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An fMRI study of emotional episodic memory in schizophrenia: Effects of diagnosis and sex

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An fMRI study of emotional episodic memory in schizophrenia: Effects of diagnosis and sex

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Résumé

La schizophrénie est une psychopathologie largement hétérogène caractérisée entre autres par d'importantes défaillances dans le fonctionnement cognitif et émotionnel. En effet, par rapport à la population générale, forte proportion de ces individus présentent une mémoire déficitaire pour les événements émotionnels. À ce jour, le peu d'études qui se sont penchées sur la mémoire émotionnelle épisodique dans la schizophrénie, ont uniquement mis l'emphase sur l'effet de la *valence* des stimuli (c'est-à-dire le caractère agréable ou désagréable du stimulus). Toutefois, aucune n'a investigué spécifiquement l'intensité de la réaction aux stimuli (c'est-à-dire une faible par rapport à une forte réaction) malgré quantité de preuves faisant montre, dans la population générale, de différents processus de mémoire émotionnelle pour des stimuli suscitant une forte réaction par rapport à ceux évoquant une faible réponse. Ce manque est d'autant plus flagrant étant donné le nombre d'études ayant rapporté un traitement et un encodage atypiques des émotions spécifiquement au niveau de l'intensité de la réponse subjective chez des patients atteints de schizophrénie. Autre fait important, il est étonnant de constater l'absence de recherches sur les différences de sexe dans la mémoire émotionnelle étant donné l'ensemble des divergences entre hommes et femmes atteints de schizophrénie au niveau de la prévalence, de l'âge de diagnostic, de la manifestation clinique, de l'évolution de la maladie, de la réponse au traitement et des structures cérébrales. Pour pallier à ces lacunes, ce mémoire a évalué : (1) l'effet de la *valence* des stimuli et de l'intensité de la réaction émotionnelle au niveau des fonctions cérébrales correspondant à la mémoire émotionnelle chez des patients atteints de schizophrénie comparativement à des participants sains; et (2) les possibles différences de sexe dans les processus cérébraux impliqués dans la mémoire émotionnelle chez des patients atteints de schizophrénie par rapport à des volontaires sains.

Ainsi, la première étude a comparé les activations cérébrales de patients atteints de schizophrénie par rapport à des participants sains au cours d'une tâche de mémoire émotionnelle dont les stimuli variaient à la fois au niveau de la *valence* et de l'intensité de la réaction subjective. 37 patients atteints de schizophrénie ainsi que 37 participants en bonne santé ont effectué cette tâche de mémoire émotionnelle lors d'une session d'imagerie par résonance magnétique fonctionnelle (IRMf). Pour toutes les conditions étudiées (images négatives, positives, de faible et de forte intensité), le groupe atteint de schizophrénie a performé significativement moins bien que les volontaires sains. Comparativement aux sujets sains, ils ont montré moins d'activations cérébrales dans les régions limbiques et préfrontales lors de la reconnaissance des images négatives, mais ont présenté un patron d'activations similaire à celui des participants sains lors de la reconnaissance des images chargées positivement (activations observées dans le cervelet, le cortex temporal et préfrontal). Enfin, indépendamment de la *valence* des stimuli, les deux groupes ont démontré une augmentation des activations cérébrales pour les images de forte intensité par rapport à celles de plus faible intensité.

La seconde étude a quant à elle exploré les différences de sexe potentielles au niveau des activations cérébrales associées à la mémoire émotionnelle dans la schizophrénie et dans la population en général. Nous avons comparé 41 patients atteints de schizophrénie (20 femmes) à 41 participants en bonne santé (19 femmes) alors qu'ils effectuaient la même tâche de mémoire émotionnelle mentionnée plus haut. Or, pour cette étude, nous nous sommes concentrés sur les conditions suivantes : la reconnaissance d'images positives, négatives et neutres. Nous n'avons pas observé de différences entre les hommes et les femmes au niveau des performances à la tâche de mémoire pour aucune des conditions. En ce qui a trait aux données de neuroimagerie, comparativement aux femmes en bonne santé, celles atteintes de schizophrénie ont

montré une diminution des activations cérébrales dans les régions corticales du système limbique (p. ex. cortex cingulaire moyen) et dans les régions sous-corticales (p. ex. amygdale) lors de la reconnaissance d'images négatives. Pour ce qui est de la condition positive, elles ont présenté, comparativement au groupe de femmes saines, des diminutions d'activations spécifiquement dans le cervelet ainsi que dans le gyrus frontal inférieur et moyen. Les hommes atteints de schizophrénie, eux, ont montré une augmentation d'activations par rapport aux hommes sains dans le gyrus préfrontal médian lors de la reconnaissance des stimuli négatifs ; ainsi que dans les régions pariétales, temporales et limbiques lors de la reconnaissance des stimuli positifs. Dans un autre ordre d'idées, notre analyse corrélationnelle a mis en évidence, chez les femmes, un lien significatif entre l'activité cérébrale et les symptômes au cours de la mémoire des stimuli positifs, alors que chez les hommes atteints schizophrénie, ce lien a été observé au cours de la mémoire des stimuli négatifs.

Bref, l'ensemble de nos résultats suggère, chez les patients atteints de schizophrénie, un fonctionnement cérébral atypique spécifiquement lors de la reconnaissance d'images négatives, mais un fonctionnement intact lors de la reconnaissance de stimuli positifs. De plus, nous avons mis en évidence la présence de différences de sexe dans les activations cérébrales associées à la mémoire épisodique émotionnelle soulignant ainsi l'importance d'étudier séparément les hommes et les femmes atteints de schizophrénie dans le cadre de recherches sur les plans cognitif et émotionnel.

Mots-clés : Différences de sexe, mémoire émotionnelle, *valence*, intensité, schizophrénie, IRMf

Abstract

Schizophrenia is characterized by prominent disturbances in cognitive and emotional functioning. For instance, individuals with schizophrenia are often impaired in their memory for emotional events compared to healthy subjects. To date, the limited research on emotional episodic memory in schizophrenia has focused on the effect of valence of affective stimuli (e.g., pleasant vs. unpleasant), while overall ignoring the effect of arousal (e.g., low vs. high) despite evidence of distinct emotional memory processes for high versus low arousing stimuli in the general population, as well as reports of abnormal processing of arousing stimuli in schizophrenia. What's more, there has yet to be examination of sex differences in the behavioral and neural correlates of emotional memory in this complex psychiatric disorder, which is astonishing considering the substantial evidence of sex differences in almost all features of schizophrenia from prevalence, mean age at onset, clinical presentation, course of illness, response to treatment and brain structure. Accordingly, this thesis examined: (1) the effect of both affective valence and arousal intensity on the brain activations associated with emotional memory in patients with schizophrenia and in healthy control participants and (2) potential sex differences in brain function during emotional memory.

The first study aimed to compare cerebral activations in patients with schizophrenia and healthy controls during memory retrieval of emotional images that varied in both valence and arousal. Using fMRI, 37 patients with schizophrenia (% male = 51; mean age =32.46) were compared to 37 healthy participants (% male = 51; mean age =31.81) while performing an emotional memory task. patients with schizophrenia performed worse than healthy controls in all experimental conditions. They showed less cerebral activations in limbic and prefrontal regions than controls during retrieval of negatively valenced stimuli, but had a similar pattern of brain activations to controls during retrieval of positively valenced stimuli (particularly in the high arousal condition)

in the cerebellum, temporal and prefrontal cortex. Both groups demonstrated increased brain activations in the high relative to low arousing conditions.

The second study explored potential sex differences in the brain activations associated with the recognition of emotional images in schizophrenia and healthy controls. 41 patients with schizophrenia (20 women) were compared to 41 healthy participants (19 women) while performing a yes/no recognition paradigm with positive, negative and neutral images in an fMRI scan. We did not observe sex differences in performance. Compared to healthy women, women with schizophrenia showed a decrease in brain activations in cortical (e.g. middle cingulate) and subcortical limbic structures (e.g. amygdala) during recognition of negative images and decreased activations during the positive condition in the cerebellar vermis, middle and inferior frontal gyrus. Men with schizophrenia had increased activations compared to healthy men in the medial prefrontal gyrus during recognition of negative stimuli and a substantial increase in brain activity during the recognition of positive pictures in parietal, temporal and limbic structures. Correlation analysis revealed significant relationships between brain function and symptoms during positive emotional memory in women and during negative emotional memory primarily in men.

Taken as a whole, our results suggest atypical brain function during retrieval of negative pictures, but intact functional circuitry of positive affect during episodic memory retrieval in patients with schizophrenia compared to healthy subjects. Moreover, our findings revealed sex differences in the brain activations associated with emotional recognition memory in patients with schizophrenia; which further highlights the importance of investigating men and women with schizophrenia separately in the context of emotional and cognitive tasks.

Keywords: Sex differences, emotional memory, valence, arousal, schizophrenia, fMRI

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Abbreviations

BA	Brodmann's area
BOLD	Blood Oxygen Level Dependent
CIHR	Canadian Institute of Health Research
DSM	Diagnostic and statistical manual of mental disorders
ERP	Event-related potentials
EPI	Echo planar imaging
fMRI	Functional magnetic resonance imaging
HA-	High arousal negative
HA+	High arousal positive
LA-	Low arousal negative
LA+	Low arousal positive
HC	Healthy controls
HM	Healthy men
HW	Healthy women
IAPS	International Affective Picture System
LA	Low arousal
MNI	Montreal Neurological Institute
NEG	Negative
NOC	National Occupational Classification
NTR	Neutral
PANSS	Positive and negative syndrome scale
POS	Positive
SCID	Clinical interview for DSM-IV
SCZ	Schizophrenia patients
SD	Standard deviation
SES	Socioeconomic status
SPSS	Statistical Package for the Social Sciences
SZ-M	Schizophrenia men
SZ-W	Schizophrenia women
ROI	Region of interest

Thank you

I am one of the fortunate ones to have had so many people in my life who have been there for me and who have supported me throughout this journey.

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Introduction

I. Schizophrenia: An overview

Evolution of the concept of schizophrenia: Kraepelin-Bleuler-Schneider

Kraepelin (1919), Bleuler (1911) and Schneider (1959) were instrumental figures in the conceptualization of schizophrenia, even though their different ideas led to inconsistencies in defining the illness over the past century (Hoenig, 1983). Kraepelin (1919) believed that schizophrenia comprised a unique disease entity with a single etiology and a distinct pathology. Because the cause was unknown, classification depended largely on the course and outcome of groups of symptoms. More specifically, Kraepelin noted a tendency towards deterioration and an outcome of mental dullness or dementia in patients with an adolescent or early adult onset of catatonia, hebephrenia, and paranoid dementia – a group he termed dementia praecox.

The term schizophrenia, which literally means “a mind that is torn asunder”, was later coined by Euegen Bleuler (1911). In contrast to Kraepelin’s neurodegenerative disorder of adolescents, Bleuler defined a set of basic symptoms considered to be unique to the disorder and present in all patients with the disorder. Moreover, he considered course and outcome of the illness to be variable (e.g. stable outcome, improvement after onset). Rather than the essence of schizophrenia being defined by delusions and hallucinations, Bleuler believed that loosening of associations, blunted affect, ambivalence and autism (now considered negative symptoms) were the fundamental symptoms of the illness.

Subsequently, Jaspers (1946) deemed that a deficit in compassionate interactions in individuals with schizophrenia and an “un-understandability” of the individual experience as significant features of the disorder. Building on this concept, Schneider (1959) defined the first-rank symptoms of schizophrenia (e.g. thoughts experienced as spoken aloud, voices making references in the third person), which

were thought by Schneider and others (Mellor, 1970) to be pathognomonic. However, with time this assertion was challenged in light of Schneiderian first-rank symptoms being present in a variety of other nonorganic psychotic psychiatric disorders (Janowsky & Risch, 1979; O'Grady, 1990).

Clearly, these three viewpoints of describing this complex and heterogeneous psychiatric disorder are distinctive. The tools currently used to define schizophrenia including DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders) and ICD-10 (International Classification of Diseases) criteria incorporate Kraepelinian chronicity, Bleulerian negative symptoms and Schneiderian positive symptoms. However, the use of different combinations and variable interpretations of these elements with restricted psychopathological validity has led to widespread criticisms (Poland et al., 1994).

The epidemiology of schizophrenia

Over the years there have been major epidemiological findings in the occurrence of schizophrenia across populations, time and socio-demographic characteristics (Tandon et al., 2008). Schizophrenia manifests itself in less than 1% of individuals in a population at some point in their lives (Perala et al., 2007; Stilo & Murray, 2010). The most recent studies suggest that the rate of 1% could be an overestimation and that the prevalence of the disorder is typically higher in developed than in developing countries, and higher in migrant groups than in native-born populations (McGrath et al., 2008; Saha et al., 2005). Additionally, a higher prevalence of schizophrenia among lower as opposed to higher socio-economic classes within communities has been steadily reported over the past century (Tandon et al., 2008).

The incidence of schizophrenia, defined as the number of new cases for a given population per year, has shown prominent discrepancies among scientific studies. A concise overview of three related systematic reviews on the incidence, prevalence, and mortality associated with schizophrenia has reported that the median incidence of

schizophrenia was 15.2/100,000 persons and that the central 80% of estimates varied greatly over a range of 7.7-43/100,000 persons (McGrath et al., 2008). Moreover, significant variations in the incidence of schizophrenia have been documented such that urbanicity, migration and male gender have been linked with an increased risk of developing the disorder (Saha et al., 2006). A relatively consistent description of schizophrenia has been documented over the last two centuries and its occurrence has been relatively stable despite changes in specific diagnostic criteria (Bleuler, 1950; Kraepelin, 1971). However, the incidence rates of schizophrenia are suggested to have fluctuated over time with some studies proposing an increase in schizophrenia (Bray et al., 2006) and others implying a decrease in the incidence of schizophrenia with time (Woogh, 2001). It is likely that changes in the tools used to diagnose schizophrenia and the manner in which cases are detected makes these assumptions difficult to interpret (Kendell et al., 1993).

The clinical features of schizophrenia

Schizophrenia is presently defined by a diverse set of signs and symptoms that are broadly classified into positive, negative, cognitive, disorganization, mood and motor symptom dimensions; with differing degrees of psychopathological expression observed across patients and throughout the course of illness (Tandon et al., 2010). Positive symptoms include delusions, hallucinations and other reality distortions while negative symptoms encompass a blunting or loss of a range of affective functions such as a loss of motivation, lack of experiencing pleasure, avolition and blunted affect. The occurrence of all types of hallucinations is about 50% in those with the disorder and of this percentage, 50% encompass auditory hallucinations (Cutting, 1990). Delusions, on the other hand, are reported to occur at some stage during the course of schizophrenia in more than 90% of those with the diagnosis (Cutting, 2002). With regards to negative

symptoms, flattening of affect is observed in approximately 50 % of acute (Andreasen, 1979) or chronic patients with schizophrenia (McCreadie, 1982).

Studies have shown that negative symptoms are generally more stable than positive symptoms and are least likely to improve over the course of illness (Addington et al., 1991; Andreasen & Flaum, 1991). For instance, Arndt and colleagues (1995) observed that while both negative and positive symptoms were already prominent at the time of the patients' first episode, during the follow-up period, the negative symptoms remained relatively stable while the positive symptoms declined. In addition, it has been suggested that negative symptoms are more closely linked to prognosis, in spite of the suffering that may be associated with psychotic symptoms (Fuller et al., 2002). Many studies have shown that the level of negative symptoms is significantly associated with a poor level of social functioning (Biehl et al., 1986; Breier et al., 1991; Fenton & McGlashan, 1992; Keefe et al., 1987); albeit others have observed similar relationships between high levels of positive symptoms and social functioning (Breier et al., 1991; Keefe et al., 1987). A surprisingly consistent pattern has emerged between impairments in cognitive ability and symptom profiles, such that cognitive impairment correlates with negative and disorganized symptoms (Andreasen, Flaum, et al., 1990; Bilder et al., 1985; Braff, 1989; Keilp et al., 1988; Merriam et al., 1990) but not with psychotic symptoms in patients with schizophrenia (Bilder, et al., 1985; O'Leary et al., 2000).

What causes schizophrenia?

Schizophrenia is a complex, incapacitating and heterogeneous psychiatric disorder, and to date the etiology of the illness remains a mystery. Even so, several theories on the origin of schizophrenia have been put forward.

The risk of developing schizophrenia increases considerably in an individual who has an affected family member, a risk that intensifies as the degree of genetic similarity with the affected family member increases (i.e. a first degree relative) (Kendler

& Diehl, 1993; Sullivan et al., 2003). Twin studies of schizophrenia show consistently higher concordance rates in monozygotic (around 50%) than in dizygotic twins (around 17%) (Cardno and Gottesman, 2000). Correspondingly, both individual twin studies and meta-analyses of twin studies estimate the heritability of schizophrenia to be roughly 80% (Riley and Kendler, 2006). Nonetheless, more than two thirds of individuals with schizophrenia do not present with a family history of the illness (Kendler et al., 1993) and no gene appears to be either sufficient or necessary for the development of schizophrenia (Tandon et al., 2008). Thus, the prevalent genetic opinion is that schizophrenia is a polygenic/multifactorial disease (Lichtermann et al., 2000). Other than genes, both pre- and perinatal complications (e.g. maternal influenza, fetal hypoxia) and other environmental elements (e.g. season of birth, cannabis use) have been linked to a substantial increase in the risk of developing the disorder (McGrath, 2011; Mittal et al., 2008; Tandon, et al., 2008; van Os et al., 2008). After decades of research what can be said with confidence is that both genetic and environmental elements are at play (Tandon et al., 2008).

It has been suggested that schizophrenia is "not the result of a discrete event or illness process at all, but rather one end of the developmental spectrum that for genetic and/or other reasons 0.5% of the population will fall into." (Weinberger, 1987). Developmental changes in the brain that span from the fetal period through young adulthood are now a vital feature of most etiological theories of schizophrenia and this neurodevelopmental hypothesis of schizophrenia is rarely challenged in the literature (Gourion et al., 2004; Walker et al., 2010; Weinberger, 1996). Simplified, the broad neurodevelopmental view of schizophrenia dictates that both genetic and prenatal factors confer vulnerability of schizophrenia by inducing pathologic processes beginning before the brain approaches its adult state in adolescence (Fatemi & Folsom, 2009; Rapoport et al., 2005). Developing in utero as early as late first or early second

trimester (Fatemi et al., 2005), these neurodevelopmental anomalies are proposed to lead to the activation of pathologic neural circuits during critical developmental time points in adolescence (sometimes due to elevated stress), ultimately guiding the manifestation of positive and/or negative symptoms (Fatemi & Folsom, 2009; Keshavan & Hogarty, 1999; Walker, et al., 2010). Yet, precisely how and in what way genetic and environmental factors might interact to cause schizophrenia and the neurobiological mechanism that may mediate such interactions remains unknown.

Treatment without a cure

As far as we know, there is no cure for schizophrenia. In spite of this, existing multi-modal regimens that embrace the use of antipsychotic medications, psychosocial interventions, as well as support with housing and financial sustenance are accessible to individuals with schizophrenia (Tandon, et al., 2010).

About half a century ago, antipsychotic drugs were established into clinical practice sparking the revolution in the pharmacotherapy of schizophrenia (Delay et al., 1952). First generation antipsychotic drugs (i.e. typical antipsychotic) have been shown to be effective in relieving the positive symptoms of schizophrenia and in preventing their reappearance in several patients (for a review see Miyamoto et al., 2005), while having little therapeutic effects on negative symptoms, mood symptoms and cognitive deficits (Fleischhacker, 1995; Hawkins et al., 1999; Tandon et al., 2009). Instead, second-generation or atypical antipsychotic drugs such as clozapine are reported to have superior therapeutic benefits for cognitive and negative symptoms (Keefe et al., 1999; Meltzer & McGurk, 1999); a conjecture that is today continuously debated (Faber et al., 2011; Keefe et al., 2007; Remington & Kapur, 2000). Interestingly, several recent studies appear to imply that atypical antipsychotic agents are no more effective than typical drugs and are not associated with better cognitive or social outcomes (Jones et al., 2006; Keefe, et al., 2007; Lieberman et al., 2005; Swartz et al., 2007). While typical

antipsychotics cause a range of side effects such as acute extrapyramidal symptoms and tardive dyskinesia (Miyamoto et al., 2002; Tandon, et al., 2010) the atypical agents produce other serious side effects including agranulocytosis, weight gain and diabetes (Lieberman & Safferman, 1992; McIntyre et al., 2001; Melkersson & Dahl, 2004). Regardless, the finding that atypical drugs increase efficacy in treatment refractory patients (Essali et al., 2010; McEvoy et al., 2006) and lower the risk of extrapyramidal symptoms (Pierre, 2005) have given the scientific community hope that a superior antipsychotic treatment for individuals with schizophrenia is achievable (Tandon et al., 2010). No matter the type of drug used, antipsychotic medications are consistently reported to be superior to placebos in reducing overall symptom severity and the risk of relapse in patients with schizophrenia (Leucht et al., 2003). It is noteworthy to keep in mind; however, that despite the reported therapeutic benefits of antipsychotic medications, the extent to which their use impacts the mortality, social functioning and overall quality of life in patients with schizophrenia are less clear and research on this topic has yielded inconsistent findings (Lehman et al., 2004; Ren et al., 2009; Thirthalli et al., 2010; Weinmann et al., 2009).

As stated by Fenton and Schooler (2000) “patients are more than the sum of their symptoms”. These authors emphasize that the management of this disabling psychiatric disorder extends beyond the use of antipsychotic drugs. The literature has yielded cumulative evidence of the efficacy of various psychosocial interventions such as psychoeducation (Giron et al., 2010; Pitschel-Walz et al., 2001), Cognitive Behavior Therapy (Gould et al., 2001; Zimmermann et al., 2005), Social Skills Training (Kurtz & Mueser, 2008), Assertive Community Treatment (Nelson et al., 2007) and Cognitive Remediation approaches (McGurk et al., 2007) on various symptom domains, albeit not all studies have found these therapies to be useful (Tandon et al., 2010). The potential benefit of using psychosocial therapies as adjuncts to pharmacotherapy in alleviating

certain symptoms, improving compliance to medication, social functioning and quality of life in individuals with schizophrenia is particularly important in light of evidence that 30% of individuals with the disorder are resistant to the classical antipsychotic drugs used today (Meltzer, 1997).

Outcome – what are the consequences of schizophrenia?

Many studies have examined the outcome or "consequences" of schizophrenia. Still, the data on longitudinal outcome have consistently run into tribulations concerning definitions of sample and measures used to assess outcome, among many other confounds and biases, making comparison between studies complicated (Allardyce & van Os, 2010).

The consequences of Kraepelin's schizophrenia were depicted as encompassing a permanent and pervasive impairment in mental functions – an inexorably deteriorating disorder (Kraepelin, 1919). Subsequently; however, he acknowledged that recovery was possible in dementia praecox (Kraepelin, 1920); a premise that has been reinforced by a growing body of research in which varying degrees of recovery have been observed in patients with schizophrenia. A systematic review of prospective studies analyzing first-episode psychosis published between 1966 and 2003 have outlined a superior outcome for 42% of the population, an intermediate outcome for 35%, and a poor outcome for 27% (Menezes et al., 2006). These authors also established a relationship between a developing country of origin with good outcome and the use of typical antipsychotic medication (versus atypical or a combination of both) and being treatment-naive at study entry with poor outcome. This review corresponds somewhat to other studies that have reported different degrees of partial or full recovery in individuals with the disorder as well as cases in which the illness has resolved completely or ended in a severe defect state (Harrison et al., 2001; Hegarty et al., 1994; Jobe & Harrow, 2005).

Outcome, in the framework of schizophrenia, is a multi-faceted concept encompassing several distinct areas of psychopathology, social functioning, quality of life and societal impact (Tandon et al., 2008). For instance, individuals with schizophrenia show an increased prevalence of comorbid psychiatric and medical illnesses (e.g. substance abuse, cardiovascular disease) (Bermanzohn et al., 2000; Leucht et al., 2007), have a decreased probability of employment and substantial impairments in quality of life (Eack & Newhill, 2007; Folsom et al., 2005) as well as an increased risk of suicide and death (Fenton, 2000; Palmer et al., 2005; Saha et al., 2007; Seeman, 2007). Given the disabling characteristics of schizophrenia, it is understandable that the illness has profound impacts on affected individuals and their loved ones. A revealing example is the observation that families of affected individuals report both a higher subjective and objective burden in concurrence with less support from social networks and professionals (Magliano et al., 2005).

At present, an acute illness onset, better premorbid functioning, improved cognitive abilities, absence of substance abuse, female sex and a later age of onset are associated with a superior outcome in patients with schizophrenia (Breier, et al., 1991; Flyckt et al., 2006; Riecher-Rossler & Rossler, 1998; Shepherd et al., 1989).

Summary

Schizophrenia manifests itself in less than 1% of the population and is broadly defined by a diverse set of positive, negative, disorganization, mood and motor symptom dimensions. Although its etiology remains a mystery, both genetic and environmental elements are at play. To date, multi-modal treatments exist for individuals with schizophrenia that encompasses the use of antipsychotic medications and psychosocial interventions. The benefit in using psychosocial therapies as adjuncts to pharmacological treatment is advantageous since about one third of patients with schizophrenia are resistant to the classical antipsychotics used today. Finally, research

has documented diverse outcomes in patients with schizophrenia varying from superior to intermediate to poor.

II. Sex differences in schizophrenia

Why is it crucial to investigate sex differences in schizophrenia? Most importantly, understanding sex differences in various clinical features of the disorder such as its clinical expression, course of illness and response to treatment will not only provide an opportunity to broaden our understanding of the complex inner workings of this psychiatric disorder but may also provide a unique opportunity to delineate more appropriate treatment regimens based on sex. Considering the vast growth of this field in the past century, this thesis focuses on some of the most prominent areas of sex differences in schizophrenia.

Epidemiology

The incidence of schizophrenia is generally higher in men than women. A systematic review of 158 studies reported a median male:female rate ratio of 1.40 (McGrath et al., 2004). In addition, ratio estimates from various different types of studies (e.g. methodologically rigorous studies, those before 1980, those using DSM-III criteria) lie between 1.27 and 1.54 and significantly exceed 1 highlighting an increased incidence of schizophrenia in men versus women (Abel et al., 2010). In the midst of studies that have found significant sex differences in favor of males, some have found the opposite pattern or no significant sex difference in incidence rates (Al Mousawi & Dunstan, 1998; Hambrecht et al., 1994; Jablenksy, 1992). Of interest, the different criteria used to diagnose schizophrenia over the years has affected the incidence rates among men and women. Lewine and colleagues (1984) found that the stricter the diagnostic criteria used, the more men than women were diagnosed with schizophrenia. For instance, schizophrenia was only diagnosable before the age of 45 according to DSM-III criteria, which lead to a greater exclusion of women and resulting in a higher proportion of men being diagnosed (Castle et al., 1993).

In contrast to the incidence data, studies have more or less consistently reported a lack of sex differences in prevalence rates (McGrath, et al., 2008; Perala, et al., 2007; Saha, et al., 2005). This has been found to be the case for various prevalence measures including combined point, period and lifetime prevalence estimates (Saha et al., 2005). To date it is unclear how to resolve the paradox of a robust sex difference in the incidence but lack of sex difference in prevalence of schizophrenia (Abel et al., 2010).

Age of onset

An earlier age of onset in men compared to women with schizophrenia is perhaps one of the most robust findings of sex differences in schizophrenia (Review by Leung & Chue, 2000; Salem & Kring, 1998). Hafner et al. (Hafner, an der Heiden, et al., 1998; Hafner, Maurer, et al., 1998) reported a peak of onset in men between the ages of 15-25 followed by a stable decline, while women have a broader peak between the ages of 15-30 with a second smaller peak between 45-49 years of age. The consistent finding of an earlier age of onset in men of about 3-5 years has been shown to exist regardless of culture (Hambrecht et al., 1992; Lewine, 1981), definition of onset (Hafner et al., 1989; Hafner et al., 1993) and definition of illness (Hafner et al., 1989; Lewine et al., 1981). Nonetheless, there exist factors that have contributed to the elimination of sex differences in age of onset. Similar to the sex difference in incidence rates, when DSM-III criteria with an age of onset limit of 45 imposed, the sex difference dissipates (Shimizu & Kurachi, 1988). In addition, the sex difference in age of onset appears to apply to sporadic but not familial schizophrenia (Albus et al., 1994; DeLisi et al., 1994; Gorwood et al., 1995). In fact, of the factors associated with elimination of sex differences in age of onset, a positive family history is the most reliable finding (Leung and Chue, 2000).

Premorbid history

A number of reports have documented poorer premorbid functioning in male than female patients on a variety of domains. More specifically, before developing schizophrenia, men are more socially isolated and withdrawn, are less able to maintain friendships and sexual relationships, have lower levels of school and work function (e.g. worse academic performance and higher frequency of job changes) compared to pre-schizophrenic women (Castle, et al., 1993; Childers & Harding, 1990; Crow et al., 1995; Goldstein et al., 1989; Larsen et al., 1996; Salem & Kring, 1998). Moreover, pre-women with schizophrenia are more than twice as likely to be married at the time of first hospitalization compared to pre-schizophrenia men (Hafner et al., 1989). Certain behaviors in childhood that precede the development of schizophrenia may be different in the sexes. For instance, male pre-schizophrenic children are inclined to demonstrate more externalizing behaviors (e.g. disruptive, agitated) while female pre-schizophrenic children show more internalizing behaviors (e.g. passive and avoidant) (Crow, et al., 1995; Done et al., 1994; Watt, 1978). Sex differences in premorbid IQ have also been reported with more pervasive premorbid IQ deficits found in men compared to women, a finding that has correlated significantly with an earlier age of onset in men (Aylward et al., 1984). It is suggested that enhanced premorbid functioning in women is attributed to their later onset allowing them to complete their education, form personal relationships, marry and work before the illness takes over (Leung and Chue, 2000).

Birth and family history

In both male and female patients, obstetric complications have been linked to an earlier age of onset of schizophrenia, a poorer course of illness and ventricular enlargement (Foerster et al., 1991; Heun & Maier, 1993; O'Callaghan et al., 1992; Owen et al., 1988). To date, the evidence of sex differences in obstetric complications is contradictory. Some have documented that mothers of female patients suffer a higher

rate of obstetric complications (Verdoux & Bourgeois, 1993), others have reported the opposite (i.e. greater incidence in mothers of male patients) (Cantor-Graae et al., 1994; O'Callaghan, et al., 1992) or have not found considerable sex differences (Heun & Maier, 1993; Hultman et al., 1997). Several studies found an association between prenatal exposure to influenza in the second trimester and the later development of schizophrenia particularly in females, while others found this relationship to be equal between men and women (Adams et al., 1993; Takei et al., 1994; van Os & Selten, 1998). Methodological issues such as small sample size and variable measures of selecting and weighting obstetric complications, among other variables, are suggested to play a role in these inconsistent findings (McNeil, 1995). Interestingly, individuals born in the winter and early spring months have about a 10% increased risk for developing schizophrenia (Schwartz, 2011). While some have found sex differences favoring both males and females in this season-of-birth effect (Chen et al., 1996; Pulver et al., 1992), this has not always been the case (Bradbury & Miller, 1985).

According to several family studies and family history studies, relatives of women with schizophrenia have a greater risk of developing the disorder as well as a higher chance of developing schizoaffective and schizophreniform illness than the family members of men with schizophrenia (Leung and Chue, 2000). For instance, Sham et al. (1994) found a lifetime risk estimate of schizophrenia to be 20.6% in the first-degree relatives of female probands and 4% in those of male probands. However, some population-based register studies have uncovered equal familial risk in the sexes (Cannon et al., 1998; Kendler & Walsh, 1995).

Clinical expression

In general, men with schizophrenia show evidence of more negative symptoms such as social withdrawal, blunted affect, lack of motivation and poverty of speech (Kay et al., 1986; Ring et al., 1991; Schultz et al., 1997) while women exhibit more affective

symptoms including depression, impulsivity, inappropriate affect, sexually inappropriate behavior and sexual delusions (Andia et al., 1995; Gur et al., 1996; Rector & Seeman, 1992). Other than being characterized by a strong affective component, women with schizophrenia are over-represented among patients with schizoaffectIve disorder and more commonly have a differential diagnosis of bipolar or affective disorder (Bardenstein & McGlashan, 1990). Sex differences in the clinical expression of schizophrenia have been reported as being overall consistent in different countries and cultures (Goldstein, 1997; Hambrecht, et al., 1992; Jablenksy, 1992). Nevertheless, there have been disputes regarding whether males are characterized by more negative symptoms and females by more positive symptoms, although many agree that both sexes experience the same level of positive symptoms (Addington et al., 1996; Kendler & Walsh, 1995; Linstrom & Von Knorring, 1994). Still, specific positive symptoms such as paranoia, persecutory delusions and auditory hallucinations have been found to be higher in women than men with schizophrenia (Goldstein, 1997; Goldstein & Link, 1988; Hambrecht, et al., 1992; Marneros, 1984; Rector & Seeman, 1992; Tien, 1991). Interestingly, age has differentially contributed to the clinical expression of schizophrenia in men and women. For instance, Gur et al. (1996) observed that women continue to show less negative symptoms than men until the eighth decade of life, but have the same degree of positive symptoms across all age groups. In a sample of older patients with schizophrenia, Lindamer et al. (1999) found a greater severity of positive symptoms in men than women in the older age group and reported that women with a late onset exhibited less severe negative symptoms in comparison to men with late onset, and relative to both men and women with early onset. Complementing this finding, others have noted a significant association between older age at onset and fewer negative and cognitive symptoms among women with schizophrenia (Grossman et al., 2008; Morgan et al., 2008).

Course of illness

More often than not, women with schizophrenia have a better prognosis than men on several different areas. However, while this sex difference is prominent in the short- (2-5 years) and middle-term (5-10 years) (Goldstein, 1988; Goldstein, et al., 1989; Salokangas & Stengard, 1990), this difference has been found to dissipate with time (i.e. in the long term; 13-40 years) (Gureje & Bamidele, 1998; Kendler & Walsh, 1995; Nyman, 1989). In a major review of over 100 outcome studies, Angermeyer et al. (1990) found that in approximately half of the studies women showed a better course of hospital treatment, experienced a shorter length of hospital stay, and survived longer in the community after their first hospital admission while the other half of studies did not observe significant sex differences in the course of schizophrenia. Other domains in which women show a more favorable prognosis than men include education, occupational functioning, social functioning (e.g. higher rates of marriage and having children), less substance abuse and less antisocial behavior (Hafner, 2003; Leung & Chue, 2000). It is of interest that the degree of psychopathology is an outcome measure that does not seem to be different between the sexes (Hafner, et al., 1993; Shtasel et al., 1992). In any case, superior social and occupational functioning in women compared to men has been reported despite similar severity in symptom profiles (Andia, et al., 1995; Goldstein et al., 1989). It is suggested that worse outcomes in men may be associated to substance abuse which is more common in men than women with schizophrenia (Abel et al., 2010; Leung and Chue, 2000), particularly since patients with a dual diagnosis are less responsive to antipsychotic medication, less compliant with taking medication and are more frequently hospitalized and homeless (DeQuardo et al., 1994; Dixon, 1999).

Response to treatment

Men and women with schizophrenia differ in their response to treatment at both the pharmacological and psychosocial level. Women with schizophrenia have been found to respond more quickly and show a greater degree of improvement on antipsychotic medications in comparison to men (Angermeyer, et al., 1990; Robinson et al., 1999; Szymanski et al., 1995; Usall et al., 2007). Usall and colleagues (2007) found that women with schizophrenia treated with both typical and atypical agents show significantly greater improvement in overall symptom severity compared with men. Moreover, women seem to require lower doses of first generation antipsychotics (Hogarty, Goldberg, & Schooler, 1974; Hogarty, Goldberg, Schooler, et al., 1974) until the age of 40 or post-menopause when the opposite pattern has been reported (i.e. women necessitate higher antipsychotic doses than men) (Seeman, 1983; 1986). Of interest, because estrogen is argued to play a protective role in women with schizophrenia by shielding them from the worse effects of the illness (Huber et al., 2004; Seeman & Lang, 1990) it is suggested that a decrease in estrogen levels after menopause possibly contributes to the higher doses required in women (Leung and Chue, 2000). Others have not documented sex-specific differences in dosage or response to antipsychotics (Magharious et al., 1998; Pinals et al., 1996). Few studies have examined sex differences in response to atypical antipsychotics and the results have been mixed. Superior cognitive improvement in female compared to male patients taking olanzapine, risperidone and clozapine has been documented (Howard et al., 2001) while some have noted no difference in men and women's response (Perry et al., 1991) or observed that female sex was a predictor of poor treatment response to second generation antipsychotic drugs (Lieberman et al., 1994; Szymanski et al., 1996). Female patients are more prone to certain side effects of clozapine (e.g. agranulocytosis, eosinophilia) than men (Alvir et al., 1993; Banov et al., 1993) and

generally experience adverse motor side effects on antipsychotics more frequently than men, with higher rates of parkinsonism, dystonia and tardive dyskinesia (Leung and Chue, 2000). Sex differences in certain social behaviors have contributed to differences in the way men and women with schizophrenia respond to treatment. One pertinent example is the observation that men with schizophrenia are less likely to comply with antipsychotic medication than women (Tunnicliffe et al., 1992) but not all have observed this sex difference in behavior (Buchanan, 1992).

To date very few studies have investigated sex differences in response to psychosocial treatments in patients with schizophrenia. The findings point towards a pattern in which males appear to benefit to a greater degree from social skills training than women, but superior post treatment functioning in females (e.g. medication compliance) implies that factors other than taught skills are more important determinants of social adjustment in affected women (Schaub et al., 1998; Smith et al., 1997).

Cognition and Emotion

Evidence of sex differences in cognitive function in schizophrenia is mixed with some studies pointing to a superior performance by male patients, others reporting the opposite or no effect of sex on cognitive impairments in individuals with schizophrenia. Seidman and colleagues (1997) documented a worse performance in male compared to female patients on the Wisconsin Card Sorting Task known to assess executive function and working memory and indicative of dorsolateral prefrontal cortex deficits. Using an extensive battery of neuropsychological tests, Goldstein and colleagues (1998) found that men with schizophrenia were significantly impaired across all cognitive domains compared with same-sex control subjects and were impaired on tests of attention, verbal memory, and executive functions relative to women with schizophrenia. On the other hand, compared to healthy women, women with

schizophrenia had decreased performance on tests of attention, executive functions, visual memory, and motor functions suggesting that women with schizophrenia may be less vulnerable to deficits in verbal processing than schizophrenic men. In contrast to this pattern of results, Lewine et al. (1996) reported greater deficits on tasks of verbal and spatial memory as well as visual processing tasks in women compared to men with schizophrenia. In a more recent study women with schizophrenia performed better than men in processing speed and verbal episodic memory whereas men outperformed women in visual working memory (Torniainen et al., 2011). Finally, quite a few of studies have not found differences between men and women in cognitive performance (Albus et al., 1997; Andia, et al., 1995; Goldberg et al., 1995; Lewine et al., 2006; Shipman et al., 2009). However, some of these studies were confounded by differences in symptom expression, age at onset and medication highlighting the importance of taking these factors into careful consideration when evaluating potential sex differences. Noteworthy, significant relationships between impaired cognitive performance and social functioning have been particularly noted in women with schizophrenia, which is suggestive that cognitive deficits have greater adverse effects on social functioning in women than men (Mueser et al., 1995; Penn et al., 1996).

Reports of sex differences in emotion processing in schizophrenia are few and far between in the scientific literature. Those that have analyzed men and women with schizophrenia separately found that women with schizophrenia are more expressive than men (Levin et al., 1985; Tremeau et al., 2005) while others have found no difference between the sexes (Davison et al., 1996). With respect to the experience of emotion, Heerey and Gold (2007) reported that women rate positive and negative images as being more pleasant and unpleasant, respectively, than did men with schizophrenia. In a study aimed at examining how individuals with schizophrenia respond to pleasant and unpleasant odors, men with schizophrenia rated the odors as

less pleasant than women with schizophrenia (Moberg et al., 2003) while a similar study found no difference between men and women in the pleasantness ratings of odors (Hudry et al., 2002). With regards to the recognition of emotions, Scholten et al. (2005) observed a sex difference in the ability to recognize facial emotions, especially negative ones, with women outperforming men. Vaskinn et al. (2007) and Weiss et al. (2007) reported similar findings such that women show a superior performance in recognizing facial emotions than men with the disorder.

Brain structure

The tentative pattern of altered brain structure in patients with schizophrenia is that men are characterized by increased neuroanatomical deficits than their female counterparts. Still, other studies have reported the reverse pattern or no significant effect of sex on structural brain abnormalities in these individuals (Leung & Chue, 2000). Methodological issues including small sample sizes, overrepresentation of men and variability in the size of brain structures of men and women in the healthy population are suggested to be at least partially responsible for the inconsistent results (Andreasen, Ehrhardt, et al., 1990; Goldstein, 1996).

Largely consistent with the direction of normal sexual dimorphism (Goldstein et al., 2001; Murphy et al., 1996; Paus et al., 1996), both structural neuroimaging and postmortem studies have reported that men with schizophrenia have enlarged ventricular-brain ratios and anterior temporal horn, smaller medial temporal lobe volumes (e.g. amygdala, hippcomapus, superior temporal gyrus) and overall smaller frontal and temporal lobe volumes compared to women with schizophrenia (For a review refer to Leung and Chue, 2000; Abel et al., 2010). Moreover, more left-lateralized abnormalities have been reported in men (Goldstein et al., 2002; Gur, R. E. et al., 2000). It is noteworthy that some have uncovered region-specific structural abnormalities in women depending on the region examined. For instance, Goldstein

and colleagues (2002) reported a significant reduction in anterior cingulate volume in women with schizophrenia relative to healthy women while there was no difference between men with and without the diagnosis. Another study found that men with schizophrenia have a higher orbitofrontal to amygdala ratio than healthy men while women with schizophrenia have a lower ratio than healthy women (Gur et al., 2004). These findings are particularly interesting in the light of reports that in the general population it is women who have greater grey matter volume of anterior cingulate than men (Paus et al, 1996) and a higher orbitofrtonal cortex to amygdala ratio than men (Gur et al., 2002), ultimately implying a disturbance of normal sexual dimorphism of brain structure in individuals with schizophrenia.

Brain function

Although there is extensive evidence of sex differences in cerebral function associated with various emotional and cognitive tasks in the general population (e.g. Domes et al., 2010; Koch et al., 2007; Wager et al., 2003), evidence of sex differences in brain activations in individuals with schizophrenia is still quite scarce. This is not surprising considering the majority of studies investigating cerebral activations associated with emotional processing and cognitive function in schizophrenia consist almost exclusively of men, and even when women are included in the sample the number of tested individuals is typically too small to allow for between-sex comparisons.

Previous work carried out by our group has uncovered distinct patterns of brain activations in men and women with schizophrenia during both cognitive (Guillem et al., 2009; Jiménez et al., 2010) and emotional processing (Mendrek et al., 2007; 2009; 2010). The overall findings point towards an alteration of the normal sexual dimorphism in cerebral activations in individuals with schizophrenia. For instance, Guillem et al. (2009) explored the differential effects of being male or female on the neural correlates of episodic memory in schizophrenia using event-related brain potentials (ERPs). They

uncovered that the direction of sex differences depended on the cognitive processes being examined. For instance, early frontal processes (related to interference inhibition) revealed an interaction between sex and diagnostic group suggesting a reversal of normal sexual dimorphism in their schizophrenia sample, while analysis of late posterior processes (suggested to reflect a mnemonic binding process) resulted in sex differences in the same direction in both patients with schizophrenia and healthy controls. Mendrek and colleagues (2007) implemented an fMRI task exploring the emotional experience of patients with schizophrenia and found that while viewing aversive pictures, men with schizophrenia exhibited more widespread and more intense activations compared to women with schizophrenia in similar brain regions where women would normally exhibit greater activations relative to men in the healthy population (e.g.cingulate gyrus, temporal cortex, cerebellum). Subsequent investigations revealed that the symptom profiles in men and women correlated differently with brain activations during processing of emotional information (Mendrek et al., 2010). Another recent study examined the recognition of emotional faces using ERPs and uncovered a lower P100 amplitude in the right hemisphere for fearful faces in men with schizophrenia compared to women which implies that sex can be an important controlling factor in early visual processing in patients with schizophrenia (Lee et al., 2010).

Summary

Sex differences in patients with schizophrenia exist in an array of domains including its epidemiology and clinical expression. Overall, men present with an earlier age of onset compared to women, women have more positive symptoms while men experience more negative symptoms, women with schizophrenia have a better prognosis, respond more quickly and show a greater degree of improvement with antipsychotic treatment relative to their male counterparts. However, the literature has

illustrated inconsistencies in these findings; sex differences in cognitive function in schizophrenia have demonstrated particularly mixed results. To date, less research has focused on uncovering sex differences in response to psychosocial treatments, the processing of emotions and brain function in men and women with schizophrenia.

III. Emotional memory in schizophrenia

It is well established in the scientific literature that individuals with schizophrenia have prominent deficits in cognition and the processing of emotional material (Heinrichs & Zakzanis, 1998; Kohler et al., 2000; Kohler & Martin, 2006; Rund & Borg, 1999). Investigating the effect of emotion on subsequent memory in individuals with schizophrenia provides a unique opportunity to examine the interaction between these two processes. This is particularly true in light of evidence that in the general population emotionally charged events often attain a privileged status in memory relative to neutral ones (Hamann, 2001; LaBar & Cabeza, 2006). What's more, emotional memory paradigms appear more ecologically valid than encoding and/or retrieval of non-emotional material, because in everyday life much of the information and events we come across holds emotional significance. In fact, it is relatively well accepted that emotion benefits cognition by prioritizing biologically relevant information (Damasio, 1994). Nonetheless, investigating emotional episodic memory in individuals with schizophrenia is still limited.

Behavioral findings

Behavioral evidence has outlined deficits in patients with schizophrenia compared to healthy controls on various dimensions associated with the processing of emotional memories. For instance, there is substantial evidence that patients with schizophrenia have impairments in independently initiating effective strategies during the encoding of stimuli into memory (Brebion et al., 1997; Iddon et al., 1998). Interestingly, when prompted to use encoding strategies, individuals with schizophrenia have shown significant improvement in mnemonic performance (e.g. Bonner-Jackson et al., 2005; Boyer et al., 2007; Koh & Peterson, 1978; Paul et al., 2005). However, some researchers who have directly compared incidental vs. intentional encoding have not found differences in memory performance in relation to diagnosis (Koh et al., 1976). In

general, the data has pointed towards a modest effect of intentional in comparison to incidental encoding on emotional memory performance in patients with schizophrenia (Herbener, 2008).

Memory performance has also depended on the type of response used in the experimental paradigm. Tasks using recognition memory are suggested to selectively target memory processes while retrieval tasks entail a combination of both memory and executive abilities (Pelletier et al., 2005). A review by Heinrichs and Zakzanis (1998) reported that recall is typically more impaired in schizophrenia than recognition. Moreover, patients with schizophrenia demonstrate greater deficits in the recognition memory of visual (e.g. pictures) vs. verbal (e.g. words) stimuli (Pelletier et al., 2005). Consistent with this, a review of emotional memory studies in schizophrenia found that in all studies using pictorial stimuli, individuals with schizophrenia had an impaired memory in comparison to healthy control subjects (Herbener, 2008).

Arousal and valence characteristics of emotional stimuli are factors that have also differentially influenced emotional memory in patients with schizophrenia and healthy subjects, though the results have been inconsistent. Some studies have found impairments in schizophrenia patient's emotional memory compared to healthy subjects (Danion et al., 2003; Hall et al., 2007; Herbener et al., 2007; Neumann et al., 2007); while others have found comparable performances between the two groups (Horan et al., 2006; Koh, et al., 1976). Looking specifically at the effect emotional valence has on memory performance in patients with schizophrenia, some studies have demonstrated an enhancement of memory for emotional (both positive and negative) in contrast to neutral stimuli in patients with schizophrenia (Calev & Edelist, 1993; Hall, et al., 2007; Mathews & Barch, 2004), others have reported the opposite (i.e. neutral better remembered than emotional stimuli) (Koh et al., 1976; Mathews and Barch, 2004) or no effect of emotional stimuli on memory (Koh et al., 1981; Neumann, et al., 2007).

Furthermore, reports have documented increased memory for negative vs. positive stimuli in patients (Calev & Edilst, 1993; Herbener et al., 2007; Mathews & Barch, 2004) while few have reported the reverse pattern (Koh, et al., 1976). Although the literature has presented conflicting results it has nonetheless outlined a tentative pattern in which individuals with schizophrenia more frequently show a lack of enhancement of emotional in contrast to neutral stimuli and also have a better memory for negative than positive stimuli (Herbener, 2008).

The majority of the published studies have focused on the effect of emotional valence of presented stimuli (i.e. stimuli that vary from positive to negative), while the effect of arousal (i.e. stimuli that vary from calm to exciting) on memory performance has rarely been examined despite indications that it contributes significantly to memory in healthy individuals. Specifically, it has been found that highly arousing stimuli are better recalled than low arousing stimuli (Bradley et al., 1992; Eysenck, 1976). Studies that have examined the effect of arousal on memory in patients with schizophrenia have outlined a better memory performance for stimuli of high emotional intensity relative to low intensity (Herbener et al., 2007; Horan et al., 2006; Mathews and Barch, 2004), but others have reported a detrimental effect of arousal on subsequent memory (Hall et al., 2007).

Despite research on emotional memory still being limited in schizophrenia, a few studies have noted a relationship between negative symptoms and impairments in emotional memory. Hall et al. (2007) uncovered a significant correlation between negative symptoms of the PANSS and recognition memory of both negative and neutral scenes such that the more negative symptoms the patients had the worse their recognition performance. Another study investigated individual PANSS symptoms and reported that patients with greater blunted affect showed a greater impairment in the recall of high arousal negative and positive words. The authors also documented similar

relationships between blunted affect and recognition memory of all emotional conditions (i.e. high and low arousal). Horan and colleagues (2006) evaluated whether self-reported trait anhedonia in schizophrenia reflects impaired memory for pleasant experiences but the authors did not find a significant association between these two measures despite schizophrenia patient's elevated trait anhedonia.

The variability in the emotional memory literature can easily be attributed to the differences in the stimuli used among studies (pictures vs. words), the type of retrieval method (recognition vs. recall), response type (old/new vs. remember/know), time of testing (delayed vs. immediate recall), as well as the clinical heterogeneity present in patients with schizophrenia. Accordingly, it is challenging to draw definite conclusions on the influence of emotion on memory in patients with schizophrenia.

Neuroimaging findings

To date, very few studies have examined the neural correlates of emotional memory in individuals with schizophrenia. Using fMRI, Whalley and colleagues (2009) reported robust medial temporal lobe activations in individuals with schizophrenia, individuals with bipolar disorder and healthy controls during viewing of positive scenes that correlated significantly with recognition memory of positive images. The direct group comparison revealed decreased activity in the bilateral amygdala in patients with schizophrenia relative to healthy participants in the cerebral activations associated with positive images versus baseline. This was found despite comparable recognition accuracies between the two groups. Another fMRI study using emotional faces found that patients with schizophrenia and healthy controls showed similar patterns of brain function associated with response bias for sad faces (e.g. parahippocampal gyrus) while response bias for happy faces revealed increased brain activations in healthy subjects compared to patients (e.g. superior frontal gyrus, amygdala and hippocampus) (Sergerie et al., 2010). Finally, Becerril and Barch (2011) explored how the emotional

valence of stimuli impacts the cerebral activations associated with an *n*-back working memory task and uncovered altered dorsolateral prefrontal cortex and hippocampus activity in individuals with schizophrenia while performing the emotionally loaded working memory task.

Summary

Deficits in patients with schizophrenia relative to healthy controls have been observed on various dimensions associated with the processing of emotional memories. Specifically, patients wit schizophrenia show impairments in initiating effective encoding strategies, they show greater deficits in recall than recognition, and have demonstrated differential deficits depending on whether the valence of the emotional stimuli was positive, negative or neutral. The effect of arousal intensity and the potential association of clinical symptoms on memory performance have been seldom examined. Functional neuroimaging studies investigating the neural correlates of emotional episodic memory in schizophrenia is slowly growing, while investigation of sex differences in this domain remains scarce.

IV. Hypotheses

At present, there are no functional neuroimaging studies that have: (1) investigated the effect stimuli of different arousal intensities (i.e. calm vs. exciting) and valence (positive vs. negative) has on the pattern of brain function during emotional memory in schizophrenia patients compared to healthy controls and (2) have explored whether being male or female differentially contributes to the pattern of cerebral activations associated with the recognition memory of emotional images in patients with schizophrenia.

Accordingly, the first goal of this thesis was to uncover the brain function associated with recognition memory of emotional stimuli that varied in both valence and arousal in patients with schizophrenia compared to healthy controls. In line with some behavioral studies of emotional memory (Danion et al., 2003; Mathews and Barch, 2004; Neumann et al., 2007) and majority of neuroimaging studies of emotion processing in schizophrenia (Gur et al., 2002; Schneider et al., 1998; Takahashi et al., 2004), we expected to observe a decreased recognition accuracy of emotional stimuli in patients with schizophrenia relative to healthy subjects and decreased cerebral activations in all experimental conditions (positive, negative, high and low arousal) in the medial temporal cortex as well as prefrontal regions previously implicated in emotion processing and memory (medial, middle frontal and orbitofrontal cortex) (Dolcos et al., 2004a, 2004b; LeDoux, 1993). In terms of the influence arousal has on memory for emotional stimuli, we expected to observe increased brain activations in the high relative to low arousal contrasts of the presented positive and negative stimuli in healthy controls. In comparison, in patients with schizophrenia we expected an increase in activity only in the high arousal conditions based on evidence that patients, compared to healthy controls, are more likely to misidentify low arousal emotional stimuli as neutral (Kohler, et al., 2000), but recognize high intensity emotions without

difficulty (Hooker & Park, 2002). With regards to valence the literature has reported mixed results and consequently no predictions were made with regards to the effect of positive vs. negative emotion on subsequent memory in patients or controls.

The second aim of this thesis was to explore sex-specific differences in the cerebral activations associated with emotional episodic memory in individuals with schizophrenia and healthy subjects. Our hypotheses were based on existing literature (Canli et al., 2002; Seidlitz & Diener, 1998) as well as previous results obtained by our group (Mendrek et al., 2010 ; Mendrek et al., 2007; Mendrek, 2009). Behaviorally, the cognitive-style hypothesis posits that men and women may differ in the way they encode, rehearse and think about emotional experiences that will ultimately lead to differences in performance (with women outperforming men; Seidlitz and Diener, 1998) and to qualitative differences in the pattern of cerebral activations during processing of emotional memories (Canli, et al., 2002; Piefke & Fink, 2005; Piefke et al., 2005). Accordingly, we predicted that patients with schizophrenia would be characterized by a decreased recognition accuracy compared to healthy subjects, but that women in both groups would have a superior recognition memory for emotional stimuli relative to men. With regards to cerebral functioning, we postulated that men and women in both groups would activate qualitatively distinct pattern of cerebral activations in regions previously implicated in emotion and episodic memory processes (e.g. regions of limbic and paralimbic cortex, parietal and prefrontal cortex) (Dolcos, et al., 2004a, 2004b; Hamann, 2001; LaBar & Cabeza, 2006; Phan et al., 2004). In addition, based on existing findings (Mendrek, et al., 2010 ; Phillips et al., 2003; Phillips et al., 1999; Stip et al., 2005), we predicted significant correlations between negative symptoms and activations in cortical structures (e.g. prefrontal, cingulate cortex), and between positive symptoms and activations in subcortical limbic structures (e.g. amygdala, hippocampus). Moreover, because it has been documented that men with schizophrenia are typically more

affected by negative symptoms and women by positive symptoms (Leung and Chue, 2000), we hypothesized that deficient brain activations during emotional memory in men would be mediated primarily by negative symptomatology, while positive symptoms would play a greater role in a distorted cerebral function in women.

Article 1

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Neural correlates of emotional recognition memory in schizophrenia: effects of valence and arousal

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Abstract:

Schizophrenia patients are often impaired in their memory for emotional events compared to healthy subjects. Investigating the neural correlates of emotional memory in schizophrenia patients is scarce in the literature. The present study aimed to compare cerebral activations in schizophrenia patients and healthy controls during memory retrieval of emotional images that varied in both valence and arousal. Using fMRI, 37 schizophrenia patients were compared to 37 healthy participants while performing a yes/no recognition paradigm with positive, negative (differing in arousal intensity) and neutral images. Schizophrenia patients performed worse than healthy controls in all experimental conditions. They showed less cerebral activations in limbic and prefrontal regions than controls during retrieval of negatively valenced stimuli, but had a similar pattern of brain activations to controls during retrieval of positively valenced stimuli (particularly in the high arousal condition) in the cerebellum, temporal and prefrontal cortex. Both groups demonstrated increased brain activations in the high relative to low arousing conditions. Our results suggest atypical brain function during retrieval of negative pictures, but intact functional circuitry of positive affect during episodic memory retrieval in schizophrenia patients. The arousal data revealed that schizophrenia patients closely resemble the control group at both the behavioral and neurofunctional level.

Key words: fMRI, emotional memory, schizophrenia, valence, arousal

1. Introduction

Deficits in cognition and emotional processing have become a hallmark of schizophrenia (Heinrichs and Zakzanis, 1998; Rund and Borg, 1999; Kohler et al., 2000; Kohler and Martin, 2006). Investigating the effect of emotion on subsequent memory in individuals with schizophrenia provides a unique opportunity to examine the potential interaction between the two processes, particularly in light of evidence that in the general population emotionally charged stimuli are often better retained in memory than neutral stimuli (Hamann, 2001; LaBar and Cabeza, 2006). Furthermore, emotional memory paradigms appear more ecologically valid than encoding and/or retrieval of non-emotional material, because in everyday life much of the information and events we come across holds emotional significance.

Investigating emotional memory in individuals with schizophrenia is still limited and shows mixed results. While some studies have found impairment in schizophrenia patient's emotional memory compared to healthy subjects (Danion et al., 2003; Hall et al., 2007; Herbener et al., 2007; Neumann et al., 2007) others have found comparable performances between the two groups (Koh et al., 1976; Horan et al., 2006). With regards to the effect emotional valence has on memory performance in patients, some studies have demonstrated an enhancement of memory for emotional (both positive and negative) in contrast to neutral stimuli in schizophrenia patients (Hall et al., 2007; Mathews and Barch, 2004) others have reported the opposite (i.e. neutral better remembered than emotional stimuli) (Koh et al., 1976) or no effect of emotional stimuli on memory (Koh et al., 1981; Neumann et al., 2007). The majority of the published studies have focused on the effect of emotional valence of presented stimuli (i.e. stimuli that vary from positive to negative), while the effect of arousal (i.e. stimuli that vary from calm to exciting) on memory performance has rarely been examined despite indications that it contributes significantly to memory in healthy individuals. Specifically, it has been

found that highly arousing stimuli are better recalled than low arousing stimuli (Eysenck, 1976; Bradley et al., 1992). Studies investigating the effect of arousal on memory in patients with schizophrenia have outlined a better memory performance for stimuli of high emotional intensity relative to low intensity (Mathews and Barch, 2004; Horan et al., 2006; Herbener et al., 2007), but others have reported a detrimental effect of arousal on subsequent memory (Hall et al., 2007).

Functional neuroimaging studies of emotional memory in healthy volunteers have reported activity in limbic regions including the amygdala, insula and cingulate cortex, as well as a range of areas in the temporal and prefrontal cortex, during recognition of items that were encoded in emotional relative to neutral contexts (e.g. Maratos et al., 2001; Smith et al., 2004). In patients with schizophrenia, studies of episodic memory (of neutral events) have demarcated a consistent and robust pattern of decreased cerebral activations in the prefrontal cortex, cerebellum and temporal lobe regions (for a meta-analysis see Achim and Lepage, 2005b). Increased cerebral activations have also been observed including hyperactivity of the hippocampus during both successful and unsuccessful mnemonic encoding (Zierhut et al., 2010) as well as a relative increase in activity in the cerebellum, visual and parietal cortex (Crespo-Facorro et al., 2001) during recognition memory in patients compared to healthy participants. Evidence of the neural correlates of emotional episodic memory in schizophrenia is limited in the literature. Whalley et al. (2009) reported robust medial temporal lobe activations in patients with bipolar disorder, patients with schizophrenia and healthy controls during memory encoding that correlated significantly with subsequent recognition memory performance. Nonetheless, there was no direct comparison between the schizophrenia and control group. Another fMRI study implemented an emotional memory paradigm with faces and reported emotion-specific differences in cerebral activations (e.g. hippocampus, parahippocampal and superior frontal gyrus)

associated with memory response bias in patients with schizophrenia and healthy subjects (Sergerie et al., 2010).

The aim of the present study was to investigate the neural correlates associated with memory retrieval of stimuli that varied in both valence and arousal, in schizophrenia patients compared to healthy controls.

In line with some behavioral studies of emotional memory (Danion et al., 2003; Mathews and Barch, 2004; Neumann et al., 2007) and majority of neuroimaging studies of emotion processing in schizophrenia outlining less sensitivity to emotional stimuli in patients relative to controls (Schneider et al., 1998; Gur et al., 2002; Takahashi et al., 2004), we expected to observe a decreased recognition accuracy of emotional stimuli in schizophrenia patients relative to healthy subjects and decreased cerebral activations in all experimental conditions (positive, negative, high and low arousal) in medial temporal cortex, as well as prefrontal regions previously implicated in emotion processing and memory (medial, middle frontal and orbitofrontal cortex) (LeDoux, 1993; Dolcos et al., 2004a; Dolcos et al., 2004b). In terms of the influence arousal has on memory for emotional stimuli, it has been found that relative to healthy controls, patients are more likely to misidentify low arousal emotional stimuli as neutral (Kohler et al., 2000), but recognize high intensity emotions without difficulty (Hooker and Park, 2002). Thus, we expected to observe increased brain activations in the high relative to low arousal contrasts of the presented positive and negative stimuli in healthy controls. In comparison, in schizophrenia patients we did not expect to observe differences in brain activations elicited by memory of neutral and low arousing stimuli but did expect increased activity only in the high arousal conditions. Previous studies investigating the neural correlates of emotional arousal have observed activations in the anterior temporal pole, visual cortex, prefrontal cortex and regions of the medial temporal lobe in high relative to low arousing conditions (Lane et al., 1999; Bradley et al., 2003) (all

regions that have previously been implicated in functional neuroimaging studies of emotional memory as well). In this regard, we postulated that a similar pattern of regions would be activated in the high relative to low arousal contrasts in our emotional memory paradigm in both groups. With regards to valence the literature has reported mixed results, with some studies revealing different neural deficits underlying processing of positive and negative affect (Schneider et al., 1998; Gur et al., 2007; Reske et al., 2009), and others showing comparable brain activations during exposure to positive and negative stimuli in schizophrenia (Dowd and Barch, 2010). Behavioral studies of emotional memory have also yielded inconsistent results (Herbener, 2008). Consequently, no predictions were made with regards to the effect of positive vs. negative emotion on subsequent memory in patients or controls.

2. Methods

2.1. Subjects

Thirty-seven schizophrenia patients (19 men, 18 women) meeting the DSM-IV criteria for schizophrenia (APA, 1994), in a stable phase of their illness (defined as no relapse within the last two months and no change in their antipsychotic treatment within the last month) and 37 healthy controls (19 men, 18 women) participated in the study. The groups were matched for age, sex, handedness (Edinburgh Inventory) (Oldfield, 1971) and parental socio-economic status (National Occupational Classification; NOC) (Census, 2001) (Table 1).

All patients were re-evaluated by experienced psychiatrists before being assigned to the research group (DSM-IV, criteria A-E); affective, schizoaffective and schizophreniform psychoses were excluded. Control participants were screened with the non-patients edition of the Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1992).

Symptom severity was rated according to the positive and negative syndrome scale (PANSS) (Kay et al., 1987). Illness onset was defined as the date of the first psychiatric consultation. All the patients received at least one atypical antipsychotic (27 patients received one, 9 received two, 1 received three. Clozapine: n=19, mean dosage= 452.63 mgs ± 77.23 mgs; olanzapine: n= 12, mean dosage= 14.58 mgs ± 5.4 mgs; risperidone: n=11, mean dosage= 3.73 ± 1.67 mgs; quetiapine: n=7, mean dosage= 585.71 mgs ± 238.85 mgs).

General exclusion criteria included age below 18 or above 45 years, past or present neurological or Axis-I psychiatric disorder, alcoholism or drug abuse, non compliance with testing procedures, abnormal uncorrected vision or any contra-indication for MRI such as a cardiac pacemaker, an aneurysm clip, a metal prostheses or cardiac valve replacement, the presence of metal in an eye or any part of the body, certain dental work or claustrophobia.

In agreement with the Declaration of Helsinki, written informed consent was obtained prior to participation in the experiment. The ability of schizophrenia patients to give informed consent was established using the guidelines of the Canadian Psychiatric Association. The study was approved by the ethics committees of the Fernand-Seguin Research Center of the Louis-H Lafontaine Hospital and the Regroupement Neuroimagerie Québec.

2.2. Experimental procedure

Prior to the memory task, participants passively viewed blocks of emotionally positive, negative, and neutral pictures while in the functional magnetic resonance imaging (fMRI) scanner. The stimuli were selected from the International Affective Picture System (IAPS) (Lang et al., 1988) based on normative valence and arousal ratings and were matched for content (e.g. people, animals, landscapes). The images differed in valence and arousal intensity resulting in 5 experimental conditions: High

arousal/positive content (HA+), High arousal/negative content (HA-), Low arousal/positive content (LA+), Low arousal/negative content (LA-) and neutral (NTR). Each image category was presented in separate blocks (i.e. one block contained only HA+ images, one contained only LA+ images, one contained only HA- images, etc.). It should be noted that although subjects were aware that a memory task would follow the emotion-processing run they were not explicitly told to try and remember the images. Instead, to ensure that participants were attentive to the presented images during encoding they were asked to indicate with the press of a button whether they saw a person or part of a person in the picture. In addition to allowing us to investigate cerebral responses to various affective stimuli, this task also served as an incidental learning procedure. This emotion processing task was then followed by an unrelated cognitive task with a duration of 15 minutes as a means of separating both incidental encoding and subsequent recognition memory.

The memory portion consisted of viewing 48.5-second blocks of emotionally positive, negative, and neutral pictures similarly to the incidental encoding task. During this task, however, 50% of the stimuli in each block originated from the emotion-processing task (previously viewed), while the other 50% were new (never before viewed). There were 16-second periods of rest separating the blocks from one another. Each block contained 10 images and each block was repeated 2 times (except NTR block which was repeated 4 times). Each picture appeared for 3000 ms followed by a blank screen with a fixation point for an average of 1.75 s (ranging from 1 to 2.5 s and giving an average inter-stimulus interval (ISI) of 4.75 s). During this memory task, participants' were to determine, by pressing the correct button, which of the stimuli were old and which were new. To assess the participants subjective emotional responses to the presented images, immediately at the end of the fMRI session, participants were re-presented with the images of each block and were asked to rate the block of images as

whole on a scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime) the intensity of experienced emotion for each block of stimuli.

2.3. fMRI data acquisition

Blood oxygenated dependent level (BOLD) signals were recorded using a single-shot, gradient-recalled echo-planar imaging sequence [repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle = 90 degrees, matrix 64 x 64 voxels] on a MRI Siemens TRIO system at 3.0 Tesla, which is operational at the Functional Neuroimaging Unit at the University of Montreal Geriatric Institute. The functional volumes were then registered to individual high-resolution co-planar anatomical images taken during the same scanning session (three-dimensional, spoiled gradient echo sequence; 28 slices, slice thickness = 5 mm, TR = 22 ms, TE = 4 ms, flip angle = 30°; matrix 256 x 256 voxels) to better identify activated structures.

2.4. fMRI data analysis

The *f*MRI data was analyzed using statistical parametric mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK) according to methods outlined by Friston and colleagues (Friston, 1995). Functional images were realigned to the mean volume of each session to correct for artifacts due to subject motion, were spatially normalized into the standardized brain template (voxel size: 3.5mm x 3.5mm x 3.5mm) and were spatially smoothed with a three-dimensional isotropic Gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio.

Statistical analyses were carried out using a standard peak-detection approach and the general linear model implemented in SPM5 to identify the dynamic cerebral changes associated with emotional episodic memory. First, fMRI data of each participant was analyzed using a fixed-effects model to investigate individual brain activation maps and to contrast the brain activity associated with different conditions.

The fixed-effects analysis produced individual contrast images that were then used as raw data for the implementation of a random-effects model to investigate the pattern of activations during the different emotional contrasts (HA-, LA-, HA+, LA+) in each group (i.e. healthy controls and schizophrenia patients). One-sample t-tests were conducted for each group to subtract brain activity associated with neutral from that associated with emotional stimuli (emotional minus neutral). Previous studies have documented increased autonomic responses as well as increased cerebral activations in schizophrenia patients relative to controls during the processing of neutral stimuli (Williams et al., 2004; Holt et al., 2006). To ensure that an increased response to neutral stimuli would not act to decrease the difference between responses to emotional and neutral images in schizophrenia patients relative to healthy controls we investigated the cerebral activations in the neutral relative to fixation conditions for both patients and controls. Considering the lack of studies investigating the neural correlates of emotional memory in schizophrenia, we performed an exploratory analysis for the entire brain volume. The threshold level for statistical significance was set at a p=0.001 corrected for multiple comparisons using the small volume correction (SVC) with the sphere volume function in SPM5 (radius = 16 mm). We also examined any potential differences between groups using a two-sample t-test with the threshold level for statistical significance at a p=0.005 uncorrected for multiple comparison. Only extent thresholds of 5 contiguous voxels were considered. Effects at each voxel of the brain was estimated using the general linear model and voxel values for the contrasts of interest generated statistical parametric maps of the t statistic (SPM *t*) that were subsequently transformed to the unit normal distribution (SPM *Z*).

2.5. Behavioral data analyses

Recognition accuracy was measured by taking into account both the hit rate and false alarm rate. The hit rate is defined as the number of old slides correctly identified

as having been seen before divided by the total number of old slides and false alarm rate is characterized by the number of distractor slides incorrectly identified as seen before divided by the total number of distractor slides (Hall et al., 2007). The recognition accuracy was calculated as the difference between the hit and false alarm rate with a maximum value of +1 (perfect recognition of stimuli presented during incidental encoding) and a minimum value of -1 (falsely reporting that they had previously seen every new picture).

To examine ratings of emotional stimuli and recognition accuracy we conducted a repeated measures ANOVA with image type (i.e. HA-, LA-, HA+, LA+ and NTR) as a within subject factor and diagnostic group (controls and schizophrenia patients) as a between subject factor. Where group or stimulus effects were detected the source of these effects was further investigated using post hoc t-tests. To account for an inflation of the type I error rate attributable to multiple post hoc testing, the threshold for significance was Bonferroni adjusted.

The demographic, clinical and behavioral data were analyzed with the Statistical Package for the Social Sciences (SPSS), version 15.0.

3. Results

3.1. Behavioral data

3.1.1. Stimulus ratings

The analysis revealed a significant main effect of image type ($F(4)=272.73$, $P<0.001$) but no significant effect of group or image type by group interaction. Post-hoc t-tests revealed that both healthy controls (HC) and schizophrenia patients (SCZ) rated the NTR images as less emotionally salient than HA- (HC: $t(36)=27.28$, $P<0.001$; SCZ: $t(36)=18.24$, $P<0.001$, two-tailed P), HA+ (HC: $t(36)=17.35$, $P<0.001$; SCZ: $t(36)=16.69$, $P<0.001$), LA- (HC: $F(36)=13.45$, $P<0.001$; SCZ: $t(36)=9.01$, $P<0.001$) and LA+ (HC: $t(36)=10.55$, $P<0.001$; SCZ: $t(36)=9.94$, $P<0.001$) images. In addition, both groups

rated HA- images as more emotional than LA- images (HC: t(36)=15.05, P<0.001; SCZ: t(36)=10.31, P<0.001). This same effect was seen for the HA+ relative to the LA+ pictures (HC: t(36)=3.96, P<0.001; SCZ: t(36)=6.27, P<0.001) (see Fig 1). Analysis of the 'person present' task inducted to ensure that participants were paying attention to the emotional stimuli during encoding revealed comparable levels of attention between patients and healthy controls (F(1)=0.056, P>0.81).

3.1.2. Recognition accuracy

The analyses revealed a significant main effect of diagnosis (F(1)=38.62, P<0.001) (with better recognition accuracy in healthy controls than in schizophrenia patients) and a significant main effect of recognition accuracy for emotional stimuli (F(4)=3.76, P<0.008). A trend was revealed in the group by accuracy interaction (F(4)=2.39, P>0.059). Post-hoc t-tests confirmed that SCZ patients performed worse than HC in all experimental conditions (P<0.001, two-tailed P). Also, HC remembered HA+ images to a greater degree than NTR (t(36)=4.02, P<0.001) whereas no difference was observed between NTR and HA-, LA- and LA+ images. HC also remembered HA+ pictures to a greater degree than HA- pictures (t(36)=-3.97, P<0.001). SCZ patients had a better recognition memory of LA- images relative to NTR images (t(36)=3.43, P<0.001) while no significant differences was observed in recognition accuracy between NTR and the other emotional images. No other comparisons reached statistical significance (see Fig 2).

3.2. fMRI results of individual groups

3.2.1. HA negative minus neutral contrast

Healthy controls activated the middle and inferior temporal cortex, middle occipital cortex, medial orbitofrontal cortex, superior medial frontal cortex, cerebellum, middle cingulated gyrus and the superior motor area. In contrast, schizophrenia patients had activity circumscribed to the middle temporal cortex (see Table 2 and Fig. 3).

3.2.2. LA negative minus neutral contrast

Healthy controls demonstrated activity in the middle temporal cortex, precuneus, middle frontal gyrus and precentral gyrus. Schizophrenia patients did not activate any significant voxels during retrieval of LA- relative to neutral images.

3.2.3. HA positive minus neutral contrast

Healthy controls activated the middle temporal cortex, inferior occipital cortex, regions of the prefrontal cortex, precuneus, anterior temporal pole, caudate, thalamus and cerebellum. Schizophrenia patients demonstrated cerebral activity in the inferior occipital cortex, prefrontal cortex, cerebellum, supramarginal gyrus, anterior temporal pole, and middle temporal gyrus (see Table 3 and Fig. 4).

3.2.4 LA positive minus neutral contrast

Healthy control participants activated the middle and inferior occipital cortex, calcarine gyrus, middle and inferior frontal cortex, superior parietal cortex, postcentral gyrus and superior motor area. Schizophrenia patients had brain activity restricted to the visual cortex.

3.2.5. HA negative minus LA negative contrast

Healthy subjects activated the fusiform and calcarine gyrus, superior frontal cortex and the cuneus during recognition of high relative to low arousal negative images. Regions activated in schizophrenia patients included fusiform and calcarine gyrus, middle and inferior occipital cortex, cerebellum and regions of the prefrontal cortex (see Table 4).

3.2.6. HA positive minus LA positive contrast

Healthy controls activated the superior parietal cortex, precuneus, and cerebellum while patients demonstrated brain activations in the angular gyrus, precuneus, inferior temporal cortex, cerebellum, anterior cingulated gyrus and regions of the prefrontal cortex.

3.3. fMRI results between groups

3.3.1. HA negative minus neutral contrast

Healthy participants activated the precuneus and middle frontal gyrus to a greater degree than patients with schizophrenia (see Table 5 and Fig. 5).

3.3.2. LA negative minus neutral contrast

Healthy participants had increased activations in the middle frontal gyrus, inferior orbitofrontal cortex and middle cingulated gyrus compared to schizophrenia patients.

3.3.3. HA positive minus neutral contrast

Healthy controls activated the middle frontal gyrus to a greater degree than the schizophrenia group while patients with schizophrenia had increased activations in the cerebellum, postcentral gyrus and inferior occipital cortex relative to healthy controls.

3.3.4. LA positive minus neutral contrast

Healthy controls activated the middle frontal gyrus and middle cingulated gyrus to a greater degree than schizophrenia patients.

3.3.5. NTRS minus baseline contrast

Patients with schizophrenia activated the precuneus, middle cingulated gyrus, anterior cingulated gyrus, inferior parietal gyrus, cerebellum, middle temporal and the middle frontal gyrus to a greater degree than the healthy comparison group during recognition of neutral images (Table 5).

4. Discussion

The main goal of the present study was to investigate the neural correlates of emotional episodic memory in schizophrenia patients relative to healthy control participants. Overall, patients activated fewer regions than controls during retrieval of negatively valenced stimuli, but had a similar pattern of brain activations to controls during retrieval of positively valenced stimuli, particularly in the high arousal condition. Also, both groups demonstrated increased brain activations in the high relative to low arousing conditions. These results are intriguing considering the overall inferior

performance in schizophrenia patients but comparable ratings of emotional stimuli relative to healthy controls.

4.1. Behavioral data

Patients with schizophrenia rated the emotional stimuli similarly to controls. The finding of explicit emotional experience being similar between healthy controls and schizophrenia patients has been consistently reported in studies using pictures (Takahashi et al., 2004; Bigelow et al., 2006), films (Earnst and Kring, 1999) as well as words with emotional content (Koh et al., 1976; Mathews and Barch, 2004).

In line with previous studies (Danion et al., 2003; Hall et al., 2007; Neumann et al., 2007), healthy controls retained more images in memory compared to patients regardless of emotional valence or arousal. In discordance with our prediction, there were no differences in recognition accuracy between emotional and neutral images in patients or in control subjects (except for patient's increased memory for LA- images and healthy control's superior memory for HA+ images). These findings are inconsistent with previous reports that emotionally valenced stimuli enhance memory (Hamann, 2001). A possible explanation for this is that emotional advantages in memory have been found to increase over longer time periods (LaBar and Phelps, 1998; Sharot and Phelps, 2004; Sharot and Yonelinas, 2008). Therefore, it is possible that the effects of emotionality in our paradigm would have become more evident with a longer interval between incidental encoding and subsequent memory. For example, a previous study (Dolcos et al., 2004a) investigating the neural correlates of emotional episodic memory in healthy individuals using similar stimuli and incidental encoding procedure as ours demonstrated a better memory for emotional compared to neutral stimuli after a 45-minute delay.

4.2. fMRI data

The retrieval of negative images (relative to the retrieval of neutral images) elicited activations in regions previously implicated in emotion processing (Phan et al., 2002) and in episodic memory (Rugg et al., 2002). In healthy participants the activated regions included the middle and inferior temporal cortex, precuneus, cerebellum, prefrontal cortex (medial orbitofrontal, superior and middle frontal) and middle cingulate gyrus, while in schizophrenia patients they were restricted only to the middle temporal cortex. The overall diminished activations during retrieval of negatively valenced relative to neutral images in schizophrenia patients are consistent with previous studies that have explored the processing of emotional stimuli (Schneider et al., 1998; Gur et al., 2002; Takahashi et al., 2004) and episodic memory (Achim and Lepage, 2005b).

Direct comparison between groups revealed that the middle frontal gyrus was activated to a lesser extent in schizophrenia patients compared to healthy controls during recognition of both negative and positive images regardless of arousal. More specifically, the right dorsolateral prefrontal cortex (BA 10) was activated during recognition memory of HA+, LA+ and LA- relative to neutral contrasts (this region was also activated in the HA- minus neutral contrast but did not survive the significance threshold) while the middle frontal gyrus at the border of the precentral gyrus (BA 6) was activated during the HA- and LA+ relative to neutral contrasts. In parallel with our finding, past episodic memory studies have documented right dorsolateral prefrontal cortex activation at or near Brodmann area 10 in healthy subjects (Squire et al., 1992; Buckner et al., 1995, 1996; Rugg et al., 1999; Achim and Lepage, 2005a). A meta-analysis by Achim and Lepage (2005b) investigating episodic-memory related activity in schizophrenia, found that patients demonstrate less activity than controls in the middle frontal region during retrieval of episodic memories. This region has been identified as playing a role in post-retrieval monitoring during episodic memory retrieval with activations, on average, in the right middle frontal gyrus reflecting simple monitoring

with an additional contribution of the left middle frontal gyrus in more complex tasks (Achim and Lepage, 2005a). Accordingly, significant activity in the right, but not left, prefrontal cortex in healthy controls falls in line with our use of a simple old/new recognition memory task.

Interestingly, the analysis of the neutral minus baseline contrast revealed that patients activated the middle frontal gyrus, precuneus and middle cingulated gyrus (as well as other structures), to a greater degree than healthy controls during recognition memory of neutral stimuli. These findings partly explain the relative underactivations in these regions in patients versus controls in the emotional minus neutral contrasts. Increased cerebral activations in response to neutral stimuli in patients with schizophrenia have been previously reported in the literature and fall in line with the idea that patients with psychosis assign emotional importance to stimuli and events that would normally be considered neutral (Holt et al., 2006; Surguladze et al., 2006; Hall et al., 2008).

Despite atypical brain function during retrieval of negative relative to neutral pictures, patients did activate the middle temporal gyrus in the high arousal condition. This region has been implicated in a higher-order visual processing; specifically in perception of the social aspect of faces (Allison et al., 2000; Adolphs, 2002) including the processing of happy and angry faces (Critchley et al., 2000; Batty and Taylor, 2003). In schizophrenia the middle temporal gyrus has been activated during processing of negative facial expressions (Phillips et al., 1999). Because a little over half of the high arousal negative images presented in our paradigm included people whose facial expressions were visible, we can interpret activation in this region as indicative of processing highly negative facial expressions by patients.

During retrieval of highly positive images, schizophrenia patients activated overall similar regions as healthy controls, a finding in stark contrast to what was

predicted and also to what has been found in some (Schneider et al., 1998; Paradiso et al., 2003; Takahashi et al., 2004) but not all (Phan et al., 2002; Taylor et al., 2005; Reske et al., 2009; Dowd and Barch, 2010) studies that have examined the processing of emotional material in schizophrenia. The overlapping areas of cerebral activations included the middle temporal cortex, inferior occipital cortex, anterior temporal pole, cerebellum and regions of the prefrontal cortex (inferior and medial orbitofrontal cortex), most of which were also activated in healthy controls during retrieval of negative images.

Activity in the orbitofrontal cortex during retrieval of positively and negatively valenced images is consistent with reports that this region plays a role not only in the processing of emotional stimuli (Bechara et al., 2000; Rolls, 2000) but in emotional memory as well. Specifically, significant orbitofrontal activity has been reported during the recollection of happy and sad life events (George et al., 1995; Heilman and Gilmore, 1998) as well as recognition of words from negative (Lewis et al., 2005) and positive relative to neutral contrasts (Maratos et al., 2001).

In the same vein, the anterior temporal pole, a relevant component of the paralimbic system, has been activated during the retrieval of emotion-laden episodic memories (Fink et al., 1996; Dolan et al., 2000), attending to subjective emotional responses (Lane et al., 1997) and processing the emotional meaning of visual stimuli (Lane et al., 1999). Of particular importance to our findings, Beauregard and colleagues (Beauregard et al., 2001) reported that during the experience of sexual arousal induced by viewing erotic stimuli, healthy males activated paralimbic structures that encompassed the anterior temporal pole. We suggest that the anterior pole activations found in both groups during retrieval of high intensity positive images is associated with imparting affective tone to experience, a conclusion derived from various lines of evidence (Mesulam, 1985).

In the present study we have found both a deficit (in the high arousal negative condition) and preservation (in the high arousal positive condition) of activation in the cerebellum of schizophrenia patients during emotional memory. Our findings suggest that the degree of activation of the cerebellum in patients with schizophrenia is largely affect-dependent. There have been conflicting findings with some reporting cerebellar under-activations (Achim and Lepage, 2005b) and others reporting over-activations during episodic recognition memory (Crespo-Facorro et al., 2001) in schizophrenia. Additionally, research endeavours investigating schizophrenia patient's response to positive and negative emotional material have either reported a lack of cerebellum activations or have not found differential activations of this region in response to pleasant relative to unpleasant stimuli (e.g. Gur et al., 2002; Paradiso et al., 2003; Taylor et al., 2005; Reske et al., 2009; Dowd and Barch, 2010). The fact that some studies have found the lateral cerebellum to be preferentially related to cognition while the medial cerebellum to be more associated with affect can perhaps shed some light on the discrepant findings (Schmahmann, 1999; 2000; 2004). There has yet to be an agreement among authors concerning the role of the cerebellum in emotion in individuals with schizophrenia (Picard et al., 2008). In healthy subjects, activations in the cerebellum has been reported during the induction of feelings of sadness, anxiety (Reiman et al., 1997; Liotti et al., 2000), happiness (Habel et al., 2005), in evoking romantic love (Bartels and Zeki, 2000) and in the "feeling" experience associated with sexual arousal (Beauregard et al., 2001). We can posit that the erotic content in a sample of the high arousal positive images used in our paradigm may have contributed to the involvement of the cerebellum in emotional recognition memory in both the healthy and patient group. Future studies are awaited to explore this intriguing question.

Previous studies exploring the processing of emotional stimuli in schizophrenia have documented differences in the cerebral activations associated with positive vs.

negative stimuli (An et al., 2003, Reske et al., 2009; Sergerie et al., 2010) or have reported comparable extents of cerebral activation for both positive and negative stimuli (Kosaka et al., 2002; Paradiso et al., 2003; Dowd and Barch, 2010). For instance, in a PET study of emotion recognition, Paradiso et al. (2003) reported that patients with schizophrenia showed little differential activation in their responding to positive versus negative stimuli. Reske et al. (2009) reported emotion-specific group differences in brain activations such that patients and healthy subjects had comparable brain activation patterns during the discrimination of happy faces while group differences surfaced in response to sad facial expressions. The discordant results in the referenced studies (including our own) can be attributed to differences in the experimental task (e.g. emotion discrimination, experience, recognition memory) and to the stimuli used (e.g. words, pictures, faces). Also, arousal levels were often not equated across emotional valence categories in the previous investigations. It is possible that when stimuli are appropriately matched in terms of arousal, the positive stimuli, relative to negative, elicit more cerebral activations, especially for highly arousing images (which is where our most robust finding came from). This further indicates the importance of considering the dimension of arousal while investigating affect.

A surprising finding was the lack of amygdala activation during recognition of negative relative to neutral pictures in healthy controls. Amygdala activation during the retrieval of emotional memories is a consistent finding in many (e.g. LeDoux, 1993; Phelps and Anderson, 1997; Hamann, 2001) but not all functional neuroimaging studies (Taylor et al., 1998; Hamann et al., 1999). One possible explanation is the habituation of the amygdala to image content. Previous studies have documented that the fMRI BOLD signal of the amygdala attenuates with repeated presentation of negative images (Breiter et al., 1996; Wright et al., 2001; Fischer et al., 2003). Also, the absence of amygdala activation is consistent with the memory-modulation theory, which posits that

a central role of amygdala function is to modulate long-term memory consolidation (McGaugh et al., 1996; Cahill and McGaugh, 1998; Packard and Teather, 1998). Hence, at short delays, similar to our paradigm, little consolidation has taken place and so the amygdala's role may not be detectable at this point.

Together, the present findings suggest a neurofunctional anomaly in the use of negative affect, but intact functional circuitry of positive affect during episodic memory retrieval in schizophrenia patients. This was observed despite comparable recognition memory for negative and positive stimuli in the patient group. Interestingly, it seems that an interaction between valance and arousal is also at play because the effect was only seen for the high arousal positive contrast. Particularly, activations in regions that have previously been reported to be functionally impaired during the processing of emotional material and episodic memory in schizophrenia (e.g. anterior temporal pole, orbitofrontal cortex, cerebellum) were intact during the high arousal positive condition suggesting that their role in emotional episodic memory is affect dependent rather than being dysfunctional altogether.

With regards to arousal, both healthy controls and patients with schizophrenia showed an increase in cerebral activations in the high relative to low arousal contrasts for both positive and negative stimuli. It is worth noting that analysis of the main effect of arousal (i.e. brain activations in the high compared to low arousal conditions with positive and negative images combined) yielded a similar pattern of results. Our findings parallel neuroimaging studies of emotion processing in healthy individuals. For example, Lane and colleagues (Lane et al., 1999) examined the impact of valence and arousal during visual processing of pictures and found increased activations during processing of high intensity relative to low intensity emotion in extrastriate visual cortex and anterior temporal areas. Similarly, Bradley and colleagues (2003) reported more widespread occipital cortex activity when healthy participants viewed stimuli associated

with primary motive states (e.g., victims of violent death, erotica) compared to less arousing and neutral stimuli. It was suggested that this increase in activity reflected "motivated attention" in which appetitive or defensive motivational engagement guided attention and facilitated perceptual processing of survival-relevant stimuli.

Investigating the impact of arousal on memory and emotion in schizophrenia is limited. In one previous study (Hooker and Park, 2002) patients with schizophrenia were able to identify vocal affect of high emotional intensity better than that of low emotional intensity. The observation of a comparable subjective emotional experience between schizophrenia patients and healthy controls has been documented in numerous studies (Berenbaum and Oltmanns, 1992; Kring et al., 1993; Kring and Neale, 1996; Iwase et al., 1999; Aghevli et al., 2003; Kring and Moran, 2008). The results of our study are no different and, in fact, we have found that this comparable individual experience of emotion was demonstrated at the level of arousal where patients with schizophrenia, similarly to controls, rated high arousing stimuli as more emotionally salient than low arousing stimuli. Taken together, these behavioral and neuroimaging data suggest that schizophrenia patients show less of an emotional deficit relative to what has previously been reported in studies exploring the cerebral activations associated with the recognition and experience of emotional stimuli in individuals with schizophrenia (Schneider et al., 1998; Gur et al., 2002; Takahashi et al., 2004).

The interpretation of this study is limited by the fact that we did not include a means to assess the subjects' potential encoding strategies during scanning. Even though the participants were not instructed to try and remember the pictures presented during encoding, they were still aware that they were going to undergo a subsequent memory task. Thus, it is possible that both groups differed in their tendency to instinctively use encoding strategies as well as in their ability to effectively use such strategies. This supposition is strengthened in light of evidence that faulty mnemonic

processes during encoding underlie memory impairments in schizophrenia (Koh and Peterson, 1978; Brebion et al., 1997; Iddon et al., 1998).

We would also like to acknowledge that because old and new images were randomly intermixed within each block, cerebral activations associated with only correct retrieval of stimuli into memory could not be ascertained. Because of this it is possible that other processes, rather than simply recognition, could have affected the pattern of cerebral activations observed which is indicative that our data more likely reflected an attempted retrieval process. For instance, potential attention lapses during the block could have caused the decreased performance and brain function in patients particularly during memory of negatively valenced stimuli. Nonetheless, the overall main goal of this study was to assess the performance and brain function associated with recognition of emotional stimuli regardless of whether the stimuli were old or new. Also, despite the fact that brain activity in response to new stimuli and old stimuli were not differentiated, both healthy controls and patients with schizophrenia (though to a lesser extent) demonstrated accuracy significantly above chance indicating that an accurate recognition process was taking place.

To conclude, our data suggest that the failure to activate brain regions during retrieval of emotional stimuli from memory in patients with schizophrenia is dependent on whether these stimuli carry a positive or negative valence. Moreover, the effects of arousal demonstrate that the experience of emotion is relatively intact in schizophrenia patients relative to what has previously been reported in functional neuroimaging studies.

Figure Legend:

Figure 1:
Subjective ratings scores in healthy controls and schizophrenia patients for all experimental conditions.
Bars represent standard error of the mean
HA- = high arousal negative, HA+= high arousal positive, LA-=low arousal negative, LA+= low arousal positive, NTR=neutral

Mean(SE) : HA- : Healthy controls(HC)= 6.92(0.17), Schizophrenia (SCZ)= 6.67(0.22); HA+: HC= 5.34(0.22), SCZ= 5.79(0.20); LA-: HC= 3.87(0.18), SCZ= 3.97(0.25); LA+: HC= 4.15(0.22), SCZ=4.17(0.25); NTR: HC=1.10(0.18), SCZ= 1.74(0.23)

Figure 2:
Recognition accuracies in healthy controls and schizophrenia patients for all experimental conditions.
Bars represent standard error of the mean
HA- = high arousal negative, HA+= high arousal positive, LA-=low arousal negative, LA+= low arousal positive, NTR=neutral

Mean(SE) : HA- : Healthy controls(HC)= 0.79(0.023), Schizophrenia (SCZ)= 0.57(0.045); HA+: HC= 0.89(0.023), SCZ= 0.55(0.049); LA-: HC= 0.82(0.038), SCZ= 0.60(0.044); LA+: HC= 0.84(0.023), SCZ= 0.57(0.053); NTR: HC= 0.79(0.022), SCZ= 0.49(0.038)

Figure 3:
Cerebral activations associated with the retrieval of high arousal negative images (top) and low arousal negative images (bottom) in schizophrenia patients and healthy controls.
HC=healthy controls, SCZ=schizophrenia patients
HA-=high arousal negative, LA-=low arousal negative
The colored bar represents the range of z-scores of the cerebral activations with significance increasing from 3 (pink color) to 7 (red color).

Figure 4:
Cerebral activations associated with the retrieval of high arousal positive images (top) and low arousal positive images (bottom) in schizophrenia patients and healthy controls.
HC=healthy controls, SCZ=schizophrenia patients
HA+=high arousal positive, LA+=low arousal positive
The colored bar represents the range of z-scores of the cerebral activations with significance increasing from 3 (pink color) to 7 (red color).

Figure 5:
Cerebral activations associated with group differences during the retrieval of negative relative to neutral images (top) and positive relative to neutral images (bottom) in schizophrenia patients and healthy controls.
HC=healthy controls, SCZ=schizophrenia patients
HA+=high arousal positive, LA+=low arousal positive, HA-=high arousal negative, LA-=low arousal negative

The colored bar represents the range of z-scores of the cerebral activations with significance increasing from 0 (pink color) to 3 (red color).

Figure 1. Subjective ratings of emotional stimuli in healthy controls and schizophrenia patients

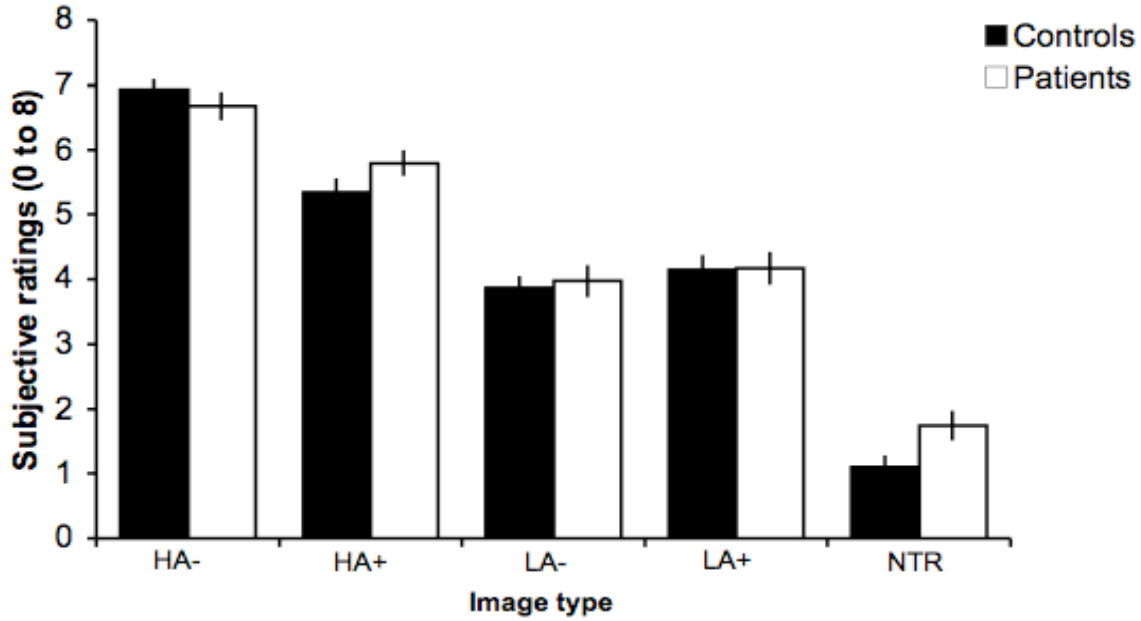

Figure 2. Recognition accuracy of emotional stimuli in healthy controls and schizophrenia patients

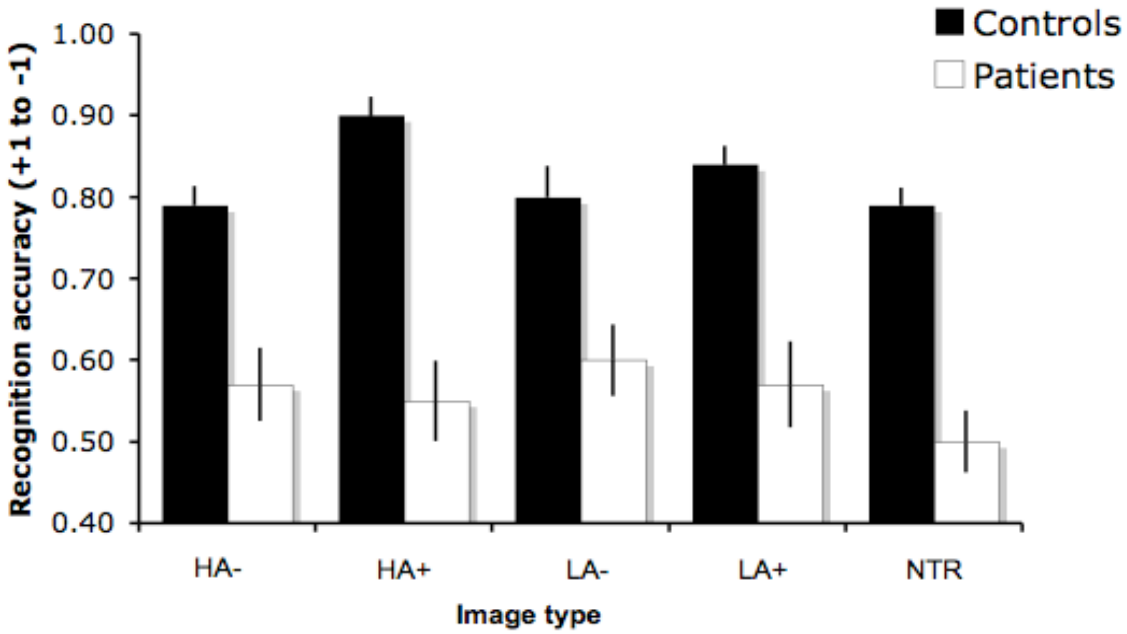

Figure 3.

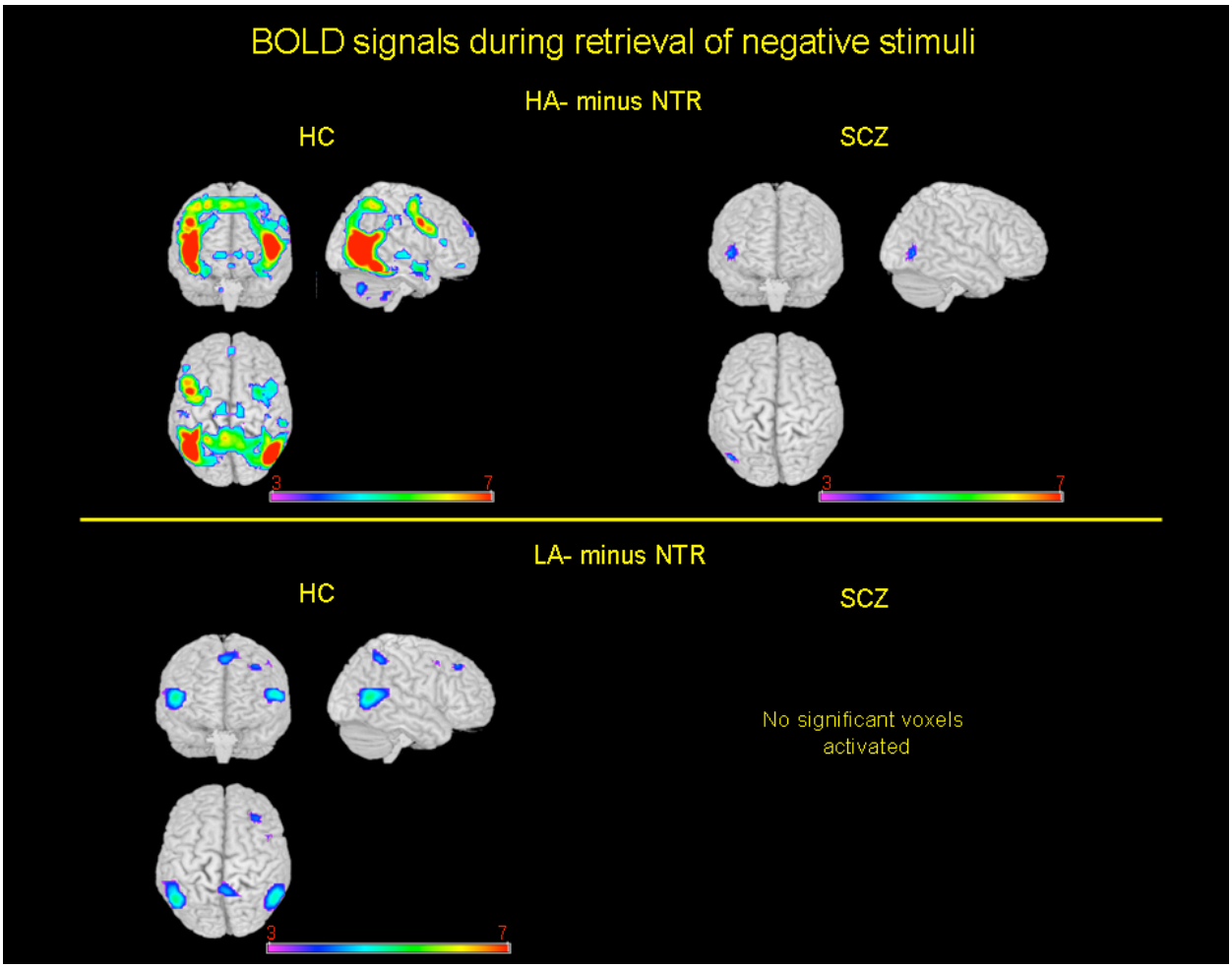
BOLD signals during retrieval of negative stimuli
HA- minus NTR
HC
SCZ
3
7
3
7
LA- minus NTR
HC
SCZ
No significant voxels activated
3
7

Figure 4.

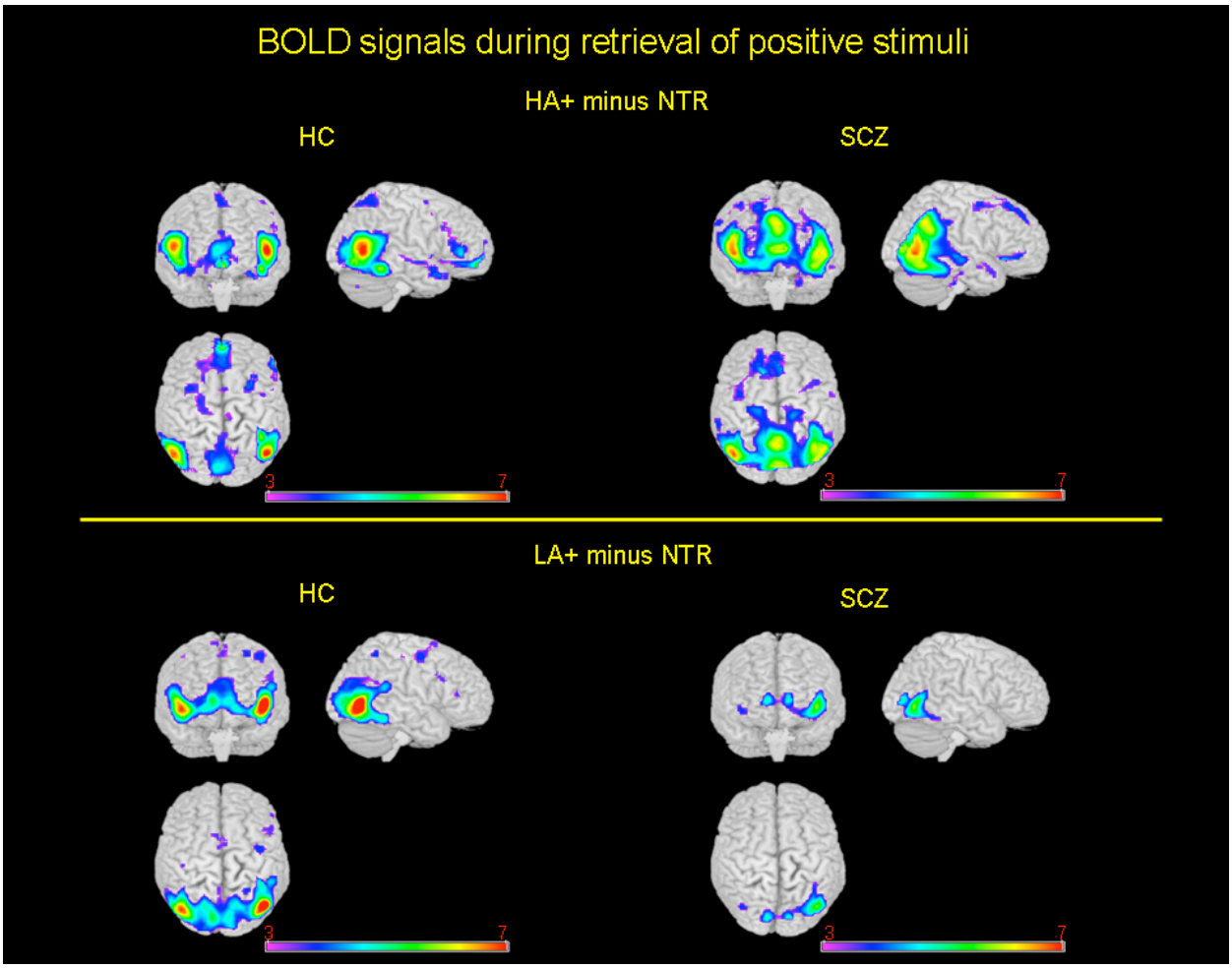
BOLD signals during retrieval of positive stimuli
HA+ minus NTR
HC
SCZ
3
7
3
7
LA+ minus NTR
HC
SCZ
3
7
3
7

Figure 5.

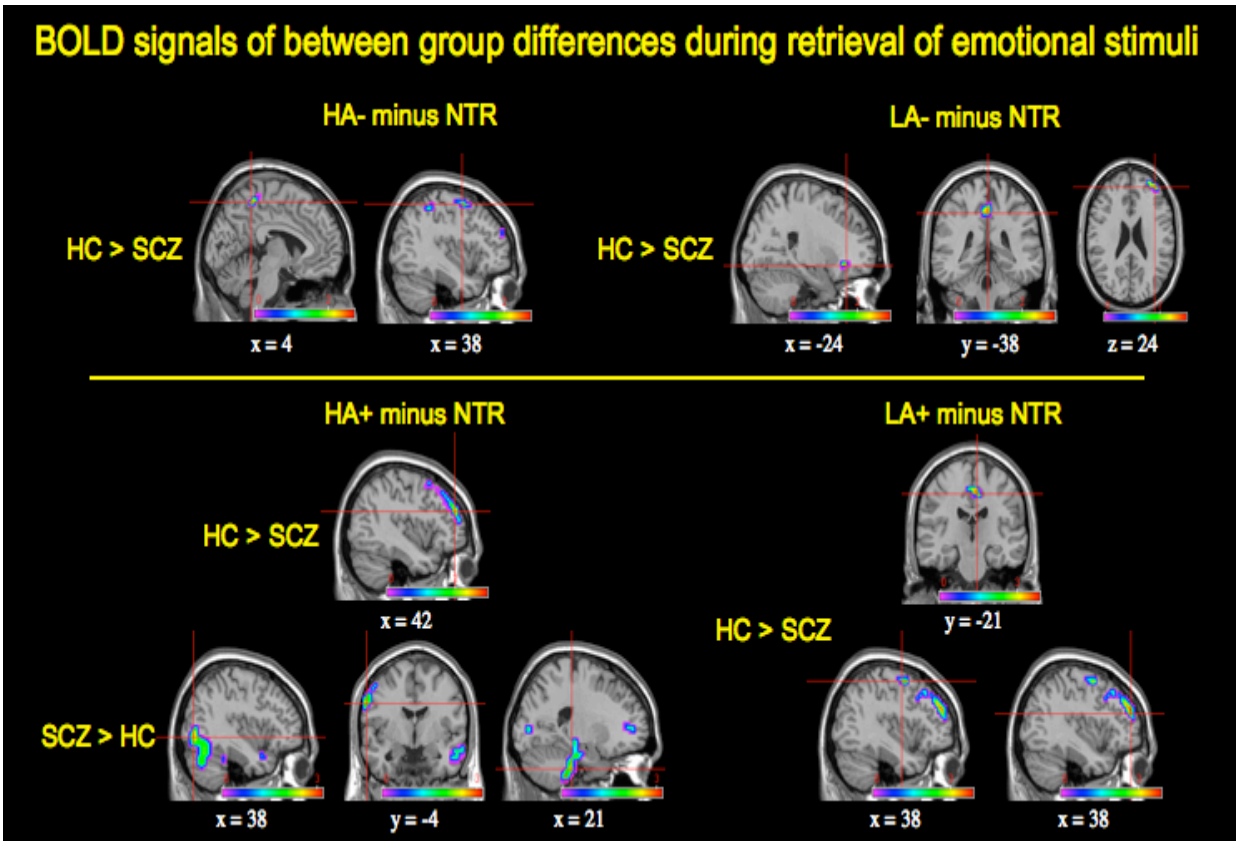
BOLD signals of between group differences during retrieval of emotional stimuli
HA- minus NTR
LA- minus NTR
HC > SCZ
x = 4
x = 38
HC > SCZ
x = -24
y = -38
z = 24
HA+ minus NTR
LA+ minus NTR
HC > SCZ
x = 42
HC > SCZ
y = -21
SCZ > HC
x = 38
y = -4
x = 21
x = 38
x = 38

Table 1. Demographic and clinical data of participants

	Schizophrenia patients		Healthy controls		
	Mean	SD	Mean	SD	P (Independent sample, two-tailed)
Age	32.46	7.66	31.81	6.91	0.70
Parental SES	2.36	1.09	2.68	0.88	0.18
Sex (% male)	51	-	51	-	-
Handedness (% right)	89	-	91	-	-
Medication (chlorpromazine equivalence)	613.92	361.02	-	-	-
PANSS Positive	18.84	6.93	-	-	-
PANSS Negative	12.59	10.95	-	-	-
PANSS General	24.05	22.59	-	-	-

PANSS=Positive and Negative Syndrome Scale, SES= Socioeconomic status; SD=standard deviation

Table 2. fMRI BOLD activations during retrieval of negatively charged images relative to neutral images

				MNI coordinates					
	L/R	Brain region	BA	x	y	Z	Z-score	voxels	P value
HA negative minus neutral									
HC	R	Middle temporal cortex	19	46	-70	0	6.77	339	0.001
	L	Middle occipital cortex	19	-46	-74	7	6.70	*	0.001
	R	Inferior temporal cortex	20	46	-49	-18	6.17	*	0.001
	R	Precuneus	7	7	-52	52	5.27	*	0.001
	L	Medial orbitofrontal cortex	11	0	52	-18	4.23	40	0.001
	L	Superior medial frontal	10	-7	63	21	3.83	46	0.003
	L	Middle cingulate cortex	24	0	7	32	3.81	64	0.005
	R	Superior motor area	6	4	21	63	3.28	14	0.012
	L	Cerebellum	-	-10	-74	-42	3.95	63	0.004
	R	Cerebellum	-	14	-74	-46	3.88	*	0.004
SCZ	R	Middle temporal cortex	19	52	-74	0	3.96	40	0.002
LA negative minus neutral									
HC	R	Middle temporal cortex	37	52	-63	7	4.42	217	0.001
	L	Middle temporal cortex	37	-52	-63	14	4.24	166	0.001
	L	Middle frontal cortex	8	-32	32	46	3.7	40	0.005
	L	Precuneus	7	-4	-56	52	3.88	85	0.003
	L	Precentral gyrus	6	-46	4	49	3.29	18	0.011
SCZ	No significant voxels activated								

L/R=Left/Right, BA=Brodmann areas, HC=Healthy controls, SCZ=Schizophrenia patients, *=Brain region is part of the same cluster as above

Table 3. fMRI BOLD activations during retrieval of positively charged images relative to neutral images

Group	L/R	Brain region	BA	MNI coordinates x	y	z	Z-score	voxel	P value
HA positive minus neutral									
HC	R	Middle temporal cortex	19	49	-70	0	5.79	263	0.001
	L	Middle temporal cortex	19	-49	-70	7	5.49	293	0.001
	L	Inferior occipital cortex	18	-46	-80	-10	4.93	*	0.001
	L	Calcarine gyrus	18	-4	-88	0	4.2	253	0.001
	L	Rectus gyrus	11	0	52	-18	4.85	98	0.001
	R	Medial orbitofrontal cortex	11	4	38	-14	3.79	*	0.001
	R	Middle frontal cortex	6	46	0	60	3.60	17	0.009
	R	Inferior frontal cortex	45	56	35	0	4.09	67	0.002
	R	Anterior temporal pole	38	32	14	-28	3.88	47	0.003
	L	Precuneus	7	0	-60	56	3.50	85	0.004
	R	Caudate	-	4	4	-4	3.41	12	0.016
	R	Thalamus	-	10	-28	-4	3.25	17	0.012
	L	Cerebellum	-	-14	-74	-38	3.21	5	0.01
SCZ	L	Inferior occipital cortex	19	-46	-74	-4	5.47	236	0.001
	R	Inferior occipital cortex	19	46	-77	-4	5.19	*	0.001
	R	Calcarine	17	10	-88	4	5.14	*	0.001
	L	Rectus gyrus	47	-14	21	-10	4.07	69	0.002
	R	Medial orbitofrontal cortex	32	4	32	-10	3.80	*	0.001
	L	Inferior orbitofrontal cortex	47	-24	32	-10	3.64	*	0.004
	L	Superior frontal cortex	8	-21	32	49	3.70	82	0.003
	R	Anterior temporal pole	38	42	10	-24	3.36	38	0.006
	R	Middle temporal cortex	21	60	-4	-21	3.26	14	0.008
	L	Supramarginal gyrus	40	-63	-38	32	3.57	34	0.005
	R	Cerebellum	-	24	-24	-28	3.59	27	0.006
LA positive minus neutral									
HC	R	Middle occipital cortex	19	46	-74	0	6.23	237	0.001
	L	Inferior occipital cortex	19	-42	-77	-7	5.57	*	0.001
	L	Calcarine gyrus	17	-10	-84	4	4.52	*	0.001
	R	Middle frontal cortex	6	42	-7	52	3.59	48	0.007
	R	Inferior frontal cortex	46	56	32	7	3.48	12	0.017
	R	Superior parietal cortex	7	28	-56	56	3.52	21	0.016
	L	Postcentral gyrus	2	-42	-28	52	3.37	8	0.018
	L	Superior motor area	6	-7	10	66	3.33	28	0.007
SCZ	R	Inferior occipital cortex	19	42	-74	-4	4.90	191	0.001
	R	Calcarine gyrus	17	14	-88	4	4,34	*	0.001
	L	Cacarine gyrus	17	-10	-84	4	4.24	*	0.001
	L	Inferior occipital cortex	19	-38	-74	-10	3.49	26	0.011

L/R=Left/Right, BA=Brodmann areas, HC=Healthy controls, SCZ=Schizophrenia patients, *=Brain region is part of the same cluster as above

Table 4. fMRI BOLD activations during retrieval of high arousal relative to low arousal images

Group	L/R	Brain region	BA	MNI coordinates x	y	z	Z-	voxels	P valu
HA negative minus LA negative									
HC	R	Fusiform gyrus	37	38	-66	-14	4.80	320	0.001
	L	Fusiform gyrus	37	-35	-66	-14	4.23	*	0.001
	R	Calcarine gyrus	17	10	-91	4	4.40	*	0.001
	R	Middle occipital cortex	19	35	-80	18	3.85	73	0.001
	R	Cuneus	19	7	-88	42	3.17	57	0.032
	R	Superior frontal cortex	6	38	-7	63	3.37	35	0.042
SCZ	L	Calcarine gyrus	17	-10	-94	-7	4.47	114	0.001
	R	Fusiform gyrus	37	42	-49	-21	4.05	*	0.001
	L	Inferior occipital cortex	19	-49	-77	-10	3.53	43	0.004
	R	Middle occipital cortex	19	38	-77	10	3.49	13	0.013
	L	Inferior orbitofrontal coretx	47	-28	28	-14	3.27	8	0.014
	L	Superior orbitofrontal cortex	47	-21	21	-14	3.27	*	0.014
	R	Cerebellum	-	14	-66	-56	3.71	9	0.012
HA positive minus LA positive									
HC	R	Superior parietal cortex	7	14	-77	52	3.72	91	0.007
	R	Precuneus	7	7	-74	60	3.48	*	0.007
	L	Precuneus	4	0	-63	66	3.05	*	0.016
SCZ	R	Angular gyrus	39	38	-63	35	4.42	105	0.001
	R	Precuneus	7	4	-63	32	4.23	*	0.001
	L	Angular gyrus	39	-42	-60	38	3.86	71	0.002
	R	Inferior temporal cortex	37	60	-49	-10	3.78	13	0.009
	R	Anterior cingulated cortex	32	18	42	4	3.37	18	0.01
	R	Medial frontal cortex	32	10	46	0	3.26	*	0.01
	L	Superior frontal cortex	9	-18	42	35	3.48	34	0.01
	R	Middle frontal cortex	9	35	21	38	3.38	47	0.006
	R	Inferior frontal cortex	9	42	14	35	3.29	*	0.006
	L	Cerebellum	-	-35	-56	-49	3.42	16	0.012

L/R=Left/Right, BA=Brodmann areas, HC=Healthy controls, SCZ=Schizophrenia patients, *=Brain region is part of the same cluster as above

Table 5. fMRI BOLD activations of group differences during retrieval of emotional images relative to neutral and neutral images relative to baseline.

Group	L/R	Brain region	BA	MNI x	MNI y	MNI Z	Z-	voxels	P valu
HA negative minus									
HC > SCZ	R	Precuneus	7	4	-46	56	2.63	74	0.004
	R	Middle frontal cortex	6	38	0	56	2.58	21	0.005
LA negative minus neutral									
HC > SCZ	R	Middle frontal cortex	10	38	49	24	2.87	44	0.002
	L	Inferior orbitofrontal	47	-24	32	-	2.72	10	0.003
	R	Middle cingulate cortex	7	1	-38	46	2.57	34	0.005
HA positive minus neutral									
HC > SCZ	R	Middle frontal cortex	10	42	46	24	2.82	78	0.002
SCZ > HC	R	Cerebellum	-	21	-28	38	2.56	118	0.005
	L	Postcentral gyrus	6	-63	-4	32	2.63	72	0.004
	R	Inferior occipital cortex	18	38	-84	-4	3.03	235	0.001
LA positive minus neutral									
HC > SCZ	R	Middle frontal cortex	10	38	49	21	3.67	37	0.001
	R	Middle frontal cortex	6	38	-4	56	3.64	*	0.001
	R	Middle cingulate cortex	31	7	-21	46	3.50	28	0.001
NTR minus baseline									
SCZ > HC	R	Precuneus	5	4	-42	56	3.34	291	0.001
	R	Middle cingulate cortex	31	7	-21	42	3.30	*	0.001
	R	Middle frontal cortex	9	46	28	35	3.02	26	0.002
	R	Middle frontal cortex	6	42	0	52	3.02	41	0.001
	L	Inferior parietal cortex	40	-42	-42	46	3.16	49	0.001
	L	Anterior cingulate cortex	32	-10	32	-10	3.23	23	0.001
	L	Cerebellum	-	-24	-88	-24	3.05	16	0.001
	L	Middle temporal cortex	39	-56	-63	21	2.90	5	0.002

L/R=Left/Right, BA=Brodmann areas, HC=Healthy controls, SCZ=Schizophrenia patients, *=Brain region is part of the same cluster as above

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Article 2

The following article entitled “Sex differences in the cerebral activations associated with emotional recognition memory in schizophrenia” was submitted to *Biological Psychiatry* in January 2012 (see proof of submission).

Title page

Sex differences in the cerebral activations associated with emotional recognition memory in schizophrenia

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Abstract

Background: Individuals with **s**chizophrenia show prominent deficits in emotional episodic memory. Examining sex-specific differences in the neural correlates of emotional memory in schizophrenia patients is non-existent, despite reports of sex differences in healthy individuals. The present study aimed to compare cerebral activations in schizophrenia and healthy men and women during the recognition memory of emotional images.
Methods: Using fMRI, 41 schizophrenia patients (20 women) were compared to 41 healthy participants (19 women) while performing a yes/no recognition paradigm with positive, negative and neutral images.
Results: There were no sex differences in performance. Compared to healthy women, schizophrenia women showed a decrease in brain activations in cortical (e.g. middle cingulate) and subcortical limbic structures (e.g. amygdala) during recognition of negative images and decreased activations during the positive condition in the cerebellar vermis, middle and inferior frontal gyrus. Schizophrenia men had increased activations compared to healthy men in the medial prefrontal gyrus during recognition of negative stimuli and a substantial increase in brain activity during the recognition of positive pictures in parietal, temporal and limbic structures. Correlation analysis revealed significant relationships between brain function and symptoms during positive emotional memory in women and during negative emotional memory primarily in men.
Conclusion: We uncovered sex-specific differences in the cerebral activations associated with emotional memory in healthy and schizophrenia individuals. The extent of these sex differences depended on the valence of the images. These findings demonstrate the importance of investigating men and women with schizophrenia separately in the context of emotional and cognitive tasks.

Introduction

The brains of men and women diverge in several ways and a plethora of sex differences in cognitive functions (Halpern, 1997; Herlitz & Rehnman, 2008; Kimura, 2004; Levy & Heller, 1992) and emotional processing (Bradley et al., 2001; Derntl et al., 2010; Hamann & Canli, 2004; Kring & Gordon, 1998; McLean & Anderson, 2009; Wager et al., 2003) have been documented, including memory for emotionally laden events. Studies have found that women possess a superior memory for emotional events compared to men (Andreano & Cahill, 2009; Cahill, Gorski, et al., 2004; Canli et al., 2002; Fujita et al., 1991; Seidlitz & Diener, 1998) and these differences have been attributed to underlying disparities between the sexes in the strategies used to process information (Fujita, et al., 1991; McGivern et al., 1997; Meyers-Levy & Tybout, 1989; Seidlitz & Diener, 1998). Complementing the behavioral studies, functional neuroimaging reports have pointed to distinct patterns of neural activity in men and women during both encoding and recognition of emotional stimuli (Bremner et al., 2001; Cahill, Uncapher, et al., 2004; Canli, et al., 2002; Ino et al., 2010; Mackiewicz et al., 2006; Piefke et al., 2005)

Schizophrenia, a heterogeneous and complex psychiatric disorder, is characterized by prominent disturbances in cognitive and emotional functioning (Heinrichs & Zakzanis, 1998; Kohler et al., 2000; Kohler & Martin, 2006; Rund & Borg, 1999) including the processing of emotional memories (for a Review see Herbener, 2008). Similarly to the general population, differences between men and women in cognitive and emotional functioning have been documented. Male patients tend to exhibit more poverty of speech and blunted affect, whereas female patients display more inappropriate affect and certain delusions and hallucinations (Andia et al., 1995; Goldstein & Link, 1988; Leung & Chue, 2000; Rector & Seeman, 1992; Tien, 1991). In a study of facial emotion processing, Scholten and colleagues (2005) observed a clear

sex difference in the ability to recognize facial emotions, especially negative ones, with women outperforming men. With regards to cognition the results have been more inconsistent. Some reports have documented greater impairment in schizophrenia men compared to women on tasks of attention, language, memory and executive functioning (Goldstein et al., 1998; Lewine et al., 2006; Longenecker et al., 2010; Seidman et al., 1997; Torniainen et al., 2011; Vaskinn et al., 2011; Walder et al., 2006), while others have reported the opposite effect (Hoff et al., 1998; Lewine et al., 1996; Torniainen, et al., 2011) or have not uncovered any significant sex-specific differences in cognitive performance (Andia, et al., 1995; Guillem et al., 2009; Lewine, et al., 2006; Shipman et al., 2009). The small number of studies that have examined sex differences in cerebral activations associated with cognition (e.g. mental rotation, episodic memory) (Guillem, et al., 2009; Jiménez et al., 2010) and emotional processing (e.g. experience of emotion) (Mendrek et al., 2007; Mendrek, 2009) in schizophrenia have provided evidence of distinct patterns of activations between men and women. The overall findings pointed towards an alteration of the normal sexual dimorphism in cerebral activations in individuals with schizophrenia.

To our knowledge there are no published reports of sex differences in the neural circuitry associated with emotional episodic memory in patients with schizophrenia, although a few functional neuroimaging studies have examined the overall differences between schizophrenia patients and healthy controls. For instance, using functional magnetic resonance imaging (fMRI) Whalley et al. (2009) reported robust medial temporal lobe activations in patients with bipolar disorder, patients with schizophrenia and healthy controls during memory encoding that correlated significantly with subsequent recognition memory performance. Another fMRI study implemented an emotional memory paradigm with faces and reported emotion-specific differences in cerebral activations (e.g. hippocampus, parahippocampal and superior frontal gyrus)

associated with memory response bias in patients with schizophrenia and healthy subjects (Sergerie et al., 2010). More recently, we observed an atypical pattern of brain function during retrieval of negative pictures, but intact functional circuitry during memory for positive pictures (particularly highly arousing pictures) in schizophrenia patients (Lakis et al., 2011). Although individuals with schizophrenia appear to be impaired in memory for emotional experiences, the evidence of neurofunctional correlates of episodic memory deficits in this psychiatric population is still limited and investigation of sex differences is non-existent.

The primary aim of the present study was to explore brain activations in men and women with schizophrenia, during recognition of positively and negatively valenced pictures, relative to same-sex healthy comparison groups. Our hypotheses were based on existing literature (Canli, et al., 2002; Piefke, et al., 2005; Seidlitz & Diener, 1998) as well as previous results obtained by our group (Mendrek et al., 2010 ; Mendrek, et al., 2007; Mendrek, 2009). Behaviorally, the cognitive-style hypothesis posits that men and women may differ in the way they encode, rehearse and think about emotional experiences that will ultimately lead to differences in performance (with women outperforming men; Seidlitz & Diener, 1998) and to qualitative differences in the pattern of cerebral activations during processing of emotional memories (Bremner, et al., 2001; Canli, et al., 2002; Piefke, et al., 2005). Accordingly, we predicted that schizophrenia patients would be characterized by a decreased recognition accuracy compared to healthy subjects, but that women in both groups would have a superior recognition memory for emotional stimuli relative to men. With regards to cerebral functioning, we postulated that men and women in both groups would activate qualitatively distinct pattern of cerebral activations in regions previously implicated in emotion and episodic memory processes (e.g. regions of limbic and paralimbic cortex, parietal and prefrontal cortex) (Dolcos et al., 2004a, 2004b; Hamann, 2001; LaBar & Cabeza, 2006; Phan et

al., 2002). In addition, based on existing findings (Mendrek, et al., 2010 ; Phillips et al., 2003; Phillips et al., 1999; Stip et al., 2005), we predicted significant correlations between negative symptoms and activations in cortical structures (e.g. prefrontal, cingulate cortex), and between positive symptoms and activations in subcortical limbic structures (e.g. amygdala, hippocampus). Moreover, because it has been documented that schizophrenia men are typically more affected by negative symptoms and women by positive symptoms (Leung & Chue, 2000), we hypothesized that deficient brain activations during emotional memory in men would be mediated primarily by negative symptomatology, while positive symptoms would play a greater role in a distorted cerebral function in women.

Methods and Materials

Subjects

Forty-one patients with schizophrenia (21 men, 20 women) meeting the DSM-IV criteria for schizophrenia (APA, 1994), in a stable phase of their illness (defined as no relapse within the last two months and no change in their antipsychotic treatment within the last month) and 41 healthy controls (22 men, 19 women) participated in the study. The groups were matched for age, handedness (Edinburgh Inventory) (Oldfield, 1971) and parental socio-economic status (National Occupational Classification; NOC) (Census, 2001) (Table 1).

All patients were re-evaluated by experienced psychiatrists before being assigned to the research group (DSM-IV, criteria A-E); affective, schizoaffective and schizophreniform psychoses were excluded. Control participants were screened with the non-patients edition of the Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1992). Symptom severity was rated according to the positive and negative syndrome scale (PANSS) (Kay et al., 1987). Illness onset was defined as the date of the first psychiatric consultation. All the patients received at least one atypical antipsychotic (26

patients received one, 15 received two. In chlorpromazine equivalence: Clozapine: n=20, mean dosage= 835 mgs ± 215.27 mgs; olanzapine: n= 11, mean dosage= 280 mgs ± 113.53 mgs; risperidone: n=15, mean dosage= 111.11 ± 58.65 mgs; quetiapine: n=9, mean dosage= 324.07 mgs ± 183.17 mgs; ziprasidone: n=2 mean dosage= 166.67 mgs ± 47.14).

General exclusion criteria included age below 18 or above 45 years, past or present neurological or Axis-I psychiatric disorder, alcoholism or drug abuse, non compliance with testing procedures, or any contra-indication for MRI (e.g., cardiac pacemaker, aneurysm clip, etc.)

In agreement with the Declaration of Helsinki, written informed consent was obtained prior to participation in the experiment. The ability of schizophrenia patients to give informed consent was established using the guidelines of the Canadian Psychiatric Association. The study was approved by the ethics committees of the Fernand-Seguin Research Center of the Louis-H Lafontaine Hospital and the Regroupement Neuroimagerie Québec.

Procedure

Prior to the memory task, participants passively viewed blocks of emotionally positive, negative, and neutral pictures while in the fMRI scanner (i.e. incidental encoding task). The stimuli were selected from the International Affective Picture System (IAPS) (Lang et al., 1988) to fit three experimental conditions: positive, negative and neutral content. Each image category was presented in separate blocks. Images with positive and negative valence were matched based on normative arousal ratings and all images were matched for content (e.g. number of people, animals, landscapes). This emotion processing task was followed by an unrelated cognitive task with a duration of 15 minutes as a means of separating both incidental encoding and subsequent emotional recognition memory.

The subsequent emotional memory task consisted of viewing 48.5-second blocks of emotionally positive, negative, and neutral pictures where 50% of the stimuli in each block originated from the incidental encoding task, while the other 50% were new. There were 16-second periods of rest separating the blocks from one another. Each block contained 10 images and was repeated 4 times. Each picture appeared for 3000 ms followed by a blank screen with a fixation point for an average of 1.75 s (ranging from 1 to 2.5 s and giving an average inter-stimulus interval (ISI) of 4.75 s). During this memory task, participants' were to determine, by pressing the correct button, which of the stimuli were old and which were new. To assess the participants subjective emotional responses to the presented images, immediately at the end of the fMRI session, participants were re-presented with the images of each block and were asked to rate on a scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime) the intensity of experienced emotion for each block of stimuli.

fMRI data acquisition and analyses

Blood oxygenated dependent level (BOLD) signals were recorded using a single-shot, gradient-recalled echo-planar imaging sequence [repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle = 90 degrees, matrix 64 x 64 voxels] on a MRI Siemens TRIO system at 3.0 Tesla, which is operational at the Functional Neuroimaging Unit at the University of Montreal Geriatric Institute. The functional volumes were then registered to individual high-resolution co-planar anatomical images taken during the same scanning session (three-dimensional, spoiled gradient echo sequence; 176 slices, slice thickness = 1 mm, TR = 19 ms, TE = 4.92 ms, flip angle = 25"; matrix 256 x 256 voxels) to better identify activated structures.

The *f*MRI data were analyzed using statistical parametric mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK) according to

methods outlined by Friston and colleagues (Friston, 1995). Functional images were realigned to the mean volume of each session to correct for artifacts due to subject motion, were spatially normalized into the standardized brain template (voxel size: 3.5mm x 3.5mm x 3.5mm) and were spatially smoothed with a three-dimensional isotropic Gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio.

Statistical analyses were carried out using a standard peak-detection approach and the general linear model implemented in SPM5 to identify the dynamic cerebral changes associated with emotional episodic memory. First, fMRI data of each participant were analyzed using a fixed-effects model to investigate individual brain activation maps and to contrast the brain activity associated with different conditions. The fixed-effects analysis produced individual contrast images that were then used as raw data for the implementation of a random-effects model to investigate the pattern of activations during the different emotional contrasts (positive minus neutral and negative minus neutral) in each group (i.e. healthy men, healthy women, schizophrenia men and schizophrenia women). The literature exploring sex differences in the neural correlates of emotional episodic memory in patients with schizophrenia is scarce and so an exploratory whole brain analysis was performed. One-sample t-tests were conducted for each group to subtract brain activations associated with neutral from that associated with emotional stimuli (emotional minus neutral). These activations maps were thresholded at the level of $p=0.01$ with the FDR correction at the whole brain level and regions were considered significant at a $p < 0.001$. We also examined any potential differences between groups within the same sex (e.g. activations in healthy women minus activations in schizophrenia women) using a two-sample t-test. Due to the strict character of the second-level analysis based on a random-effects model the statistical maps were thresholded at the level of $p=0.005$ uncorrected for multiple comparisons and regions were considered to be significant at a $p < 0.005$. Similar and more liberal

thresholds were used in recent fMRI studies because the analyses were based on a random effect model (Aleman & Swart, 2008; Jiménez, et al., 2010; Lakis, et al., 2011). However, the majority of the activation was also significant when corrected for multiple comparisons, suggesting that it is unlikely that they were type I errors. In addition to the whole brain analysis, the hippocampus, amygdala and medial prefrontal cortex bilaterally were selected as a priori regions of interests (ROI) based on previous functional neuroimaging studies of emotional memory (Dolcos, et al., 2004a, 2004b; Hamann, 2001; Kensinger & Corkin, 2004; LaBar & Cabeza, 2006). The centers for each of our a priori ROIs were produced using the Mask for ROI Analyses software (MARINA) (Walter et al., 2003). This software provides 3D masks based on the Automated Anatomical Labelling (AAL) (Tzourio-Mazoyer et al., 2002). AAL uses the anatomical boundaries of each region using the MNI template as a reference. A search sphere (radius=16 mm) was applied to the centre of each ROI using the small volume correction function in SPM5 except for the amygdala in which a sphere of 8 mm was implemented. The AAL tool in SPM provided the anatomic labeling of each activation peak within the ROI. For the a priori search, a probability threshold for multiple comparison of a corrected $p < 0.05$ and a z-score 1.67 was used (Poline et al., 1997). Effects at each voxel of the brain was estimated using the general linear model and voxel values for the contrasts of interest generated statistical parametric maps of the t statistic (SPM *t*) that were subsequently transformed to the unit normal distribution (SPM *Z*).

To assess correlations between clinical symptoms and brain function, second-level regression analyses were performed in SPM5. Positive and negative symptoms were entered as covariates of interest that were correlated first with brain function during recognition memory of positively valenced images and then with the cerebral activations associated with memory of negative stimuli. Statistical maps were

thresholded at a level of p=0.001 uncorrected (Whalley, et al., 2009), and regions were considered significant at a p<0.001. These correlation analyses were done for schizophrenia men and women separately at the whole-brain level. For the first and second-level statistical analyses only contiguous voxels greater than or equal to 5 were considered as significant.

Behavioral data analyses:

Recognition accuracy was measured by taking into account both the hit and false alarm rate. The hit rate is defined as the number of old slides correctly identified as having been seen before divided by the total number of old slides and false alarm rate is characterized by the number of distractor slides incorrectly identified as seen before divided by the total number of distractor slides (Hall et al., 2007). The recognition accuracy was calculated as the difference between the hit and false alarm rate with a maximum value of +1 (perfect recognition of stimuli presented during incidental encoding) and a minimum value of -1 (falsely reporting that they had previously seen every new picture).

To examine ratings of emotional stimuli and recognition accuracy we conducted a repeated measures ANOVA with image type (i.e. positive, negative and neutral) as a within subject factor and group and sex as between subject factors. The source of significant group or stimulus effects was further investigated using post hoc t-tests.

Recognition accuracy data from 4 subjects (one in each group) were missing due to recording errors while the participants were being scanned and the subjective rating data from 4 subjects were missing (2 healthy women, 1 healthy man and 1 schizophrenia man). The demographic, clinical and behavioral data was analyzed using the IBM Statistical Package for the Social Sciences (SPSS), version 19.0.

Results

Behavioral results

For the subjective emotional responses to the images (Figure 1), we found a significant main effect of condition ($F(2)=511.55$, $p<0.001$) as well as a significant interaction between group and condition ($F(2)=8.26$, $p<0.001$). There were no significant group ($F(1)=2.11$, $p>0.05$) or sex differences ($F(1)=0.081$, $p>0.05$). Post-hoc t-tests revealed that healthy controls rated both the positive and negative images as being more emotionally salient than the neutral images (Positive vs. Neutral: $t(37)=16.69$, $p<0.001$; Negative vs. Neutral: $t(37)=22.97$, $p<0.001$). The same pattern was seen in the patient group (Positive vs. Neutral: $t(39)=14.84$, $p<0.001$; Negative vs. Neutral: $t(39)=15.78$, $p<0.001$). Further investigation revealed that despite a lack of group differences in the experience of emotional stimuli, individuals with schizophrenia rated the neutral images as being more emotional than did healthy subjects ($t(77)=-3.24$, $p<0.002$).

The analysis of recognition accuracy (Figure 2) revealed a significant main effect of group ($F(1)=39.184$, $p<0.001$), a significant main effect of condition type ($F(2)=13.69$, $p<0.001$) and an interaction between condition type and group ($F(2)=6.73$, $p<0.002$). No significant effect of sex was observed ($F(1)=0.045$, $p>0.05$). Post-hoc t-tests confirmed that patients with schizophrenia had a worse recognition memory performance relative to the healthy controls for the positive ($t(77)=6.63$, $p<0.001$), negative ($t(77)=3.51$, $p<0.001$) and neutral pictures ($t(77)=6.33$, $p<0.001$). In addition, the post-hoc analysis revealed that schizophrenia patients had an increased recognition accuracy for negative compared to neutral images ($t(38)=4.34$, $p<0.001$) and positive compared to neutral images ($t(38)=1.74$, $p<0.09$), although this effect only approached significance. Healthy controls, on the other hand, demonstrated a superior mnemonic performance for the emotional relative to neutral images (Positive vs. Neutral: $t(38)=4.57$, $p<0.001$; Negative vs. Neutral: $t(38)=2.09$, $p<0.043$).

fMRI results in individual groups

Brain activations during recognition memory of positive images (Table 2)

Men: During the recognition memory of positively valenced images, healthy men activated the visual cortex, fusiform gyrus, middle and inferior temporal gyrus, cerebellum, superior and inferior parietal gyrus, inferior and middle frontal gyrus, the amygdala and hippocampus. Schizophrenia men had activations in the visual cortex, fusiform and inferior temporal gyrus, cerebellum, inferior parietal and postcentral gyrus, precuneus, middle and inferior frontal gyrus, hippocampus, amygdala and the anterior temporal pole.

Women: Healthy women activated the visual cortex, fusiform gyrus, cerebellum, regions of the prefrontal cortex, precentral gyrus, supplementary motor area, pallidum, thalamus, insula and hippocampus. Women with schizophrenia activated regions of the visual cortex, fusiform gyrus, inferior frontal gyrus, precentral gyrus, supplementary motor area, hippocampus, parahippocampal gyrus and middle temporal pole.

Brain activations during recognition memory of negative images (Table 3)

Men: Healthy men activated the visual cortex, fusiform and inferior temporal gyrus, superior and inferior parietal gyrus, inferior frontal gyrus, amygdala and the hippocampus. Similarly, men with schizophrenia had activations in regions of the visual cortex, fusiform gyrus, superior and inferior parietal gyrus, inferior frontal gyrus and the medial orbitofrontal cortex.

Women: During recognition memory of negative images healthy women activated the visual cortex, fusiform gyrus, inferior temporal gyrus, thalamus, pallidum, superior and inferior parietal cortex, inferior and middle frontal gyrus, inferior OFC, precentral gyrus, supplementary motora area, cerebellum, insula, amygdala, hippocampus and anterior temporal pole. Schizophrenia women activated the visual cortex, fusiform gyrus, inferior parietal and frontal gyrus.

fMRI results of between group differences

Brain activations during recognition memory of positive images (Table 4 and Figure 3)

Men: Schizophrenia men, in comparison to healthy men, had increased activations in the inferior and middle temporal gyrus, regions of the parietal cortex, the superior frontal and precentral gyrus, lingual gyrus, cerebellum, insula, amygdala, anterior temporal pole and parahippocampal gyrus.

Women: Schizophrenia women showed decreased activity in the lingual gyrus, rolandic operculum, middle and inferior frontal gyrus, vermis and calcarine gyrus compared to healthy women.

Brain activations during recognition memory of negative images (Table 5 and Figure 4)

Men: Men with schizophrenia activated the medial prefrontal gyrus to a greater degree than healthy men.

Women: Women with schizophrenia activated significantly fewer brain regions relative to healthy women including the cerebellum, thalamus, pallidum, regions of the temporal and visual cortex, supplementary motor area, superior parietal and precentral gyrus, amygdala, middle cingulated gyrus, anterior temporal pole and the hippocampus.

Correlation analyses between cerebral activations and clinical symptoms

Relationship between clinical symptoms and brain function during recognition of positive stimuli (Table 6)

Women: We observed a negative relationship between negative symptoms and the brain activations associated with memory of positive images in the superior parietal gyrus, inferior frontal gyrus and angular gyrus. A negative relationship also surfaced between positive symptoms and activations in the insula. Finally, a positive correlation between positive symptoms and brain activations in the precentral gyrus was observed.

Relationship between clinical symptoms and brain function during recognition of negative stimuli (Table 7)

Women: The analyses revealed a negative relationship between positive symptoms and cerebral activations in the left inferior frontal gyrus. Thus, the greater the positive symptoms in women the less the inferior frontal gyrus is activated during recognition memory of aversive images. A similar negative relationship was observed between negative items of the PANSS and the right inferior frontal gyrus.

Men: A significant negative correlation was observed between negative symptoms and brain activations in the anterior temporal pole, insula, precuneus, middle frontal gyrus, middle and superior temporal gyrus, cerebellum and supplementary motor area.

Discussion

We observed activations of distinct neural networks in healthy and schizophrenia men and women during the recognition memory of emotionally positive and negative stimuli. Women with schizophrenia had decreased brain activations relative to healthy women. In contrast, men with schizophrenia demonstrated an overall comparable pattern of brain activations during recognition of negative stimuli and a substantial increase in brain activity during the recognition of positively laden pictures relative to healthy men. Moreover, the correlation analysis revealed distinct relationships between brain function and symptoms in schizophrenia men versus women.

Behavioral data

We did not observe significant sex differences in behavior. Healthy controls and individuals with schizophrenia reported a comparable experience of the emotional pictures but the patient group had a decreased recognition accuracy of the emotional images relative to healthy participants. Our observation of similar subjective experience of emotionally laden stimuli among individuals with schizophrenia and healthy subjects is a well-established finding (Aghevli et al., 2003; Berenbaum & Oltmanns, 1992; Iwase et al., 1999; Kring et al., 1993; Kring & Moran, 2008; Kring & Neale, 1996). This finding,

in conjunction with the differences in the pattern of cerebral activations between patients and healthy subjects, provides further support for the notion of a discrepancy between the experience and expression of emotion in schizophrenia (Kring & Neale, 1996; Hempel et al., 2005; Takahashi et al., 2004). Despite patient's decreased performance relative to the healthy controls, the emotional memory effect was preserved in both groups such that more emotional than neutral pictures were accurately recognized. This result is consistent with previous reports that emotionally valenced stimuli enhance memory relative to neutral stimuli (Hamann, 2001; LaBar & Cabeza, 2006).

fMRI data

Despite comparable behavioral performances men and women with schizophrenia had very different pattern of brain activations during both positive and negative recognition memory relative to same-sex controls. Previous studies in the general population have observed comparable mnemonic performance between the sexes but qualitatively differential pattern of brain activations during emotional memory suggesting the use of distinct yet equally effective cognitive strategies in men and women (Bremner, et al., 2001; Canli, et al., 2002; Piefke, et al., 2005). It has been proposed that memory processing in women relies on a more detailed elaboration of information while memory processing in men is mainly driven by schemas or overall information theme (Meyers-Levy & Maheswaran, 1991; Meyers-Levy & Tybout, 1989). However, in the present study we did not include any means to assess the participant's potential cognitive strategies during scanning and so it remains unknown if men and women in both groups differed regarding their strategies of encoding and generating responses during the memory tasks. Future studies may clarify this possibility.

During the recognition memory of negative images, women with schizophrenia showed less activation compared to healthy women in an extensive network of brain

regions that included cortical (e.g. middle cingulate gyrus and subcortical limbic structures (e.g. thalamus, amygdala, hippocampus). During the positive condition, schizophrenia women showed decreased activity in a smaller network of brain regions that included the cerebellar vermis as well as the middle and inferior frontal gyrus. This pattern of findings mimics other studies outlining deficits in the cerebral activations associated with episodic memory (Achim & Lepage, 2005; Ragland et al., 2009) and the processing of emotion (Gur et al., 2002; Schneider et al., 1998; Takahashi, et al., 2004) in individuals with schizophrenia compared to healthy controls.

Men with schizophrenia, on the other hand, showed an increase in brain activations compared with healthy men during positive and negative recognition memory. The medial prefrontal cortex, activated more in schizophrenia men relative to healthy men during negative recognition memory, is thought to be essential for mediating interactions between cognition and emotion (Gusnard et al., 2001; Ochsner et al., 2002; Taylor et al., 2003). Two previous functional neuroimaging studies have reported increased activations in the medial prefrontal cortex in patients relative to healthy participants during processing of emotional material (Hempel et al., 2003; Taylor et al., 2005). Of particular relevance, Taylor and colleagues (Taylor, et al., 2005) asked subjects to view aversive images selected from the IAPS collection (similar to the content of our task) and provide on-line subjective ratings of each image. Similarly to the present results in male patients, they observed overall no group differences except for an increase in activation in schizophrenia participants in the left medial prefrontal cortex (despite comparable emotional experience). The authors put forward that activity in this region may play a compensatory role. Similarly, Hempel and colleagues (2003), in an emotion-labelling task (positive and negative emotion combined) observed an increase in activity in the medial prefrontal cortex in individuals with schizophrenia relative to healthy participants despite a significant decrease in performance. Again, the

authors suggested that this activity could reflect a compensatory, yet inefficient, effort for deficits in more basal limbic functions.

With regards to the recognition of the positive images, men with schizophrenia had increased activations in comparison to healthy men in regions associated with emotional processing (insula, anterior temporal pole, amygdala), as well as those implicated more generally in episodic memory (parietal and temporal cortex). The lateral/posterior parietal cortex (angular, supramarginal gyrus and superior parietal lobule) and medial parietal cortex (precuneus) have been implicated in the successful retrieval of episodic memories (Cabeza et al., 2008; Davidson et al., 2008; Sestieri et al., 2011; Wagner et al., 2005) and have been found to be activated during successful recognition in individuals with schizophrenia (Lepage et al., 2010). Of relevance, the dorsal parietal (BA 7) and ventral parietal cortex (BA 39/40) are suggested to reflect top-down and bottom-up attention processes that interact closely during episodic memory retrieval (Cabeza, et al., 2008); and it has been suggested that activity in the dorsal parietal cortex increases as a function of retrieval effort (Cabeza, 2008; Cabeza, et al., 2008). Although top-down attention processing may not be of primary importance in a simple yes/no recognition memory task, we can reason that men with schizophrenia, relative to healthy men, are increasing their retrieval efforts during the memory paradigm, albeit ineffectively in light of their inferior performance.

Despite its prominent role in the modulation of negative emotional memories, a role for the amygdala in the processing of positive emotional memories has also been observed (Hamann et al., 1999). This region is suggested to play an important role in filtering, gating, and processing emotional information (Grace, 2000; Laviolette, 2007; Phelps, 2006). Hence, it is possible that the increased activity in the right amygdala in patient men reflects an impaired gating of sensory input containing emotion. Kosaka et al. (2002) put forth a similar interpretation when they observed exaggerated right

amygdala activity in patients compared to controls during recognition of positive facial expressions.

The majority of studies that have observed comparable or increased cerebral activations in patients relative to controls during processing of emotion and episodic memory did not examine the neural responses in men and women separately or contained samples that consisted mostly of males (An et al., 2003; Crespo-Facorro et al., 2001; Hempel, et al., 2003; Hempel, et al., 2005; Reske et al., 2009; Sergerie, et al., 2010; Taylor, et al., 2005). Thus, it is possible that in the above referenced studies men with schizophrenia exhibited less of a deficit in brain function relative to women. Although this notion remains highly speculative due to the clinical heterogeneity of tested patients, the differences in the task and stimuli used among studies and of course the lack of investigation of sex differences; it is reinforced by our previous work in which we observed an increase in brain function in patients relative to healthy controls during the recognition memory of positive images using overall the same patient sample as the present study (Lakis, et al., 2011). Specifically, our current findings show that it is men and not women with schizophrenia who were driving this increase in neural activity.

Despite aforementioned sex differences in the pattern of cerebral activations both men and women with schizophrenia failed to activate limbic areas, including the amygdala and hippocampus, during recognition of negative images. Two prominent negative emotions, fear and anger, have been shown to be particularly salient for individuals with schizophrenia (Mandal et al., 1998) and the neuroimaging literature supports the notion that abnormal amygdala and hippocampal functioning together with other regions that play an important role in the modulation of affect and emotional memories may be responsible for impaired emotion processing (particularly the perception of fear) in individuals with schizophrenia (Paradiso et al., 2003; Phillips, et

al., 2003; Phillips, et al., 1999; Russell et al., 2007; Schneider, et al., 1998; Takahashi, et al., 2004; Williams et al., 2004). In line with this idea, our current findings show that the overall inability to activate limbic and paralimbic areas in men and women with schizophrenia may be specific to negative emotion processing.

In addition to qualitative differences in the pattern of cerebral activations in men and women with schizophrenia, our results provide new evidence of different relationships in men and women between brain function associated with emotional recognition memory and specific symptomatology. We observed an inverse correlation between limbic regions (e.g. insula, anterior temporal pole, cerebellum) and negative symptoms only in men during recognition of negative pictures. The literature concerning the relationship between negative symptoms and activations in limbic areas has been somewhat inconsistent. For instance, an inverse relationship (Mendrek, et al., 2010), a positive relationship (Gur et al., 2007) or no significant correlation between negative symptoms and brain function during processing of unpleasant stimuli (Takahashi, et al., 2004), have been demonstrated.

Contrary to our expectations, we did not observe a significant relationship between positive symptoms and subcortical limbic structures activations in women. Nonetheless, an inverse correlation between activity in the insula and positive symptoms was present in women during recognition of positive images. The association of positive symptoms with activation in limbic regions during processing of emotional stimuli in individuals with schizophrenia has been previously reported. However, in these studies an association with psychotic symptoms (in particular paranoia) and overactivity of limbic regions (particularly the amygdala) during processing of threatening/aversive stimuli was reported (Phillips, et al., 1999; Taylor et al., 2002). Although not a subcortical limbic structure, the insula has afferent and efferent connections with the amygdala and other limbic regions that include the medial and

orbitofrontal cortices and anterior cingulate gyrus (Augustine, 1996). Activity in the insula has been associated with successful retrieval of items from emotional contexts (Hamann, 2001; LaBar & Cabeza, 2006), with internally generated recalled emotions and with cognitively demanding emotional tasks (Phan, et al., 2002). It should be mentioned that the patient sample recruited for this study were in a stable phase of their illness and so it is possible that there is insufficient variation in the positive symptoms of participants with schizophrenia to show a clear correlation with subcortical limbic structures. Examination of a more symptomatic group of patients could clarify this point.

In line with our hypotheses, we observed a negative correlation between negative symptoms and prefrontal cortex activation in men (during recognition of negative images) and women (during recognition of both negative and positive images). The inverse relationship between the presence of negative symptoms and prefrontal cortex activation is consistent with the findings of other studies indicating that negative symptoms of schizophrenia are related with “hypofrontality” (Semkovska et al., 2001; Weinberger & Berman, 1996). Likewise, we have previously noted an inverse relationship between the presence of negative symptoms and prefrontal cortex activation during the processing of sadness-inducing images in individuals with schizophrenia (Mendrek, et al., 2010). Overall, the correlation data show that the degree with which clinical symptoms are associated with cerebral activations during emotional recognition memory in men versus women depends on the valence of the presented stimuli, but more studies are needed in this area.

We would like to acknowledge that the interpretation of the present study is limited by the fact that old and new images were randomly intermixed within each block, and so cerebral activations associated with only correct retrieval of stimuli into memory could not be ascertained. Because of this, it is possible that other processes, rather than simply recognition, could have affected the pattern of cerebral activations; as such

our data more likely reflect an attempted retrieval process. Also, despite the fact that brain activity in response to new stimuli and old stimuli were not differentiated, both healthy controls and patients with schizophrenia (though to a lesser extent) demonstrated accuracy significantly above chance level, indicating that an accurate recognition process was taking place.

To conclude, we observed that the degree with which individuals with schizophrenia show an atypical pattern of activations in limbic, prefrontal and parietal regions during recognition of emotional pictures compared with healthy controls depends on whether the individual is male or female and depends, to a certain extent, on the valence of the presented stimuli. These findings, in conjunction with past functional neuroimaging literature (Guillem, et al., 2009; Jiménez, et al., 2010; Mendrek, et al., 2010 ; Mendrek, et al., 2007; Mendrek, 2009) demonstrate the importance of investigating men and women with schizophrenia separately in the context of emotional and cognitive tasks.

Table/Figure legends

Figure 1. Subjective ratings in schizophrenia and healthy men and women

HM=Healthy men, HW=Healthy women, SZ-M=Schizophrenia men, SZ-W=Schizophrenia women

Bars represent standard error of the mean

Figure 2. Recognition accuracy in schizophrenia and healthy men and women

HM=Healthy men, HW=Healthy women, SZ-M=Schizophrenia men, SZ-W=Schizophrenia women

Bars represent standard error of the mean

Figure 3. Cerebral activations associated with the recognition of positive images in schizophrenia and healthy men and women.

HM=Healthy men, HW=Healthy women, SZ-M=Schizophrenia men, SZ-W=Schizophrenia women

The colored bar represents the range of z-scores of the cerebral activations with significance increasing from light blue to orange.

Figure 4. Cerebral activations associated with the recognition of negative images in schizophrenia and healthy men and women.

HM=Healthy men, HW=Healthy women, SZ-M=Schizophrenia men, SZ-W=Schizophrenia women

The colored bar represents the range of z-scores of the cerebral activations with significance increasing from light blue to orange.

Table 1. Demographic and clinical characteristics of schizophrenia and healthy men and women.
SES = Socioeconomic status
SD=Standard deviation in parentheses
* = Significant $p<0.05$ between men and women

Table 2. Cerebral activations associated with the recognition of positive images in schizophrenia and healthy men and women.

* = Brain region is part of the same cluster
OFC=orbitofrontal cortex
SMA=Supplementary motor area
BA=Brodmann area; L/R=Left/Right

Table 3. Cerebral activations associated with the recognition of negative images in schizophrenia and healthy men and women.

* = Brain region is part of the same cluster
OFC=orbitofrontal cortex
SMA=Supplementary motor area
BA=Brodmann area; L/R=Left/Right

Table 4. Direct comparisons between groups of the same sex during recognition of positive images in schizophrenia and healthy men and women.

HM=Healthy men, HW=Healthy women, SZ-M=Schizophrenia men, SZ-W=Schizophrenia women
* = Brain region is part of the same cluster
BA=Brodmann area; L/R=Left/Right

Table 5. Direct comparisons between groups of the same sex during recognition of negative images in schizophrenia and healthy men and women.

HM=Healthy men, HW=Healthy women, SZ-M=Schizophrenia men, SZ-W=Schizophrenia women
SMA=Supplementary motor area
* = Brain region is part of the same cluster
BA=Brodmann area; L/R=Left/Right

Table 6. Correlations between brain activations and recognition memory of positive images in schizophrenia men and women

SZ-W=Schizophrenia women
BA=Brodmann area; L/R=Left/Right

Table 7. Correlations between brain activations and recognition memory of negative images in schizophrenia men and women

SZ-M=Schizophrenia men, SZ-W=Schizophrenia women
SMA=Supplementary motor area
BA=Brodmann area; L/R=Left/Right

Figure 1.

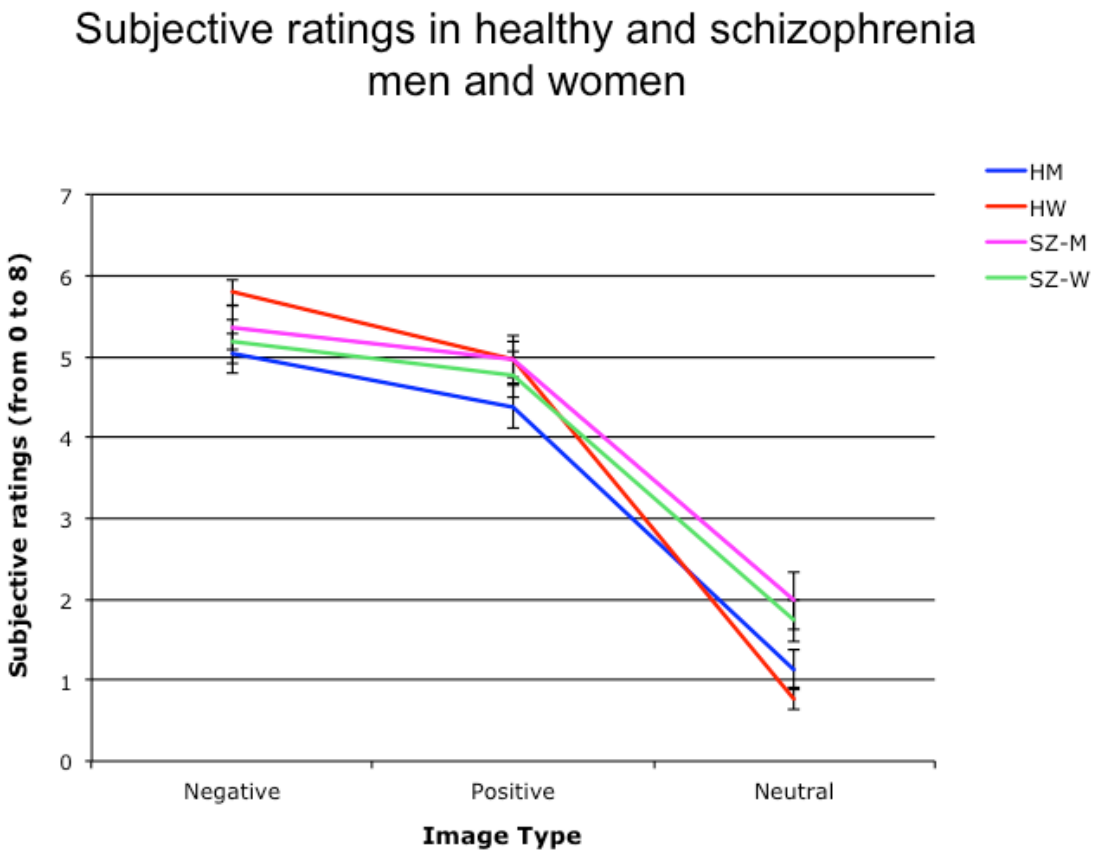
Subjective ratings in healthy and schizophrenia men and women
HM
HW
SZ-M
SZ-W
Subjective ratings (from 0 to 8)
0
1
2
3
4
5
6
7
Negative
Positive
Neutral
Image Type

Figure 2.

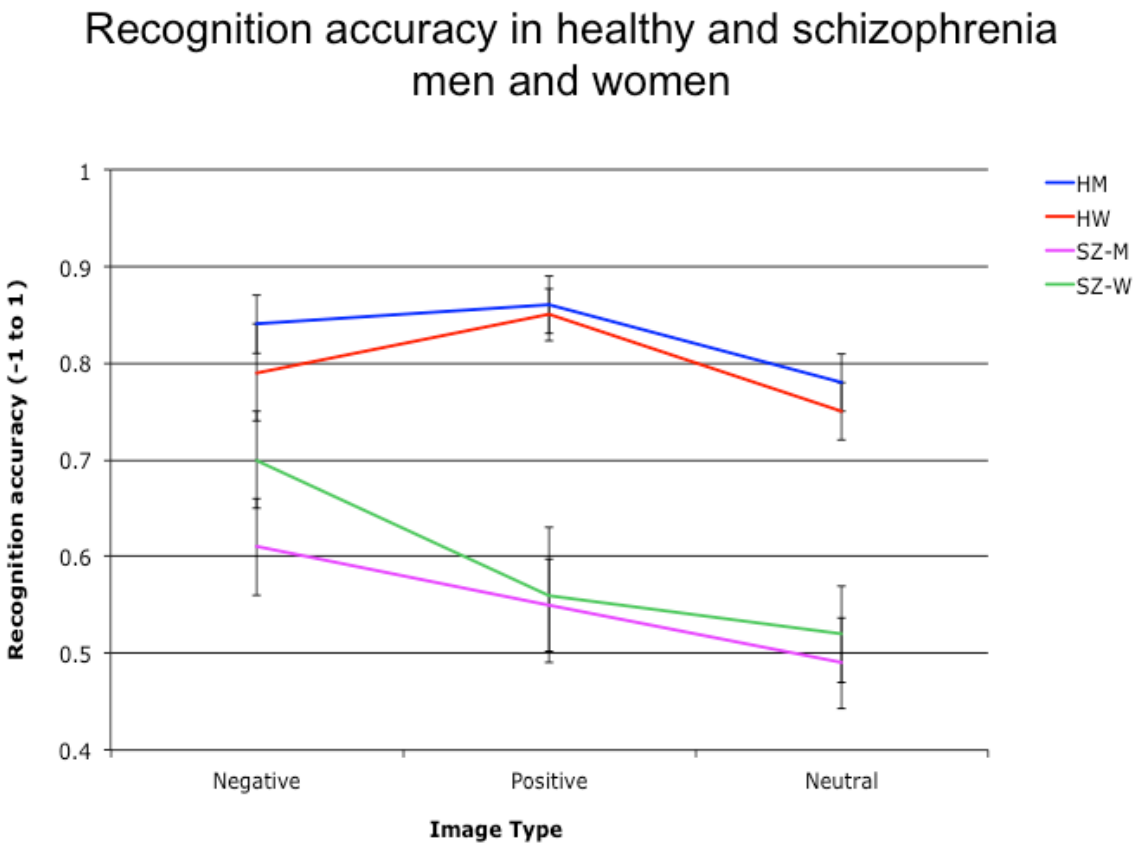
Recognition accuracy in healthy and schizophrenia men and women
Recognition accuracy (-1 to 1)
1
0.9
0.8
0.7
0.6
0.5
0.4
Negative
Positive
Neutral
Image Type
HM
HW
SZ-M
SZ-W

Figure 3.

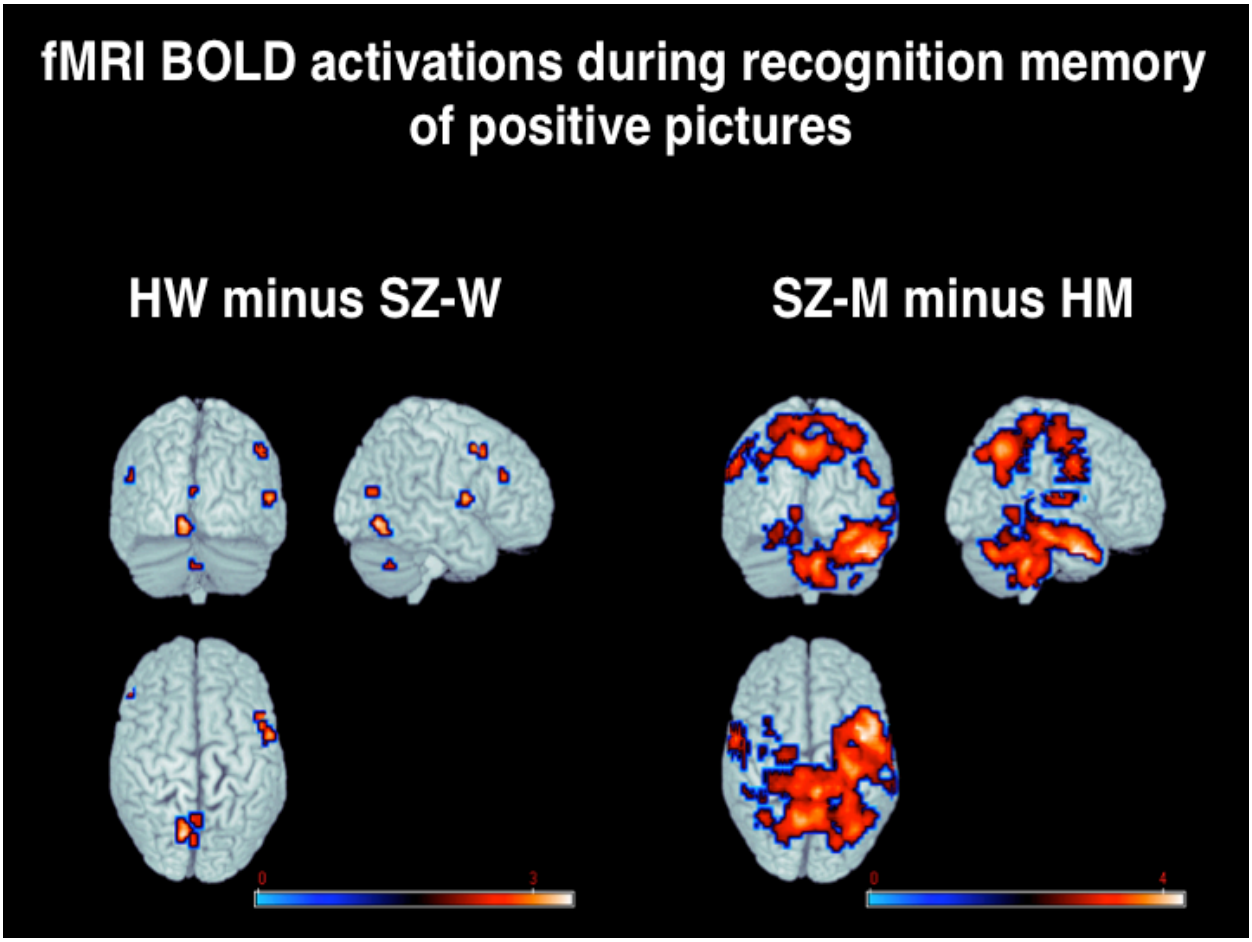
fMRI BOLD activations during recognition memory of positive pictures
HW minus SZ-W
SZ-M minus HM
0
3
0
4

Figure 4.

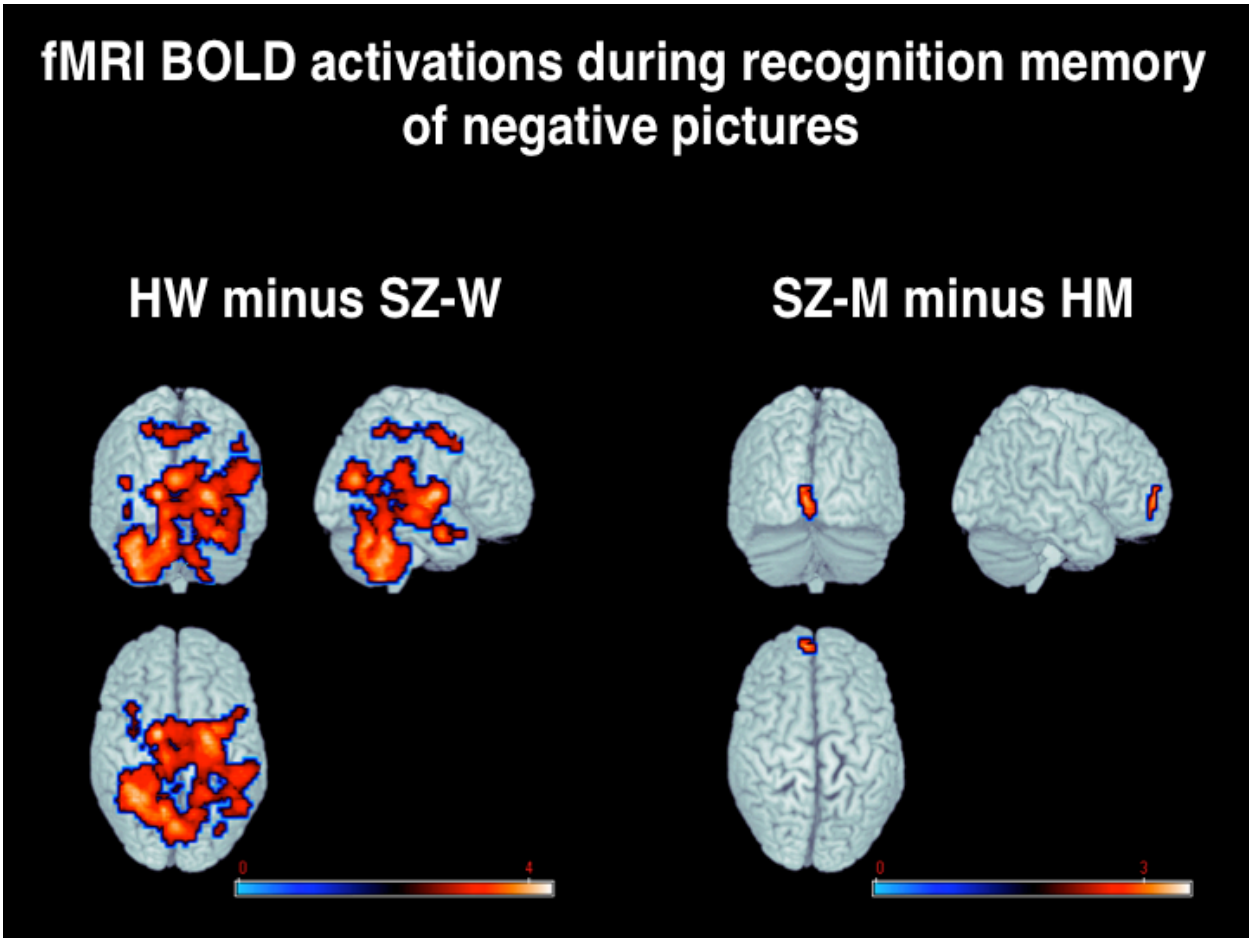
fMRI BOLD activations during recognition memory of negative pictures
HW minus SZ-W
SZ-M minus HM
0
4
0
3

Table 1. Demographic and clinical characteristics of men and women

	Subjects with schizophrenia		Normal control subjects	
	Women (N= 20)	Men (N= 21)	Women (N= 19)	Men (N= 22)
Age (years)	32.75 (6.37)	31.09 (7.42)	31.89 (8.86)	30.54 (7.81)
Parental SES	2.57 (1.06)	2.76 (0.75)	2.05 (1.11)	2.43 (1.11)
Handedness, No. right (%)	20 (89.37)	17 (59.4)	18 (68.36)	18 (54.36)
Age at onset (mean and SD)	24.55 (6.17)	20 (3.58) *		
Duration of Illness years (mean and SD)	8.2 (5.8)	11 (7.83)		
Chlorpromazine equivalents, mg	473.33 (306.9)	711.90 (377.16) *		
PANSS positive	19.80 (7.85)	18.14 (5.64)		
PANSS negative	21.2 (8.37)	19.52 (4.87)		
PANSS general	43.15 (12.85)	39.38 (6.16)		

Table 2. Brain activations during recognition of positive images

Anatomical area	L/R	Healthy women						Schizophrenia women					
		BA	MNI coordinates			Z-score	Voxels	BA	MNI coordinates			Z-score	Voxels
			x	y	z				x	y	z		
Fusiform gyrus	L	19	-28	-66	-14	5.34	5616	37	-35	-60	-14	6.30	4115
	R	37	35	-52	-18	5.63	*	37	32	-49	-18	6.33	*
Lingual gyrus	L	18	-4	-80	-10	5.64	*	18	-21	-80	-10	6.73	*
Superior occipital	R	18	10	-98	18	5.63	*	7	28	-66	38	3.87	*
Calcarine	L	17	-7	-91	-4	5.46	*	17	-10	-88	-7	6.74	*
Middle occipital	L	18	-14	-102	4	5.06	*	19	-24	-91	7	5.98	*
	R	19	32	-77	28	3.79	*	18	24	-91	4	7.01	*
Cerebellum	L	-	-28	-60	-58	3.51	21						
Hippocampus	L	-	-21	-21	-14	3.49	49	-	-21	-28	-7	3.64	76
	R	-	21	-28	-7	3.12	10	-	21	-28	-4	3.73	110
Parahippocampal gyrus	L							28	-18	-28	-14	3.70	100
Middle temporal pole	R							38	35	7	-32	3.25	7
Inferior frontal	R	9	60	14	32	4.35	490	9	42	7	24	4.13	178
Middle frontal	R	6	49	-4	52	4.06	*						
Inferior OFC	R	47	35	32	-7	3.55	*						
Insula	R	47	38	28	-4	3.48	*						
Inferior frontal	L	46	-52	28	24	3.83	128						
Precentral gyrus	L	6	-49	0	35	3.28	22	9	-42	4	35	4.04	74
Inferior OFC	L	47	-38	32	-18	3.74	83						
SMA	L	6	-4	-7	56	3.36	90	6	-4	7	56	3.45	18
	R	6	10	7	70	3.75	*						
Superior medial frontal	L	10	-10	63	32	3.47	11						
	R	8	4	35	57	3.29	8						
Pallidum	L	-	-21	0	4	3.22	15						
Thalamus	R	-	21	-28	-4	3.12	10						
		Healthy men						Schizophrenia men					
Middle occipital	L	17	-18	-94	-4	7.72	5006						
	R	18	28	-88	0	7.19	*	19	28	-88	14	5.43	4995
Calcarine	L							17	7	-94	0	6.66	*
	R	17	14	-94	4	7.39	*						
Fusiform	L	19	-35	-70	-14	7.23	*	19	-32	-74	-18	5.57	*
	R	19	35	-63	-18	7.16	*	20	35	-38	-24	6.25	*
Lingual	L							30	-14	-32	-4	4	*
	R	17	24	-91	-4	7.10	*	18	10	-84	-14	6.23	*
Inferior occipital	L							19	-35	-80	-7	5.54	*
	R	18	32	-84	-4	7.04	*						
Cuneus	L							19	-7	-94	28	4.47	*
	R							19	10	-91	28	5.02	*
Middle temporal	L	37	-46	-70	7	6.2	*						
Inferior temporal	R	37	49	-63	-4	6	*	21	42	-4	-32	3.83	20
Cerebellum	L	-	-7	-74	-32	5.26	*	-	-10	-84	-18	5.76	*
	R	-	7	-70	-35	4.75	*						
Superior parietal	L	7	-24	-56	42	5.21	*						
Inferior parietal	L	40	-46	-38	46	3.80	8	40	-46	-42	52	3.95	56
Postcentral gyrus	L							2	-49	-24	49	4.11	*
Precuneus	R							7	4	-70	38	3.84	*

Hippocampus	L	-	-24	-28	-6	4.82	98	-	-18	-28	-7	4	12
	R	-	24	-28	-6	4.98	71	-	18	-32	-4	4.14	72
Amygdala	L	-	-24	-7	-12	4.61	42	-	-21	0	-21	3.74	5
	R							-	28	4	-28	3.83	15
Anterior temporal pole	L							28	-28	7	-24	3.74	8
Inferior frontal	L	44	-46	10	24	5.78	219						
	R	9	52	14	32	6.42	392	9	49	7	28	3.92	18
Middle frontal	R	6	38	-4	52	4.20	29	6	38	-7	52	3.90	5

Table 3. Brain activations during recognition of negative images

Anatomical area	L/R	Healthy women						Schizophrenia women					
		BA	MNI coordinates			Z-score	Voxels	BA	MNI coordinates			Z-score	Voxels
			x	y	z				x	y	z		
Middle occipital gyrus	L	19	-42	-84	10	6.47	7995	19	-24	-91	7	5	2976
	R	39	42	-77	14	6.43	*	18	32	-84	0	5.65	*
Inferior occipital gyrus	L							19	-38	-66	-10	5.84	*
	R	18	46	-80	-10	6.28	*						
Calcarine fissure	L	17	-7	-91	-7	5.82	*	18	4	-84	-4	5.85	*
Cuneus	R	18	10	-98	18	5.72	*						
Inferior temporal	R	37	49	-63	-10	5.79	*						
Fusiform	L	19	-32	-66	-14	5.70	*	37	-38	-56	-14	5.75	*
	R	37	42	-49	-18	5.77	*	10	38	66	-14	5.73	*
Lingual gyrus	R	18	7	-84	-7	5.65	*	18	18	-80	-14	5.97	*
Thalamus	L	-	-14	-10	0	3.68	*						
Pallidum	R	-	24	-11	-4	3.69	*						
Superior parietal	L	7	-10	-84	49	5.19	*						
Inferior parietal	L	7	-28	-56	52	4.26	*	40	-35	-42	42	3.61	32
Inferior OFC	L	47	-38	32	-18	3.48	22						
Inferior frontal	L	45	-46	24	18	3.69	347						
Middle frontal	L	9	-56	18	35	3.37	*						
Precentral	L	20	-35	-7	-46	3.56	*						
Inferior frontal gyrus	R	46	52	21	24	5.15	721	9	46	7	28	3.32	6
Middle frontal	R	6	49	-4	52	3.81	*						
Precentral	R	9	42	4	32	4.84	*						
Insula	R	47	38	28	-4	3.75	*						
SMA	R	6	7	10	52	3.55	170						
Superior frontal	R	6	18	4	74	3.46	*						
Hippocampus	L	-	-32	-7	-28	3.53	49						
Amygdala	L	-	-24	0	-18	3.20	26						
	R	-	28	0	-28	3.11	10						
Anterior temporal pole	L	38	-32	10	-24	3.03	63						
Insula	L	13	-32	24	0	3.04	7						
Cerebellum	L	-	-21	-32	-46	3.19	12						
		Healthy men						Schizophrenia men					
Fusiform gyrus	L	37	-35	-63	-10	6.85	4165	37	-35	-60	-21	5.29	3701
	R	37	42	-49	-18	7.8	*	37	32	-49	-21	5.54	*
Inferior temporal gyrus	R	37	42	-63	-10	7.33	*	37	42	-60	-10	5.51	*
Middle occipital	L	19	-24	-91	4	5.94	*	19	-35	-84	0	5.24	*
	R	39	42	-77	14	6.31	*	19	42	-74	4	4.78	*
Inferior occipital	L	19	-42	-74	-10	6.34	*	19	-35	-80	-10	5.18	*
	R	19	42	-74	-4	6.85	*	19	35	-74	-4	5.34	*
Superior occipital	R							19	14	-98	24	5.67	*
Calcarine gyrus	R	17	10	-94	0	6.64	*	17	10	-94	4	5.81	*
Cuneus	R	18	14	-98	7	6.54	*	18	21	-94	10	5.59	*
Lingual gyrus	R	18	7	-84	-7	6.53	*	18	14	-56	4	3.87	*
Superior parietal	R	7	28	-60	49	4.53	*	7	28	-70	52	3.46	39
Inferior parietal	L	7	-28	-52	46	4.73	45	40	-35	-42	42	4.24	41
Amygdala	L	-	-28	0	-18	4.63	28						

	R	-	32	-2	-14	4.09	12						
Hippocampus	L	-	-14	-28	-10	4.68	48						
	R	-	21	-32	-7	5.20	97						
Inferior frontal	L	9	-42	14	28	5.20	222	46	-46	18	24	3.24	5
	R	9	46	14	24	5.63	209	9	49	7	28	3.29	12
Medial OFC	L							11	-4	52	-14	3.63	5

Table 4. Direct comparisons between groups of the same sex during recognition of positive images in schizophrenia and healthy men and women.

Anatomical area	L/R	HW greater than SZ-W					
		BA	MNI coordinates			Z-score	Voxels
			x	y	z		
Lingual gyrus	L	18	-10	-74	-10	3.15	29
Rolandic operculum	R	6	60	0	7	3.04	16
Middle frontal	R	8	52	14	42	2.89	16
Vermis	R	-	0	-63	-42	2.73	9
Inferior frontal	L	46	-52	28	21	2.71	6
Calcarine	L	23	-4	-77	10	2.66	9
		SZ-M greater than HM					
Inferior temporal	R	20	46	-4	-32	3.85	1132
Middle temporal	R	21	52	4	-32	3.81	*
Precuneus	L	7	-4	-63	42	3.69	728
	R	7	7	-56	42	3.57	*
Postcentral	R	3	24	-38	60	3.40	*
Postcentral gyrus	L	6	-60	-4	35	3.55	71
Precentral	L	4	-52	-7	46	3.13	*
	R	6	32	-14	49	3.35	135
Superior frontal	R	24	21	-4	52	2.91	*
Angular gyrus	L	40	-38	-49	32	2.81	20
Inferior parietal	L	40	-49	-42	38	2.66	*
Angular gyrus	R	39	46	-63	28	3.24	42
Lingual	L	18	-10	-52	-4	2.96	55
Cerebellum	L	-	-10	-60	-21	2.83	*
	R	-	38	-56	-52	2.88	10
Anterior temporal pole	L	28	-32	4	-28	2.92	11
Parahippocampal gyrus	L	36	-24	-35	-14	2.90	41
Inferior temporal	L	36	-35	-32	-14	2.70	*
Amygdala	R	-	32	0	-28	3.09	33
Insula	L	13	-38	-10	21	2.75	5

Table 5. Direct comparisons between groups of the same sex during recognition of negative images in schizophrenia and healthy men and women.

Anatomical area	L/R	BA	MNI coordinates			Z-score	Voxels
			x	y	z		
		HW greater than SZ-W					
Cerebellum	L	-	-35	-56	49	3.84	1926
thalamus	L	-	-14	-7	4	3.79	*
pallidum	R	-	24	-10	4	3.75	*
Inferior temporal	R	37	46	-52	-18	3.04	*
Inferior temporal	L	36	-42	-38	-10	2.92	13
Superior temporal	L	41	-42	-38	10	3.08	21
calacarine	L	18	0	-74	14	3.62	204
Cuneus	R	31	21	-70	21	2.99	*
Middle occipital	R	19	35	-74	7	2.86	13
Amygdala	R	-	32	-4	-28	3.53	35
Middle temporal gyrus	R	21	46	0	-28	3.01	69
Middle cingulum	L	24	-7	-7	46	3.14	104
	R	24	7	-10	49	2.95	*
SMA	R	24	4	-4	46	3.01	*
Superior temporal pole	L	38	-35	10	-24	2.92	30
Hippocampus	L	-	-32	-4	-28	2.79	25
Superior parietal	L	7	-21	-52	52	3.04	23
Precentral	R	9	52	7	38	2.89	21
Lingual	L	18	-10	-52	-4	2.74	8
		SZ-M greater than HM					
Medial prefrontal gyrus	L	10	-7	56	0	3.25	28

Table 6. Correlations between brain activations and recognition memory of positive images in schizophrenia men and women

Positive Emotion	L/R	BA	Anitomical area	MNI coordinates			Z-score	Voxels
				x	y	z		
SZ-W	Negative correlation – Negative symptoms							
	L	7	Superior parietal gyrus	-21	-56	42	3.44	39
	R	9	Inferior frontal gyrus	32	7	28	3.11	24
	L	9	Inferior frontal gyrus	-42	4	24	2.95	8
	R	7	Angular gyrus	24	-60	42	3.00	10
	Positive correlation – Negative symptoms							
	R	4	Precentral gyrus	35	-24	49	3.07	23
	Negative correlation – Positive symptoms							
	R	13	Insula	32	24	7	3.04	12

Table 7. Correlations between brain activations and recognition memory of negative images in schizophrenia men and women

Negative Emotion	L/R	BA	Anitomical area	MNI coordinates			Z-score	Voxels
				x	y	z		
SZ-M	Negative correlation – Negative symptoms							
	R	38	Anterior temporal pole	52	4	-7	3.73	301
	R	22	Insula	49	-4	0	3.57	*
	R	41	Superior temporal gyrus	56	-24	10	3.08	*
	R	7	Precuneus	7	-46	60	3.33	171
	L	21	Middle temporal gyrus	-63	-24	-4	3.26	64
	R	9	Middle frontal gyrus	28	49	35	3.17	74
	R	-	Cerebellum	7	-77	-46	3.02	71
	L	-	Cerebellum	-18	-70	-52	3.00	*
	R	6	SMA	4	-18	63	3.01	72
	L	8	Middle frontal gyrus	-28	35	42	3.02	8
SZ-W	R	46	Inferior frontal gyrus	52	38	10	3.10	15
SZ-W	Negative correlation – Positive symptoms							
	L	46	Inferior frontal gyrus	-49	42	13	2.98	8

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V. General Discussion

The research documented in this thesis is the first to: (1) examine the neural correlates of emotional recognition memory of stimuli that differed in both valence (positive vs. negative) and arousal (high vs. low) in individuals with schizophrenia and (2) to reveal distinct pattern of brain activations associated with emotional recognition memory in men and women with schizophrenia.

In the first study, we observed that, relative to healthy controls, individuals with schizophrenia had a similar pattern of brain activations during the recognition of highly arousing positive and neutral images and decreased brain activations during the recognition of negative pictures. This was observed despite an overall inferior recognition memory performance in patients with schizophrenia compared with healthy controls. Moreover, patients with schizophrenia resembled healthy controls such that both groups showed increased brain activations during the recognition of high relative to low arousing images, which paralleled the comparable subjective ratings of the emotional stimuli in both groups.

In the second study, we uncovered sex differences in the cerebral activations associated with the recognition memory of positively and negatively valenced pictures. Specifically, men with schizophrenia demonstrated an increased pattern of brain function compared to healthy men while women with schizophrenia showed decreased activations relative to their healthy same-sex counterparts. Interestingly, the extent of sex differences within groups of the same sex (e.g. healthy men vs. schizophrenia men) depended on the valence of the presented stimuli. For instance, men with schizophrenia activated an extensive network of brain regions encompassing regions of the limbic, parietal and temporal cortex in the positive condition compared to healthy men, but only activated the medial prefrontal gyrus to a greater degree than healthy men during the negative condition. In addition, we observed that clinical symptoms were significantly

associated with brain function during positive emotional memory in women and during negative emotional memory primarily in men. These findings suggest that the degree with which clinical symptoms are associated with cerebral activations during emotional recognition memory in men versus women depends on the valence of the presented stimuli.

The numerous studies that have investigated the processing of emotional material and episodic memory in individuals with schizophrenia have generally reported a pattern of decreased cerebral activations relative to healthy subjects in several regions implicated in affect (e.g., hippocampus, amygdala, medial prefrontal, orbitofrontal cortex, and cingulate cortices) and episodic memory (e.g. parietal, prefrontal cortex) (Achim & Lepage, 2005; Gur, et al., 2002; Schneider, et al., 1998; Takahashi, et al., 2004). Others, however, have observed either an increased or a similar pattern of cerebral activations between both groups (Crespo-Facorro et al., 2001; Dowd & Barch, 2010; Kosaka et al., 2002; Reske et al., 2009; Zierhut et al., 2010). It is clear that the lack of straightforward findings in emotion, episodic memory and more recently emotional episodic memory studies cannot easily be reconciled. However, based on the findings of meta-analyses investigating both emotion and memory processing in schizophrenia, the general consensus is that patients with schizophrenia present with a decreased pattern of brain function compared with controls (Achim & Lepage, 2005; Li et al., 2010). Interestingly, the findings of our first study illustrate that the extent with which individuals with schizophrenia activate or deactivate neural networks during the processing of emotional memory depends both on the valence and arousal levels of presented stimuli. To date, several studies have focused solely on investigating the processing of negative emotion in schizophrenia perhaps because, despite a general impairment in the perception of emotion, individuals with schizophrenia are highly sensitive to certain negative emotions of fear

and anger (Mandal et al., 1998). Of the studies that have included both negative and positive stimuli, arousal levels across emotional valence categories were often not equated or the analysis of high vs. low arousing stimuli was not investigated. Hence, it is possible that when stimuli are appropriately matched in terms of arousal, the positive stimuli, relative to negative, elicit more cerebral activations, especially for highly arousing images (which is where our most robust finding came from).

The findings of our second study further demonstrated that the degree with which patients with schizophrenia show deficits in brain activations during the recognition of emotional memories depends on whether the patient is male or female. For instance, of the studies that have observed comparable or increased cerebral activations in patients relative to controls during processing of emotion and memory, very few have included women and, even when they did, the sample sizes were typically too small to allow for examination of sex differences (An et al., 2003; Crespo-Facorro, et al., 2001; Hempel et al., 2003; Hempel et al., 2005; Reske, et al., 2009; Sergerie, et al., 2010; Taylor et al., 2005). Thus, it is possible that in the above referenced studies men with schizophrenia exhibited less of a deficit in brain function relative to women (as was observed in our second study). Although this notion is tentative due to the clinical heterogeneity of tested patients, as well as differences in the task and stimuli used among studies and of course the lack of investigation of sex differences; it is reinforced by our first study in which we observed an increase in brain function in patients relative to healthy controls during the recognition memory of high arousal positive and neutral images using overall the same patient sample (Lakis et al., 2011). Specifically, our second study illustrates that the increased neural activation is largely driven by male patients.

Valence and arousal are generally treated as independent factors, but real-world experience and laboratory studies (including our own) suggest that they often interact

with one another (Canli, et al., 2002; Hall, et al., 2007; Lane et al., 1999). Unfortunately, few studies have systematically investigated the interaction between arousal and valence as well as investigating sex differences. Our research group has recently taken strides in this area by uncovering sex differences in healthy participants, mediated by both valence and arousal, in the ERP responses associated with emotional episodic memory (Glaser et al., 2012). Bearing this in mind, an analysis of sex differences in patients with schizophrenia using stimuli that differ in both valence and arousal in the context of an emotional memory paradigm warrants further attention. Combined, the results of the present thesis emphasize the importance of taking the affective valence and arousal levels of emotional stimuli as well as the sex of tested individuals into account when designing experimental tasks focusing on the interaction between cognition and emotion.

Differences in the cognitive strategies used during the encoding and/or recognition of emotional information may have contributed to the observed group and sex-specific differences during performance of the emotional memory paradigm. Some studies have observed that individuals with schizophrenia are just as likely as healthy controls to spontaneously use encoding strategies facilitating the retrieval of verbal stimuli (Kirchhoff, 2009). However, most studies have found that patients with schizophrenia fail to generate effective mnemonic strategies during the encoding and subsequent retrieval of information into memory (Iddon et al., 1998; Koh, 1978) but when prompted to use strategies that incite deep semantic processing of certain stimuli, they show an enhancement in memory performance (Bonner-Jackson, et al., 2005; Koh & Peterson, 1978; Ragland et al., 2005; Ragland et al., 2003). This effect is reportedly greater during the incidental encoding of material into memory (Bonner-Jackson et al., 2008). Further, the results of Bonner-Jackson and colleagues (2008) show that when

memory strategies are provided, patients with schizophrenia activate the same neural systems implicated in memory formation as healthy controls.

With regards to the general population, some studies suggest the existence of differences in the way men and women process information and in the cognitive strategies used to retrieve this information from memory. For instance, it has been hypothesized that males employ a schema-based strategy to assess recognition while females exhibit a greater tendency to engage in elaborate and detailed message processing and hence employ a detailed strategy during recognition (Meyers-Levy & Maheswaran, 1991; Meyers-Levy & Sternthal, 1991). Likewise, Fujita and colleagues (1991) have proposed the "affect-intensity" hypothesis, which suggests that women have a superior memory compared to men because they experience life events with a greater intensity and therefore more deeply encode such events into memory. Thus, according to the view of Fujita et al. (1991), women will have a similar pattern of cerebral activations during the recognition of emotional stimuli but to a greater degree than men. In contrast, if the subjective emotional experience of the presented stimuli is comparable between the sexes, the superior mnemonic performance in women would disappear and there would be no significant difference in the pattern of brain function. Subsequently, Seidlitz and Diener (1998) came forth with the "cognitive-style" hypothesis and postulated that men and women differ in their way of encoding, rehearsing and thinking about emotional experiences that will ultimately lead to differences in performance and to qualitatively distinct patterns of cerebral activations during the processing of emotional episodic memories. In addition, this view implies that any sex-specific difference in memory performance or brain activations will persist even if the subjective emotional experience of the presented stimuli is comparable between the sexes. Taking into consideration the qualitatively different pattern of brain activations that we observed in both healthy and schizophrenia men and women as well

as the comparable subjective emotional experience of the presented affective pictures observed between the sexes, we believe that the results of the current thesis fall in line with the "cognitive-style" hypothesis. Moreover, the sex differences in cerebral function in conjunction with the lack of sex differences in recognition accuracy may indicate the use of distinct yet equally effective cognitive strategies in men and women– a notion that has been proposed by previous studies with a similar pattern of findings (Bremner et al., 2001; Canli, et al., 2002; Piefke, et al., 2005). Our experimental memory task was designed in such a way that participants were not instructed to try and remember the pictures presented during encoding but they were still aware that they were going to undergo a subsequent memory task. Hence, following the literature in the healthy population, it is possible that men and women in our patient group differed in their tendency to instinctively generate encoding strategies and in their ability to effectively use such strategies. This is especially intriguing in light of recent reports that, despite similar error scores between male and female schizophrenia-spectrum patients during performance of a working memory task, men and women differed with regards to the cognitive strategy used to manage the task (Lecardeur et al., 2010). Albeit not an emotional memory task, these findings suggest that differences between women and men could be missed if behavior alone is taken into account. Thus, examining strategy use during cognitive tasks is necessary to better understand differences between females and males throughout task performance (Lecardeur & Mendrek, 2012). It is important to mention that the design of the present study did not allow us to ascertain the participant's potential cognitive strategies during scanning and so it remains unclear how this could have influenced brain and behavioral performance during the recognition task. Future studies that implement qualitative comparisons between the encoding and retrieval strategies used by men and women would clarify this possibility.

Another important factor to take into consideration when interpreting the results of the present thesis is that both old and new images were randomly intermixed within each block and so cerebral activations associated with only correct retrieval of stimuli into memory could not be ascertained. Because of this feature of the experimental design, it is possible that other processes, rather than simply recognition, could have affected the pattern of cerebral activations observed, which is indicative that our data more likely reflected an attempted retrieval process. Of the very few studies that have investigated the neural correlates of emotional episodic memory in schizophrenia, none have examined the brain regions activated during the retrieval of old (or already seen) stimuli into memory. For instance, Whalley and colleagues (2009) implemented a design in which accurate recognition accuracy was correlated with cerebral activations during the encoding of emotional information into memory. In contrast, Sergerie et al. (2010) did analyze their functional data with the contrast of subjective old (i.e. hits and false alarms) minus subjective new (i.e. misses and correct rejections) for sad and happy facial expressions but only reported the brain regions that correlated significantly with behavioral response bias. Disentangling the cerebral activity associated with correct and incorrect recognition memory makes it possible to extricate the effects of emotion on brain activations during the process of retrieval versus successful retrieval. Hence, it would be possible to delineate the neural networks involved in the process, separate from the success, of a retrieval attempt. It is worth noting that healthy controls and patients with schizophrenia who participated in this study also underwent an event-related potential session while performing the same emotional memory paradigm. This was done to observe brain function associated with memory of emotional stimuli with an increased temporal resolution but also to allow us to explore cerebral function associated with correct versus incorrect recognition of emotional images into memory. We are currently in the process of exploring this data.

Regarding the existence of sex differences in the overall expression of schizophrenia, the bulk of studies have suggested that differences in the development of the brain between men and women, controlled by the influence of sex steroid hormones and genetic factors, forms the foundation of sex differences in the behavior, performance and expression of schizophrenia (Abel, et al., 2010; Hafner, et al., 1998; Mendrek, 2007; Seeman & Lang, 1990). The development of a male or female brain depends on the type of circulating hormone and the level of hormonal activity present during the development of the embryo in the womb. More specifically, the presence of testosterone influences a "male" brain to mature during early development while the lack of androgens will permit a "female" brain to develop through a passive mechanism by default (Zaidi, 2010). Still, studies have demonstrated that estrogen does in fact play an active role in the differentiation of the female brain and that this occurs at a later time period than testosterone-related processes (Dohler, 1991; Dohler et al., 1984). Also of relevance, there exists evidence of several brain regions implicated in emotion and cognition (e.g. amygdala, hippocampus and cerebellum) that are altered during brain development due to sex steroid hormones (Dean & McCarthy, 2008; Galea et al., 2006) and so it is not unexpected that functional neuroimaging studies have outlined differences between men and women during performance of emotional and cognitive tasks. Thus, differences between male and female patients with schizophrenia may be caused, at least in part, by the normal sexual dimorphism of the brain, due to which men and women differentially recruit brain regions to perform certain cognitive and emotional tasks. On the other hand, because of the effect of sex steroid hormones on region-specific differentiation of the brain during prenatal and perinatal periods, a differential vulnerability of male and female brains to early, schizophrenia predisposing brain lesions may take place (Leung and Chue, 2000). Interestingly, the slower rate of development of the male brain may make it more susceptible to early brain insults

contributing to a more severe form of the illness in men compared to women (Hafner, 2003). Of note, a particularly strong argument has been made regarding the organizational/structural and activational/functional effects of estrogen in providing a protective mechanism for women with schizophrenia in the development of the disorder and accounting for sex differences in schizophrenia (Leung & Chue, 2000; Seeman, 1996, 1997; Seeman & Lang, 1990).

VI. Conclusion

This thesis illustrates that the affective valence and degree of arousal of presented stimuli is important to take into account when investigating episodic memory in patients with schizophrenia. Another important variable is the sex of tested individuals since a multitude of studies in the general population, and in the schizophrenia population (albeit less frequently), have outlined significant differences between men and women in the brain activations associated with emotional and cognitive tasks (Domes et al., 2010; Gur, R. C. et al., 2000; Koch et al., 2007; Wager et al., 2003; Weiss et al., 2003). Our research has the potential to make an important contribution to the understanding of emotional episodic memory in schizophrenia as well as sex differences in the brains of patients with schizophrenia, which will further contribute to the advancement of the basic mechanisms of emotional memory in this population (a feat that is underexplored thus far in the literature). Moreover, the results of the present research, as well as the findings of other research endeavors investigating differences between men and women with schizophrenia, have the potential to influence future development of sex-based clinical interventions for schizophrenia (e.g. at the level of antipsychotic medication use, psychosocial and cognitive remediation therapy). For instance, at the molecular level and regardless of sex, advances in individualized therapy are already being made. Specifically, the field of pharmacogenomics aims to select drugs with the greatest chance of benefit and the least likelihood of harm in individual patients based on their genetic make-up, i.e., individualized therapy (Basile et al., 2002). Considering this, it is also important to keep in mind that biological differences between males and females also contribute substantially to disease susceptibility and males and female may have a different spectrum of genetic variants underlying disease, which could in turn affect treatment response and outcome (Pinsonneault and Sadee, 2003). Unfortunately, the majority of schizophrenia research

combines men and women into one experimental group or consist primarily of all male samples. Also, psychiatric services for patients with schizophrenia are usually developed for men, as the archetypal patient with schizophrenia is male. However, male and female patients with schizophrenia have clear and obvious differences in the way their brains function during important cognitive and emotional tasks (as was observed in our research) that are (1) highly impaired in schizophrenia and (2) relevant for everyday social functioning, so why should they be given the same clinical treatments? Although the possibility of sex-specific treatment in schizophrenia is intriguing it remains highly speculative due to the lack of research initiatives that take sex as a relevant covariate of interest when exploring the underlying brain circuitry associated with important emotional and cognitive tasks.

VII. References

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