brain which is related to social processing, then this may explain our findings in Chapter 3, whereby we found altered activation in SZ across all task conditions.

5.3.2.2 The relation of context and ToM

ToM is a well-studied domain of social cognition, and for patients with SZ, it is a particularly critical area of research, as it is related closely to their community functioning. Although ToM is typically defined as the ability to infer or attribute the mental states of others (M. Green et al., 2008), we show that context has a particularly important role in ToM deficits in SZ. These results build upon those of Lavoie et al., (2016) who found similar results in healthy participants. As the number of studies assessing ToM continues to grow, it is of utmost importance to better define ToM and to incorporate this new definition into future studies. Given that the majority of ToM tasks do involve context to some degree, the inclusion of context in the definition would be an important first step. For instance, the results suggest that the classic definition of ToM could be revised to state: "the ability to infer or attribute the mental states of others based upon prior knowledge and surrounding contextual information." Such a revised definition would increase awareness of the role of context in ToM, shifting the focus from the study of ToM in SZ as a purely social phenomenon to highlighting its cognitive basis. This could also benefit future studies of the neural underpinnings of ToM in SZ to encourage contrasts to take note of the level of context involved and include this in their interpretations. Finally, it could open a discussion about whether the few tasks with minimal or arguably no contextual information should continue to be included as ToM tasks (e.g. the Reading the Mind in the Eyes task; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001).

Alternatively, given all of the heterogeneous definitions, tasks, and subdivisions of SZ, it may be useful to disregard the term ToM altogether. Recently, (Schaafsma et al., 2015) called for the deconstruction of ToM into its component processes in order to reconstruct a new definition. According to this view, simply categorizing ToM into different subtypes is not enough because it leaves the original concept of ToM unaltered. Instead, ToM should be deconstructed into well-defined and testable sub-components, which could include perceptual discrimination and categorization of socially relevant stimuli, semantic or conceptual knowledge, executive, and motivational processes. Then, in the reconstruction phase, ToM could be assembled by combining together the most basic building blocks, followed by processes that build upon the basic processes, and finally, different subtypes of ToM could then be created based on those that share similar intermediate processes. This would then allow for more homogeneous subtypes, as well as the removal of tasks that do not fit into any of these definitions.

5.3.3 On the understanding of ToM deficits in SZ

5.3.3.1 Neurobiological underpinnings of ToM in SZ

During the time of writing this thesis, a meta-analysis was published that addressed the neurobiological alterations associated with ToM in patients with SZ (Kronbichler et al., 2017). The study which combined 21 fMRI studies of ToM in SZ to date, is an important addition to the literature of ToM in SZ, given the heterogeneity of ToM tasks and findings to date. Results showed a mix of hyper- and hypoactivation in brain regions typically associated with ToM tasks. Particularly, hyperactivation was found in the bilateral dorsal TPJ, a region in which has been associated with processing incongruent context in the REMICS task (Lavoie et al., 2016; see also Chapter 2). Hypoactivation was also found in a large cluster of the mPFC, in the right premotor cortex, left orbitofrontal cortex, and left ventral TPJ. This meta-analysis also divided tasks based on general task types (i.e., visual vs verbal; cognitive vs affective; implicit vs explicit), with results for individual task type analysis varying significantly. However, interestingly, the mPFC was affected in SZ across all task types. Alteration of mPFC activation across all types of tasks may be related to task-related suppression of the DMN as was found in Chapter 3. Accordingly, our results also showed altered activation of a large cluster in the mPFC that was consistently suppressed across all types of tasks, regardless of the type of context.

Importantly, these results from Kronbichler et al., (2017) highlight that altered brain activation in patients with SZ spans different brain networks and may implicate a variety of functions, including higher-order cognitive domains, such as attention (Kronbichler et al., 2017). While highlighting the heterogeneity among task types, it also suggests that the DMN may be involved in ToM tasks. Overall, results of the present thesis combined with the current literature, suggest that patients have altered brain activation in the mPFC and TPJ, and these alterations can have implications for both social processing and context processing.

5.3.3.2 ToM deficits in SZ: The relation to functioning

The groundbreaking meta-analysis of 52 studies addressing the correlation between social cognition and neurocognition and functioning (Fett et al., 2011) showed that ToM was most strongly related to community functioning. This finding has typically been interpreted as highlighting the importance of understanding and improving ToM in SZ; however, it could also represent an important indicator of the complexity of ToM. Particularly, this heightened relation of ToM to functioning may occur because ToM incorporates components of both social cognition and neurocognition and is therefore inherently more complex than the others studied. Indeed, community functioning, as defined in this meta-analysis, incorporate a variety of everyday activities, such as independent living skills and social or work functioning. Therefore, it would stand to reason that a concept including basic sensory, neurocognitive, and social cognitive resources would be most indicative of functioning.

Therefore, while ToM abilities in SZ may hold the key to improved functioning, it likely not a simple fix, given the complexity of this concept. However, the present findings do highlight the importance of targeting deficits specifically in context, which will be discussed in the following section.

5.3.4 On treatment for social deficits in SZ

The ultimate goal of research targeting social deficits in SZ is to eventually find treatment that can improve functioning and quality of life for these individuals. The results in this thesis can be applied in a general sense to potential routes for future treatment approaches.

5.3.4.1 Targeting social anxiety in SZ

As highlighted by our study and others, anxiety disorders are common comorbidities in SZ (Achim et al., 2011; Roy et al., 2015; Sutliff, Roy, & Achim, 2015). These disorders are thus an important source of heterogeneity among SZ which are likely associated with altered neurobiological underpinnings and barriers to treatment. A paper published in Psychiatric Times by our team (Achim, Sutliff, & Roy, 2015) reviews obstacles and potential strategies for treating comorbid anxiety disorders, including social anxiety in SZ. Evidence suggests that different pharmacotherapy strategies may be helpful for individuals with comorbid social anxiety. For instance, switching antipsychotic medication to aripiprazole has been associated with reduced social anxiety symptoms and improved quality of life (Stern, Petti, Bopp, & Tobia, 2009). In addition, interventions of cognitive behavioral therapy in this population have shown promising results, with improvement in anxiety, depression, quality of life, and general psychopathology (Michail, Birchwood, & Tait, 2017).

To the best of our knowledge, there have been no studies published regarding cognitive remediation specifically targeting the comorbid anxiety population in SZ. However, based on our findings that individuals with schizophrenia and social anxiety disorder display less impaired cognitive symptoms, this could be an important area for future interventional strategies to target. Particularly, cognitive remediation programs used in SZ may provide the best improvement if they are adaptable and utilize one's strengths and weaknesses in the training program (Reeder et al., 2016). Importantly, as shown in Chapter 1 (Sutliff et al., 2015), individuals with SZ with and without social anxiety disorder may show a different clinical presentation with differing levels of symptoms and self-perceptions which could therefore be included in such a therapeutic approach. Notably, in patients with SZ and comorbid social anxiety disorder, less impaired cognitive symptoms, specifically attention and abstract thinking, may be an important strength to harness in future intervention strategies.

5.3.4.2 Targeting context processing deficits in SZ

For patients with SZ as a whole, cognitive remediation has been used to target social and non-social cognition. Particularly, given the link of functioning and ToM in SZ, several approaches have focused particularly on improving ToM abilities in this population. A meta-analysis by Kurtz & Richardson (2012) examined the findings from cognitive remediation strategies aimed at improving social cognition in SZ. From the seven studies identified, the meta-analysis showed that cognitive remediation interventions had a moderate effect on ToM abilities, but there was a great deal of heterogeneity among studies, including the strategies used, the duration of intervention, and the outcomes. The common thread among the studies targeting ToM abilities, however, is that the training focused explicitly on training social abilities. An approach by Horan et al., (2009), for instance, developed an intervention in which individuals were trained to identify complex emotions, decode social cues, and understand how one's emotions could affect one's thoughts and behaviors in social situations.

Evidence presented in this thesis would suggest that an alternate approach would be beneficial – rather than focusing on improving social abilities, training strategies could focus on improving individuals' abilities to process context. There is indeed proof that by targeting nonsocial cognition, patients with SZ can have improved ToM abilities in a small case study (Thibaudeau et al., 2017). This is important because the main concept behind cognitive remediation is based on the neuroplasticity of the brain, in which we have continuous capacity for physical and functional changes. Therefore, by consistently performing exercises that are relevant to a particular neural process, an individual can stimulate those brain regions and eventually lead to enhancement of that process (Eack, 2012). Cognitive remediation often also focuses on not only discrete exercises during the session but also encourages application of certain training in one's daily life, which could result in further strengthening of newly formed connections. Given this information, targeting the neurobiological underpinnings of a given process would be of importance for optimal outcome. Therefore, interventions for ToM in SZ should focus on improving context processing abilities, particularly on the ability to process surrounding information and incorporate it with previously held knowledge. For instance, an intervention targeting social abilities in SZ may benefit from focusing on the moment in various situations where one needs to gather relevant information and decide which information would be most relevant or irrelevant.

5.4 Conclusions

In summary, the present thesis confirms both task-related and illness-related factors have important impacts on social deficits in SZ. First of all, this thesis demonstrates that social anxiety disorder in SZ is a prevalent comorbidity in SZ that is related to both symptom presentation and perceived social rank in SZ. Second, this thesis highlights that in individuals with SZ overall, affected context processing are implicated in ToM task-related deficits. Individuals with SZ may therefore have difficulties in encoding or integrating new contextual information in order to update their mental model of the cause of an event. Third, patients show a reduced ability to modulate large-scale brain networks in response to different types of context. Deficits in context processing may be particularly relevant to real-world social situations where there is a dynamic, continuous flow of contextual information that must be processed. Based on this evidence and previous findings in the literature, future studies should consider social anxiety disorder in the study and treatment of individuals with SZ. Additionally, context processing deficits in SZ may represent a core deficit that could be targeted in future interventions aimed at improving social abilities in SZ. Generally speaking, the presented evidence underlines the need to rethink how ToM is studied and measured in order to address the inherent role of context. In conclusion, this thesis suggests the importance of considering heterogeneity in both SZ and in ToM in future research of social processing in SZ.

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