Depression, social anxiety and self-esteem in first episode psychosis

A cross-sectional study

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SUMMARY

Treatment of psychotic disorders has mainly focused on reducing positive psychotic symptoms, while comorbid disorders such as anxiety and depression have received less attention. There seems to be two main reasons for this. Firstly, there has been a general lack of awareness of other symptom dimensions co-occurring in psychosis due to the hierarchical approach to diagnostic evaluations. Symptoms of emotional dysfunction, defined as mood symptoms and/or anxiety disorders following the Diagnostic and Statistical Manual of mental disorders (DSM-IV), have not been acknowledged because they are regarded less important in severe psychotic disorders both with regard to diagnosis and treatment. Secondly, studies show that even though clinicians acknowledge the co-occurrence of other symptom dimensions, there is no consensus as to whether it should be treated as a separate condition or not (Addington et al., 2002).

The current thesis focused on depression and social anxiety and seeks to conceptualize these co-occurring symptom dimensions in the context of psychotic disorders. Depression and social anxiety interact, as people afflicted by these disorders have a common tendency to make negative evaluations of themselves in relation to others and the world. Embedded in this context lies a feeling of inferiority and low self-esteem. Consequently, a focus on self-esteem was natural.

In the first paper (paper I) we investigated the prevalence and time course of lifetime major depressive episodes in first episode psychosis (FEP) and examined whether there were differences between those with and without previous episodes. We also examined possible contributing factors to development of depressive symptomatology. Almost 50% of the sample had experienced one or more lifetime episodes of major depression, with no indications of demographic or clinical differences. Poor premorbid childhood adjustment, substance abuse and excitative symptoms were associated with higher levels of current depressive symptomatology. Furthermore, findings indicated possible gender differences regarding alcohol and excitative symptoms as possible explanatory factors related to depressive symptoms. Alcohol use was associated with current severity of depression in men while excitative symptoms were associated in women.

In the second paper (paper II) we examined whether premorbid adjustment was associated with the afflicted individuals' self-esteem and whether lowered self-esteem may contribute to the development of delusions and hallucinations in FEP. We found indications that premorbid adjustment was an important factor in the development of self-esteem, and that reduced self-esteem was significantly associated with raised level of positive psychotic symptoms.

The third and fourth papers (paper III and IV) were concerned with symptoms of social anxiety disorder. Paper III was a psychometric paper aimed at validating the Liebowitz Social Anxiety Scale – self-rated version. This is a widely used scale, but the self-rated version has never been validated when applied to psychotic disorders. We reproduced factor analytically derived subscales similar to those found elsewhere in the literature in non-psychotic samples. Furthermore, the scales showed satisfactory psychometric properties. Additionally, we found support for the assumption that the scale measures social anxiety as an independent domain in psychotic disorders.

In paper IV we found that severe social anxiety was related to poor premorbid- and current functioning in addition to level of depression, but not to level of current psychotic symptoms. Insight into illness was more related to level of social anxiety and depression than to psychotic symptoms. Furthermore, higher level of social anxiety and depression were associated with poorer quality of life.

The findings of the present thesis support the relevance of an active approach towards recognition and treatment of emotional dysfunction as it is prevalent and constitutes a major additional burden for patients with a first episode of psychosis.

LIST OF PAPERS

The present thesis is based upon the papers listed below.

Paper I

Depression and depressive symptoms in first episode psychosis.

Kristin Lie Romm, Jan Ivar Røssberg, Akiah Ottesen Berg, Elizabeth Ann Barrett, Ann Færden, Ingrid Agartz, Ole A. Andreassen, Ingrid Melle. J Nerv Ment Dis. 2010 Jan;198(1):67-71.

Paper II

Self-esteem is associated with premorbid adjustment and positive psychotic symptoms in first episode psychosis.

Kristin Lie Romm, Jan Ivar Røssberg, Charlotte F. Hansen, Elisabeth Haug, Ole A. Andreassen, Ingrid Melle. (submitted)

Paper III

Assessment of social anxiety in first episode psychosis using the Liebowitz social anxiety scale as a self-report measure.

Kristin Lie Romm, Jan Ivar Røssberg, Akiah Ottesen Berg, Charlotte F. Hansen, Ole A. Andreassen, Ingrid Melle.
Eur Psychiatry. 2010 Oct 29. (Epub ahead of print)

Paper IV

Severe social anxiety in early psychosis: associated with poor premorbid functioning, depression and reduced quality of life

Kristin Lie Romm , Ingrid Melle , Christian Thoresen , Ole A. Andreassen, Jan Ivar Røssberg. (submitted)

1. INTRODUCTION

1.1. Perspectives and definitions

1.1.1. Psychosis

Several definitions of psychosis are in use. The most narrow one restricts psychosis to 'delusions or prominent hallucinations, with the hallucinations occurring in the absence of insight into their pathological nature'(American Psychiatric Association, 1994). A broader definition includes hallucinations and delusions even when the individual accepts the experience as a result of reality distortion, while the broadest definition comprises disorganized speech, grossly disorganized or catatonic behaviour. Furthermore, psychosis occurs across a range of diagnostic categories of psychotic disorders such as; non affective psychotic disorder, affective psychoses, substance-induced psychotic disorder and psychotic disorder due to a general medical condition.

Currently there is an ongoing debate concerning the relationship between psychosis and diagnostic categories as they do not seem to represent discrete nosological entities (Linscott et al., 2010). A growing body of evidence suggest overlap between the psychotic diagnostic categories in genetic liability, and even between schizophrenia and bipolar disorder (Lichtenstein et al., 2009). There might instead be broader susceptibility for psychotic disorders that is expressed across the different diagnostic categories, also reflected in similar clinical characteristics (Simonsen et al., 2009). Furthermore, there is research suggesting that symptoms previously considered to be characteristic of psychotic disorders are prevalent in the community at large (van Os et al., 2000). These subclinical psychotic experiences are in most cases transitory and are typically expressed in adolescence and young adulthood (Hanssen et al., 2005). A recent systematic review advocates for the psychosis continuum model by finding evidence for a 'psychosis proneness-persistence-impairment model' of psychotic disorder (van Os et al., 2009). In this model, the usually transitory psychotic experiences can be modified to more persistent psychotic experiences with clinical need for care due to exposure to environmental and psychological risk factors such as psychological trauma, cannabis or urbanicity. However, the underlying pathological mechanisms for this rare transition are still unknown.

1.1.2. First episode psychosis

Considering the continuum hypothesis, research into the early phases of psychotic disorders is particularly relevant as the different contributing factors that are in play during transition from normality to pathology will be present. The danger of misinterpreting research findings due to chronicity, recall bias or the effects of long-term medication is reduced during early stages of the disorder. There exists a substantial literature stating the importance of early detection and intervention. Embedded in this logic is an understanding of psychotic disorder as a dynamic, biopsychosocial, reversible process, which can be prevented, delayed, modified and reversed (Read, 2004). This thesis will focus on patients with a first episode of psychosis; excluding substance induced psychotic disorder and psychotic disorder due to a general medical condition.

1.1.3. Diagnostic criteria

There are several subgroups comprised by the term psychotic disorder in the various classification systems such as the DSM and the ICD. The basis for the patient samples studied in this thesis is the broader schizophrenia spectrum disorders included in the DSM-IV: Schizophrenia, Schizoaffective disorder, Schizophreniform disorder, Delusional disorder, Brief psychotic disorder and Psychotic disorder Not Otherwise Specified (NOS). Furthermore, the diagnostic category Major depressive episode with mood incongruent symptoms is included.

Schizophrenia is considered the most severe of the psychotic disorders. As defined in the DSM-IV diagnostic system, the symptoms have to be present for more than 6 months and include at least one month of active-phase symptoms. Active phase symptoms include two (or more) of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour or negative symptoms (Criterion A). In addition, a significant reduction in social functioning in comparison to former level of achievement must be present (Criterion B). Even though there are defined subtypes (Paranoid, Disorganized, Catatonic, Undifferentiated and Residual) the clinical picture varies greatly among patients within these subcategories, depending on which criteria the individual fulfil.

The prevalence rate of schizophrenia has usually been estimated to be between 0.5 % and 1% (American Psychiatric Association, 1994). A recent review points to the fact that there are larger variations between sites than formerly recognized (McGrath et al., 2008). The authors found that the median lifetime prevalence for schizophrenia were 4.0 per 1,000 and for lifetime morbid risk 7.2 per 1,000.

Age of onset differs, but in general, median age of onset is considered to be in adolescence and young adulthood for men and some years later for women. Most patients who develop schizophrenia have had a longer period prior to the first psychotic outbreak with unspecific, non-psychotic prodromal symptoms such as social withdrawal, loss of interest in school or work, depression and anxiety (Yung and McGorry, 1996;Hafner et al., 1999). On average, this period has been reported to last 1-2 years. Another aspect which is assumed to have an impact on the course and outcome of the disorder is the period from onset of manifest psychotic symptoms until onset of adequate treatment (the Duration of Untreated Psychosis-DUP) (Larsen et al., 1998;Melle et al., 2008). A long DUP is associated with poorer outcome (Melle et al., 2005;Marshall and Rathbone, 2006).

There are several reasons why this disorder is rated as one of the most costly disorders in the Western world (approximately 1 % of the Gross National budget) (Johannessen, 2002). Firstly, there are considerable costs due to expensive health care including medication and frequent use of health services. Furthermore, patients with schizophrenia may experience reduced cognitive capacity and less tolerance for stress (Green, 1996). These obstacles, combined with stigmatisation may also result in reduced ability to join the active work force.

Treatment of these disorders is still challenging. The conventional approach is a focus on pharmacological treatment of positive psychotic symptoms in combination with psychosocial treatment and rehabilitation. Psychotherapy is offered to a limited extent, unfortunately still depending upon varying economic and professional resources available at the different treatment sites.

Schizophreniform Disorder is defined by the same symptom clusters that characterize schizophrenia, but the duration of manifest psychotic symptoms is shorter, from 1 to 6 months. A decline in social functioning is not required.

Schizoaffective Disorder: There must be an uninterrupted period of illness during wich there is either a Major Depressive Episode or a Manic Episode, or a Mixed Episode concurrent with symptoms that meet criterion A for Schizophrenia.

Delusional Disorder is defined by minimum 1 month of non-bizarre delusions. Other active phase symptoms are not permitted.

Brief Psychotic Disorder is limited to manifest symptoms of psychosis lasting for more than one day and less than one month.

Psychotic Disorder (NOS) includes psychotic symptomatology, but where inadequate or contradictory information makes it impossible to draw firm conclusions about diagnosis, or disorders with psychotic symptoms that do not meet any of the criteria for a specific psychotic disorder.

Major Depressive Episode with mood-incongruent psychotic symptoms (MDE) is characterized by a primary depressive episode with hallucinations or delusions that has no apparent relationship to the depressive themes. There are good reasons to include this group in the current thesis. The psychotic symptoms resemble those seen in the psychotic disorders listed above. Some of these patients will eventually convert to a diagnosis within the schizophrenia spectrum after some time (Haahr et al., 2008). Furthermore, the continuum hypothesis combined with recent research indicating that the presence of a history of psychosis in bipolar disorder works as a common denominator predicting outcome in both schizophrenia patients and bipolar patients (Simonsen et al., 2009).

1.1.4. Psychiatric comorbidity in psychotic disorders

Psychiatric comorbidity is common in psychotic disorders. Nevertheless, the focus on co-occurring syndromes has been neglected. This is partly due to the hierarchical foundation of the diagnostic system (Bermanzohn et al., 2000). As described by Surtees and Kendell;

"Psychiatric diagnosis are arranged in a hierarchy in which any given diagnosis *excludes* the symptoms of all higher members of the hierarchy and *embraces* the symptoms of the lower members" (Surtees and Kendell, 1979). There were made changes when moving from DSM-III to DSM-IV to capture the heterogeneity of schizophrenia by: 1) permitting more than one diagnosis on Axis 1 and 2) changing the formulation of the exclusion rules (excludes lower diagnosis if they are 'better accounted for by a higher order diagnosis) (Bermanzohn et al., 2000). However there is still a lack of awareness of these potentially treatable comorbid conditions and a lack of common guidelines.

A recent review concluded that substance abuse, depression and anxiety are the most common comorbid disorders in schizophrenia: 47 % of the patients will have a lifetime diagnosis of substance abuse, and 50 % experience depression. Furthermore, estimated lifetime prevalence for panic disorder was 15 %, for posttraumatic stress disorder 29 % and for obsessive/compulsive disorder 23 % (Buckley et al., 2009). Social anxiety disorder has received less attention, but epidemiologic studies have reported this to range between 14 % and 39% (Cosoff and Hafner, 1998;Pallanti et al., 2004;Bermanzohn et al., 2000;Cassano et al., 1999).

1.2. Emotional dysfunction

Recently, there has been an increasing interest in research concerning emotional dysfunction or the role of emotions in psychosis. Presumably because of a lack of clear definition, different terms have been applied in various studies. DSM-IV describes emotional dysfunction as a characteristic symptom of schizophrenia, but without providing a clear definition (American Psychiatric Association, 1994). The term emotional dysfunction has been used repeatedly to describe symptoms of mood and anxiety disorders, including PTSD and reduced self-esteem (Birchwood et al., 2005;Birchwood et al., 2006;Watson et al., 2006;Smith et al., 2006). Other terms that have been used interchangeably with emotional dysfunction is emotional disturbances, emotional distress or emotional disorders (Green et al., 2006;Kuipers et al., 2006;Garety et al., 2001;Freeman et al., 2001;Garety et al., 2005;Freeman and Garety, 2003). Despite the diverse nomenclature, the main focus has been on symptoms related to mood and anxiety disorders according to the diagnostic

criteria of DSM-IV. In the current thesis, the term emotional dysfunction will be used to describe symptoms of depression and anxiety, including reduced self-esteem. The basis for this choice is related to the theoretical framework in which the results of the present thesis will be contextualized.

There seems to be mainly three reasons why emotional dysfunction in psychosis has received little attention. Historically, the division between neurosis and psychosis distinguishing 'affective illness from madness proper' by Jaspers, has made a huge impact upon how co-occurring symptomatology such as mood or anxiety disorders has been viewed in this context (Freeman and Garety, 2003;Jaspers, 1963). Even though neurosis as a concept dates back to the 18th century and then comprised both neurological and psychological states (Beer, 1996), it was the interpretation made by Freud during the 19th century that formally linked it to anxiety disorders, even though Freud himself later on declared that neuroses and psychoses were intimately related (Freud, 1924). It became accepted that in contrast to the psychosis, the neurosis let part of the premorbid person intact, including insight, while psychosis was viewed as a mental state qualitatively different and psychologically irreducible (Roth, 1963). The heritage from this conceptualisation seems in part responsible for the lack of research on emotional difficulties in psychosis. It has to be noted that with DSM-III, the concept of neurosis was left behind as there has been a drift away from the psychoanalytic tradition, but the nosological change has not left a vacuum as the phenomenology has remained unchanged.

The second main reason for this reduced focus is the previously mentioned hierarchical system of diagnosis. Embedded in this system lies an assumption that there is a kind of etiological hierarchy where you find the "organic psychosis" (meaning psychosis resulting from damage at known brain-sites) in one end, followed by the "non-organic" psychosis and then mood and anxiety disorders at the opposite end (Freeman and Garety, 2003). Following this, research has chose to focus on these states as representing clearly separate conditions.

Thirdly, the search and belief in a single cause of illness may have hampered the research concerning emotional dysfunction in psychosis. According to this hypothesis, there should be a single unitary cause underlying all serious disorders, where the other features of the

disorder merely represent consequences of the underlying essence of the disorder (Kendler et al., 2010).

Additionally, recent research has emphasised that psychosis is not, in all aspects, qualitatively different from normal experiences (van Os et al., 2000;Freeman et al., 2008). The symptoms of psychosis occur in normal non-clinical samples. Psychotic symptoms can be provoked in otherwise well-functioning individuals when undergoing sensory deprivation. It can be triggered by life-events and many patients do show insight into their symptoms and difficulties. Moreover, the assumption that psychotic symptoms and the patients reaction to these experiences are impossible to understand, has turned out to be wrong (Freeman et al., 2001). In other words it is possible to understand both psychosis and emotional dysfunction in the same psychological framework, and there is no obvious reason to draw a sharp distinction between these constructs. For instance, recent research has found support for the view that paranoia can be conceptualized as a type of anxious fear (Freeman et al., 2008). Thus, to be able to have a clear overview when approaching psychotic disorders whether it is in the clinic or research settings, we need to link psychology with the biological and the social context assuming that these factors will have different levels of explanatory power depending on individual differences in vulnerability.

Studies have demonstrated that depression, low self-esteem and anxiety are not only common, but highly correlated with each other in psychosis (Watson et al., 2006;Freeman and Garety, 2003). Furthermore, emotional dysfunction has shown to express itself not only during the prodromal phase and to be prevalent through the first episode of psychosis, but actually manifest itself before psychosis symptom development. Taking this into account, the possibility that emotional dysfunction not only accompany psychotic symptoms, but actually might influence psychosis, is important. In other words, emotions can be viewed as potential contributory factors to both symptom development and maintenance.

Previous research trying to decipher these relations, has pointed towards the possibility of different pathways to emotional dysfunction in psychosis, not necessarily mutually exclusive (Birchwood, 2003): 1) emotional dysfunction developing along a disturbed developmental pathway, 2) emotional dysfunction intrinsic to the psychosis, and finally, 3) emotional

dysfunction as a reaction to the psychotic episode. Following this theory, each pathway may hold some specific factors that exert a pathoplastic effect on the development of emotional dysfunction. The papers in this thesis are based on the same theoretical framework. It examines further different factors assumed to be of importance for the development of emotional dysfunction in psychosis and its associations to other clinical symptoms.

1.3. Depression

1.3.1. Definition: Major Depressive Episode-DSM-IV

According to DSM-IV a Major Depressive Episode (MDE) is characterized by a period of at least two weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities. In addition, the individual must experience at least four of the following symptoms; changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans or attempts. The symptoms must be present for most of the day, nearly every day and mark a significant difference from the person's habitual state of mind.

When a mood disorder such as a MDE is superimposed on a diagnosis of psychotic disorder, an additional diagnosis of Depressive Disorder Not otherwise Specified (MDE-NOS) is applied.

1.3.2. Prevalence rates of depression in psychotic disorder

The prevalence rate of depression in schizophrenia varies widely across published studies (from 7-75%), but with an average prevalence rate of 25% (Addington et al., 2002;Hirsch and Jolley, 1989;Koreen et al., 1993;Siris, 1991). These variations are probably due to the wide heterogeneity in the study populations with regard to diagnoses, chronicity and assessment tools used. Studies of depression in schizophrenia have also been inconsistent since the term "depression" could include considerations of the affect, the symptom or the clinical syndrome (Gift et al., 1980;Siris, 2000). While discussing depression as an affect, we are discussing the individual's subjective momentary mood state. Even though it might be lowered, it is not necessarily pathological if otherwise appropriate for the situation.

Depression as a symptom is defined as a sad mood state causing subjective distress. It might not be enduring or accompanied by other features of depression. The syndrome is a more complex entity consisting of a certain set of symptoms and endurance as previous described. The interchangeable use of these expressions without clearly statements about how they are defined has blurred this field of research.

However, few studies have examined depressive symptoms in patients with a first episode psychosis. Häfner and coworkers (Hafner et al., 2005) studied depressed mood in 232 first episode patients with schizophrenia and found that the lifetime prevalence of depressed mood at first admission was 83%. Sim and coworkers (Sim et al., 2004) examined psychiatric comorbidity among 79 patients with a first episode psychosis and found that 13 patients (16.5%) met the DSM-IV criteria for a depressive disorder. Koreen and coworkers (Koreen et al., 1993) found among 70 first episode psychosis patients that the prevalence of depressive symptoms was 75% for meeting the criteria based on either Hamilton Rating Scale for Depression scores or the Research Diagnostic Criteria, but only 22% of the patients met both criteria.

1.3.3. Conceptualisation of depression in psychotic disorder

During the last ten years the acknowledgement that depression might occur in all phases of psychotic disorders has led to new theories about possible pathways to depression in line with the previously described pathways to emotional dysfunction (Birchwood, 2003); 1) Depression as the product of a developmental pathway, 2) depression as intrinsic to the psychosis diathesis and 3) depression as a psychological reaction to the psychotic episode. The stress-vulnerability model of psychosis which hypothesises that psychosis exists as a final common path of neuropsychiatric decompensation can serve to enhance our understanding of the developmental pathway (Zubin and Spring, 1977). There are numerous factors influencing normal emotional development and functioning. These comprise psychological, social and biological factors.

Traumatic interpersonal experiences and lack of opportunities to develop adequate coping skills are examples of psychosocial stressors known to precipitate the development of psychosis. High rates of traumatic histories among individuals with a psychotic disorder has

been proposed as a precipitating factor (Greenfield et al., 1994). Furthermore, there are now clear evidence that social environment such as urban living, deprivation, being member of marginalized group, migration and living in the Western world influence both morbidity and outcome in psychotic disorder (Harrison et al., 2001). Finally, several biological mechanisms could be involved in the development of psychosis, including factors suspected to influence normal development such as intrauterine viral infection, poor prenatal nutrition, birth injuries and childhood head trauma (Siris, 2000).

In addition, recent research has discovered probable common genetic risk factors for both psychotic and affective disorders (Craddock et al., 2006). To sum up, biopsychosocial risk factors commonly known to influence mood and be associated with development of depression, have been associated with development of psychosis.

In the second pathway in which depression is defined as a state integral to the psychotic state of mind, depression is understood as a more or less 'normal' reaction to the distress linked to individual psychotic symptoms. Several studies have pointed to the stress resulting from the affect generated by voices such as anger, fear or elation (Chadwick and Birchwood, 1994;Trower, 2004). In a study of 62 patients, beliefs about the power and meaning of voices showed a close relationship with coping behaviour and affect and accounted for the high rate of depression in the sample (Birchwood and Chadwick, 1997). Fifty-three per cent were at least moderately depressed and 24 % were severely depressed. Of those who believed that their voices were malevolent, 68% were at least moderately depressed, while the same figures for those who believed their voices was benevolent was 35%, or benign 47%. Of those who believed their voices were very powerful, 60% were at least moderately depressed compared with 25% in the group who rated their voices to be powerless. Another study focusing on persecutory delusions and accompanying emotional distress, found that among 25 individuals with persecutory delusions only four had no significant symptoms of depression (Freeman et al., 2002). Higher feelings of control were associated with lower level of depression and lower level of delusional distress. Furthermore, there was a trend for higher evaluation of the power of the persecutor to be associated with higher levels of depression. The same study found that all participants reported use of safety behaviours

assumed to alleviate emotional distress. This is interesting if we view psychosis as arising from an interaction between psychotic and non-psychotic experiences (Garety et al., 2001). One could imagine that these safety behaviours not only alleviated emotional distress caused by the unpleasant thoughts about persecution, but that withdrawal at the same time exacerbated depression by isolation and loss of correctional input.

The third pathway, perceiving depression as the result of a psychological reaction to the psychotic episode, has been linked to several factors. The term post psychotic depression was described by McGlashan and Carpenter in 1976 (McGlashan and Carpenter, Jr., 1976). It comprises factors of possible explanatory power that still constitutes an important framework for the understanding of depression revealing itself in the aftermath of the psychotic episode. In a dynamic formulation they view post psychotic depression as 1) a reaction to the psychosis and a blow to previous self-esteem, 2) a loss of old ways of coping and loss of omnipotence in the self and significant others, 3) a symptomatic reaction to facing the necessity to change, to individuate, and to take responsibility for one's own life. Research has focused upon related factors such as how insight into illness, perceived stigmatisation and appraisal of the psychotic episode might trigger depression in vulnerable patients (Birchwood et al., 1993;Iqbal et al., 2000;Karatzias et al., 2007;Yanos et al., 2008). The social ranking theory is applied in some of these studies, where the perceived loss of status in the social hierarchy as a consequence of the psychotic disorder is followed by a feeling of defeat and entrapment which in turn fuels depressive symptomatology (Gilbert and Allan, 1998).

Lastly, there are numerous conditions that have the possibility to mimic or induce depression in individuals affected by a psychotic disorder as well as in the general population, such as cardiovascular disorders, infections, autoimmune diseases, anaemia, cancer and metabolic, neurological and endocrine disorders (Bartels and Drake, 1988). In addition various pharmaceutical agents used in the treatment of somatic disorders have depression as a known possible side-effect. Neuroleptic-induced depression is a term more acknowledged in earlier literature, but worth mentioning. The causal relationship behind this theory lies in the involvement of the dopamine synapses in the mesolimbic dopamine

reinforcement system or the dopamine reward system. The inhibition of this by a antipsychotic drug has been promoted as a contributing factor to symptoms of depression and depressive disorder among individuals diagnosed with a psychotic disorder (Harrow et al., 1994). However, others have found depressive symptoms to decrease following antipsychotic treatment in the acute psychotic phase (Knights and Hirsch, 1981). The introduction of second generation antipsychotics with less pronounced dopaminergic blockade has further reduced the focus on this relationship. Another important factor that might mimic depression is the complex of negative symptoms in psychotic disorder such as passive withdrawal, avolition, anhedonia or apathy.

Gender differences in the prevalence of both schizophrenia and depression have consistently been reported. Previous studies in schizophrenia spectrum disorders have shown men to have earlier onset, poorer premorbid functioning and different premorbid behavioural predictors of psychosis (Leung and Chue, 2000). Women have been shown to have more affective symptoms, more self-destructive behaviour and more often troubled relationships (Koster et al., 2008;Bardenstein and McGlashan, 1990). There are also differences in the prevalence of depressive symptoms, even though Addington and coworkers found that differences in level of depressive symptoms in males compared to females disappeared when diagnostic limits were broadened to include a wider diagnostic spectrum and not restricted to narrowly defined schizophrenia (Addington et al., 2002). To be aware of possible gender differences is of importance since there are clear indications of differences in the prevalence and clinical picture of depression in the general population, with a higher prevalence and more atypical depressive features in females (Halbreich and Kahn, 2007). From a clinical perspective, possible gender differences could imply the need for a more gender specific assessment and treatment approach. There are also indications of a more significant role of substance use, mainly alcohol, in male depression (Walinder and Rutzt, 2001)

1.3.4. The relevance of depression in psychotic disorder

Most importantly, depression in psychotic disorder is associated with increased suicidality (Drake et al., 1985;Fenton, 2000). A recent reexamination of suicide risk in schizophrenia

estimated a lifetime suicide prevalence of nearly 6 % of those observed from first admission or onset (Palmer et al., 2005). Furthermore, and maybe more striking, was the fact that among first-admission and new-onset samples, 30,6 % of deaths were due to suicide, compared to 4,9 % in samples independent of duration of illness. Thus, the risk of suicide is most common in the early phases (including the periods before and after onset). This highlights the importance of an active approach towards recognition and treatment of depression and other factors that might contribute to hopelessness and suicidal ideation.

Among patients with a psychotic disorder, depression and depressive symptoms have shown to be associated with a higher incidence of relapse and rehospitalisation (Herz and Lamberti, 1995). This is not only an economical burden for society, but most importantly an additional psychological burden for the patient. In line with this, depression has been linked to reduced level of social functioning and reduced quality of life (Sim et al., 2004).

Even though depressive symptoms appear to be common among patients with schizophrenia spectrum disorders, there is a growing awareness of the fact that depression is an underdiagnosed and undertreated comorbid condition in this patient group (Addington et al., 2002; Sim et al., 2004), and clinical guidelines are still lacking.

There is thus a lack of research on depressive symptoms and depression among patients with a first episode psychosis. Furthermore, to our knowledge, no previous study examined depressive symptoms at start of treatment. Thus, further knowledge about the prevalence, developmental factors and time course of depression in relation to psychotic symptoms is needed. More information about factors that influence the rate or severity of depressive states would also aid the development of clinical guidelines on treatment of depression in schizophrenia (Addington et al., 2002).

1.4. Social anxiety disorder

1.4.1. Definition: Social anxiety disorder-DSM-IV

Social anxiety disorder as described in DSM-IV is characterized by a marked and persistent fear of social interaction or social performance situations in which embarrassment may

occur (American Psychiatric Association, 1994). Exposure to a feared situation almost inevitably provokes an immediate anxiety response, even though the individual recognizes that the fear is excessive or unreasonable. Individuals suffering from social anxiety tend to avoid the anxiety provoking situations. The diagnosis is appropriate only if the anxiety symptoms interfere significantly with the persons daily routine, occupational functioning or social life, or if the person is markedly distressed by the anxiety disorder. The disorder should not be better accounted for by another mental or medical condition. If the individual has another condition, the fear and avoidance is not limited to concern about its social impact. Social anxiety disorder typically has an onset in the mid-teens and can be preceded by a childhood history of social inhibition and shyness. Later onset can be characterized as abrupt, typically after a stressful or humiliating situation. The course is often continuous and the individual becomes trapped in a viscous circle where the pattern of avoidance behaviour prohibits opportunities for recovery by gaining positive experiences and a sense of mastery. Generalized social anxiety disorder: The term is applied if the fears include most social situations as initiating or maintaining conversations, participating in small groups, dating, speaking to authority figures, attending parties. People suffering from generalized social anxiety disorder usually fear both public performance situations and social interaction situations. Furthermore, they will be more likely to manifest deficits in social skills and to experience severe social and work impairment.

1.4.2. Prevalence rates of social anxiety in psychotic disorder

Social anxiety disorder is considered to be one of most prevalent anxiety disorder in schizophrenia. A meta-analysis by Achim and coworkers (Achim et al., 2009) showed pooled overall prevalence rates for social anxiety disorder in schizophrenia to be approximately 15%. Others have found it to vary from 14% to 39 % between different studies (Cosoff and Hafner, 1998;Pallanti et al., 2004;Bermanzohn et al., 2000;Cassano et al., 1999).

1.4.3. Conceptualisation of social anxiety in psychotic disorder

Even though there has been an increasing interest in research focusing on anxiety symptoms in psychotic disorders, the understanding of how anxiety disorders are related to different aspects of psychotic disorders still remains unclear (Braga et al., 2004). Reviewing the

literature, the three possible pathways previously described to explain development of emotional dysfunction, have been applied to enhance the understanding of social anxiety in psychotic disorder (Birchwood et al., 2006;Voges and Addington, 2005;Gumley et al., 2004a); 1) Social anxiety as a pre-morbid developmental disorder and a vulnerability marker for schizophrenia 2) Social anxiety as a core component of the psychotic syndrome, and 3) Social anxiety emerging as a psychological reaction to the psychotic episode.

Concerning the first possibility, social anxiety evolving through a developmental pathway to psychosis, the Edinburgh High-Risk Study found early "situational anxiety" to be one of the best predictors of conversion to psychosis in a high-risk group with two or more relatives with a history of psychosis (Johnstone et al., 2005;Owens et al., 2005). The social withdrawal factor concerned with anxiety and introversion was found to be the strongest predictor in their assessments, more important than psychotic-like experiences. It has to be noted that these individuals were non-psychotic on entry into the study. Contrary to this, Hafner et al. did not find any indications in their study that individuals diagnosed with schizophrenia were inferior in social status compared to age and gender matched controls from the general population prior to the development of a psychotic disorder (Hafner et al., 1999). Furthermore, Birchwood et al. failed to find any differences in premorbid peer-relations in a group of first episode patients with social anxiety disorder compared to first episode patients without social anxiety disorder (Birchwood et al., 2006). They concluded that the group with social anxiety disorder might have had a latent premorbid anxiety acting as a vulnerability marker for developing social anxiety as a reaction to the psychosis. To our knowledge, no study has explicitly made any effort to explore this further and to what extent premorbid functioning interacts upon the development of social anxiety in psychotic disorders is still unclear.

Concerning the second possible pathway, studies have found support for the view that social anxiety is a core component of the syndrome, or at least a co-occurring process that might both initiate and exacerbate positive psychotic symptoms (Freeman et al., 2008). Several studies have repeatedly found anxiety to be associated with paranoid thoughts and persecutory delusions (Startup et al., 2007;Martin and Penn, 2001;Freeman et al.,

2001;Lincoln et al., 2009). A central idea in this theory is that delusions are false positive beliefs that are held with a certain degree of conviction. As beliefs are linked to emotions, these beliefs will consequently convey anxiety if the idea represents a threat to the individual. Fear of negative evaluation is central to social anxiety and represents a threat to the individuals self. Hence, the idea that threat in the context of social anxiety and in persecutory delusions may share common predictors is quite plausible as the threat content can be quite similar. Pallanti and coworkers (Pallanti et al., 2004) found no relationship between positive or negative symptoms and social anxiety, while others again have found social anxiety to be related to negative symptoms only, and not to positive symptoms (Voges and Addington, 2005). The last finding is intriguing from a cognitive approach. As safety behaviour is commonly used to reduce perceived threat in both persecutory delusions and social anxiety, there is a risk of mislabelling social anxiety as negative symptoms.

The third pathway perceives social anxiety as a result of the psychotic episode. Embedded in this theory lies the individuals appraisals of psychosis involving loss of social role, shame and enforced low status (Iqbal et al., 2000). A negative appraisal of psychosis and self has also been associated with post-psychotic depression. Iqbal and coworkers explained this in terms of depressogenic life events (Iqbal et al., 2000). Certain events are more likely to enhance depression than others, especially if they comprise feelings of loss, humiliation and entrapment. There are findings supporting this by demonstrating that individuals with psychosis and a concurrent social anxiety disorder, exhibit more negative beliefs about psychosis and have lower levels of self-esteem than controls without social anxiety disorder (Gumley et al., 2004b). There are several studies showing that particularly schizophrenia carries severe stigma and that there is a tendency to internalise these stigma with subsequent development of shame and reduced self-esteem (Birchwood et al., 1993;Corrigan and Watson, 2002). Hence, implicit in this third pathway, is the assumption that social anxiety has to be linked to a certain degree of insight into illness for these processes to take place. There are only few studies trying to explore this relationship between social anxiety and insight into illness, but they have found this association to be present (Birchwood et al., 2006;Iqbal et al., 2000).

1.4.4. The relevance of social anxiety in psychotic disorder

The importance of focusing on social anxiety disorder among patients with psychosis is apparent. Despite the previously described difficulties in conceptualising social anxiety in this context, it has been demonstrated that important outcome measures are clearly related to social anxiety.

Firstly, a close relationship between social anxiety disorder and poorer quality of life (Pallanti et al., 2004) has been revealed in patients with a longer duration of illness. This is in line with findings in a previous review, pointing to the fact that major determinants of subjective quality of life in people with severe mental illness is the level of psychopathology, especially anxiety and depression (Hansson, 2006). Taking into account that social anxiety has been reported to be the most frequently occurring co-morbid disorder with depression (Stein et al., 1990) and seems to precede depression in the general population (Kessler et al., 1999;Stein and Chavira, 1998), this is not a surprising finding. However, compared to the general population, the raised suicide rate in psychotic disorders underlines the importance of focusing on factors known to contribute to depression (Melle et al., 2006). Furthermore, previous studies have demonstrated that social anxiety seems to inhibit help-seeking behaviour for depression (Pilkonis et al., 1980).

Secondly, social anxiety has been associated with poorer social functioning in schizophrenia (Blanchard et al., 1998). This was supported by a study by Pallanti et al. who found significant impairment in three of five areas of adjustment when they compared patients with schizophrenia with and without social anxiety; work/job, socialization, and personal well-being (Pallanti et al., 2004). Both samples consisted of patients with a long history of psychosis. Only a few studies of first episode psychosis have addressed this problem. Voges and Addington examined this relationship and found a strong association between social anxiety and social functioning (Voges and Addington, 2005). Another study found first episode patients with social anxiety to be more actively withdrawn than patients without comorbid social anxiety (Birchwood et al., 2006). More research is warranted as social functioning is important to enhance quality of life and the ability to adapt to society in general, which at present is a major obstacle for the majority of these patients.

To sum up, these three pathways constitute a reasonable theoretical framework for understanding the development of social anxiety in psychosis, but more studies are warranted as the underlying mechanisms are still unclear. There are clear advantages of studying patients with early psychosis. It implies reduced possibility of persecutory thinking and social anxiety blending up due to chronicity, and a reduced recall bias with regard to premorbid functioning. However, few studies have been performed among first episode psychosis patients (Birchwood et al., 2006;Voges and Addington, 2005;Michail and Birchwood, 2009).

1.5. Self-esteem

1.5.1. Definition and relation to DSM-IV

Self-esteem is a complex concept, comprising appraisal of self- worth based on personal achievements and anticipation of evaluation by others. A search of the DSM-IV-TR revealed that the term-self-esteem appears in 24 diagnostic contexts, as a criterion for disorders, as a criteria for disorders being considered for inclusion in future DSM editions and as an associated feature of disorders (Kernis, 2005). Despite the relatively clear associations between self-esteem and a vast array of psychopathological conditions (Silverstone, 1991), the precise role of self-esteem still remains blurred.

Reviewing the literature on self-esteem while exploring the different definitions applied in previous studies, confirms the complexity of this field. Morris Rosenberg defined self-esteem in terms of the individual's positive or negative attitude toward the self; "When we speak of high self-esteem, then, we shall simply mean that the individual respects himself, considers himself worthy; he does not necessarily consider himself better than others, but he definitely does not necessarily consider himself worse; he does not feel that he is the ultimate in perfection but, on the contrary, recognizes his limitations and expects to grow and improve. Low self-esteem on the other hand, implies self-rejection, self-dissatisfaction, and self-contempt. The individual lacks respect for the self he observes. The self-picture is disagreeable, and he wishes it otherwise" (Rosenberg, 1989).

This definition describes global self-esteem which develops over time. Furthermore, Rosenberg made distinctions between what he called barometric and baseline instability (Rosenberg, 1986). With baseline instability he meant long-term fluctuations in ones self-esteem that gradually changes over a longer period of time. As an example he pointed to decreases in self-esteem level that are common in children as they move from the relatively secure stability of the elementary school to the more insecure environment in the middle school. This decrease is followed by a slow but steady increase in self-esteem through the high-school years. In contrast, barometric instability reflects the short term fluctuations in ones contextually based *global* self-esteem.

Even though Rosenberg described instability as an essential component of the construct of self-esteem, this has been taken further by theorists such as Michael Kernis. He elaborates on Rosenbergs approach by accepting that global self-esteem is a reflection of the individual's representation of how he typically feels about himself across time and context (Kernis, 2005). This, he calls level of self-esteem. However, as a contrast to this, he introduces the term self-esteem stability which refers to the magnitude of *short-term* fluctuations that people experience in their contextually based *immediate* feelings of self-worth. This is not measureable with global measures of self-esteem, but is typically measured by instructions to base their responses on "how they feel at the moment".

Crocker and Wolfe on the other hand, have defined global self-esteem as a model in which people have a typical, or average, *trait* level of self-esteem, but where their momentary or *state* level of self-esteem will be fluctuating around this trait level based upon the individuals' contingencies of self-worth (Crocker and Wolfe, 2001). As an example, some people will base their self-worth on their ability to make people laugh, while other will base it on their mathematical skills. Most people hold multiple contingencies of self-worth, and they may hold them in varying degree. It is the person's interpretation of the event or circumstance, and its relevance to his or her contingencies of self-worth, that determines both if and how strongly an event will inform judgements of overall self-worth or global self-esteem (McFarland and Ross, 1982;Crocker and Wolfe, 2001).

1.5.2. Self-esteem and psychiatric conditions

Even though not uniformly low, self-esteem is often found to be compromised among persons with mental illnesses (Van Dongen, 1996). Low self-esteem is of considerable interest because it is both a possible consequence and a cause of psychiatric symptoms (Greenberg et al., 1992;Karatzias et al., 2007;Blairy et al., 2004). In line with this, studies show that stigmatization and self-stigmatization may lower self-esteem in persons with mental illness (Link et al., 2001). On the other hand, low self-esteem also appears to increase the risk of psychiatric disorders such as depression, eating disorders and substance abuse (Silverstone and Salsali, 2003).

1.5.3. Self-esteem and psychotic disorder

In psychotic disorders, low self-esteem has been implicated both in the development of delusions (Bentall et al., 2001;Barrowclough et al., 2003) and the maintenance of psychotic symptoms (Garety et al., 2001).

How treatment failures, functional loss, demoralization and stigmatization may lower self-esteem in patients with severe mental illnesses appears evident. However, to what extent low levels of self-esteem in severe mental disorders could be based on factors predating the onset of psychosis, and how this in turn may increase vulnerability to more severe symptoms, has not been thoroughly explored.

One would assume that people's global level of self-esteem would be affected by experiences in early childhood and adolescence. In line with this, studies have suggested that difficult childhood experiences such as childhood loss and social marginalization contribute to a cognitive vulnerability accompanied by a negative view both towards the person himself and towards others (Greenberg et al., 1992;Birchwood, 2003;Garety et al., 2001). Based on this, one could hypothesize that individuals with a history of poor premorbid adjustment (both social and academic) could be more prone to negative self-evaluation and reduced global self-esteem. To our knowledge only one study has examined the relationship between premorbid adjustment and self-esteem in patients with schizophrenia spectrum disorder (Gureje et al., 2004). They found no relationships between self-esteem and premorbid adjustment in recovered psychotic patients. However,

premorbid adjustment was not captured with a specific instrument, a factor that may account for the negative results.

There is a vast body of literature on the relationship between low self-esteem and symptom formation in severe mental disorders, both psychotic and affective disturbances. Bowins and Shugar found that the contents of patients' delusions were consistent with patients' global self esteem, and suggested that low self-esteem accounted for the persistence of delusions (Bowins and Shugar, 1998). Barrowclough and colleagues found a significant correlation between negative self-evaluation and a wider variety of positive symptoms (hallucinations and delusions) in schizophrenia (Barrowclough et al., 2003), while Smith and coworkers found that patients with a low level of self-esteem and more depressive symptoms had more intense auditory hallucinations with more negative content (Smith et al., 2006).

Other studies have, contrary to this, found higher levels of self-esteem in patients with delusional disorder compared to depressed patients (Candido and Romney, 1990). However, they found that the group without depressive symptoms had significantly higher levels of grandiose ideations than the other groups, which may account for the elevated levels of self-esteem. The authors concluded that persecutory delusions may reflect an attributional style protecting the individual from low self-esteem. Other studies have found equal levels of self-esteem in patients with delusions and matched healthy controls with both groups demonstrating higher levels than depressed patients (Lyon et al., 1994). Finally, others have found that self-esteem acted independently in contributing to depression in psychosis (Fannon et al., 2009).

Hence, even though there are indications for an association between psychotic symptoms and self-esteem, there are still uncertainties regarding the direction of previous findings. Is the reduced self-esteem a result of the psychotic disorder, or was self-esteem reduced before the onset of psychosis? If self-esteem was reduced even before onset of psychotic symptoms, one possible factor to mirror this relationship would be premorbid adjustment, particularly premorbid social adjustment as this could be related to low self-esteem. This is of importance in order to understand the mechanisms behind the development of psychotic symptoms, and to improve treatment as self-esteem can be influenced by therapeutic

interventions such as cognitive behavioural therapy for psychosis (Hall and Tarrier, 2003;Hodgekins and Fowler, 2010).Previous studies on the relationship between premorbid adjustment, low self esteem and positive symptoms have all included patients with chronic psychotic disorders, where the effects of a long-term severe illness may significantly confound relationships. To our knowledge, no previous studies have examined these relationships in patients coming to their first treatment for a psychotic disorder with less prominent effects of treatment failures and subsequent disappointments.

2. AIMS OF THE THESIS

The overall aim of the thesis was to gain more knowledge about emotional dysfunctions in the early phase of psychotic disorders.

Paper I

In paper I we aimed to describe the time course of lifetime SCID-I verified Major Depressive Episode (MDE) in first episode psychosis and examining differences in demographic and clinical characteristics between patients with and without a lifetime history of MDE. Finally we wanted to examine how different patient characteristics were associated with current level of depressive symptoms. An emphasis was put on gender differences.

Paper II

In paper II we aimed to investigate to what extent premorbid adjustment is related to self-esteem in first episode psychosis, to what extent self -esteem is related to the level of hallucinations and finally, we explored to what extent self-esteem is related to the level of delusions in general and persecutory delusions in particular.

Paper III

In paper III we aimed to validate the Liebowitz social anxiety scale (self-rated version) in a first episode psychosis sample. Finally, we explored the role of self-esteem as a possible predictor of social anxiety while adjusting for current level of delusions, suspiciousness and depression.

Paper IV

In paper IV we aimed to investigate whether first episode patients with high levels of current social anxiety symptoms revealed poorer premorbid functioning and stronger associations to clinical correlates such as current psychotic symptoms and depression. Furthermore we wanted to explore if they had lower levels of current functioning, better insight and lower self-esteem than patients with no or minor symptoms of social anxiety. Finally, we wanted to explore if social anxiety per se was a possible independent predictor of quality of life.

3. METHODS

3.1. Design

The present thesis is based upon data from the Thematically Organized Psychosis (TOP) Study, which is a large ongoing translational research study. The design of the current study is naturalistic and cross-sectional with focus on first episode psychosis patients. The overall aim of the TOP study is to investigate clinical and biological characteristics of schizophrenia spectrum and bipolar disorders in order to gain more knowledge about underlying pathoplastic factors. Clinical and neurocognitive data has been collected, along with data from functional and structural MRI and genetic information. The study is affiliated with the University of Oslo and Oslo University Hospital (including three of four psychiatric units in Oslo). Furthermore, there are participants from two neighbouring counties and one unit in mid-Norway, Innlandet Hospital Trust. All clinical participants were recruited consecutively from both in-patient and out-patient units. The Norwegian catchment area patient admittance system allows for a high degree of patient representativity, as all people are offered public mental health care when needed within a given catchment area.

3.2. Material

The TOP-study has aimed at including all consecutively admitted patients with a psychotic disorder in treatment at any of the connected hospitals. Inclusion to the TOP-study started late 2002, and the inclusion process is still running. To be eligible for inclusion, the patients had to be aged between 18 and 65 years, have a DSM-IV diagnosis of psychotic or bipolar disorder or major depression with mood incongruent symptoms. Exclusion criteria were; having an IQ below 70, history of serious brain damage, a diagnosis of a developmental disorder or not being able to speak nor understand Norwegian language. All patients were in treatment and were referred from their main clinician. Emphasis was put upon the ability to give informed consent before inclusion to the project.

The study samples in the present thesis comprised three partly overlapping samples of first episode psychosis patients recruited to the TOP-study (see Appendix 2. for an overview of the different samples). First episode patients were defined as patients being treated with

antipsychotic medication in adequate dosage for less than a year, and if being treated previously, not treated more than 12 weeks or until remission. The sample described in paper I mostly consists of individuals included at an earlier time point than the samples represented in paper II-IV. These patients are recruited from the hospitals in Oslo County and the two neighbouring counties that at the given time point were connected to the TOP-study. A hospital representing mid-Norway, Innlandet Hospital Trust, was connected to the general TOP-study during the inclusion period. Their contribution is reflected in paper II-IV as will be discussed later.

The number of patients in each sub-study was selected depending on whether they had been assessed with specific assessment tools found relevant to answer the chosen research questions represented by the four papers. In paper I, 122 patients had been assessed with the Calgary Depression Scale for Schizophrenia (CDSS), in paper II 113 had been assessed with the Rosenberg Self-Esteem Scale (RSES), in paper III and IV , both comprising the same sample, 144 had been assessed with the Liebowitz Social Anxiety Scale (LSAS-SR). There are several reasons why the samples are only partly overlapping. The RSES and the LSAS-SR were added to the study protocol at a late stage of inclusion to the TOP-study. Data for paper I was thereby drawn from an earlier population. Regarding the RSES, one of the inclusion sites missed adding this form into their protocol. This was discovered at a later stage, and the form was then added. Unfortunately, this reduced the number of subjects available for analysis in paper II. The samples in paper III and IV are identical.

In paper I and II, patients with Major depression with mood incongruent symptoms as their primary diagnosis were not included. Paper I explores depression as a comorbid symptom dimension, and as such the inclusion of individuals with depression as their primary diagnosis did not seem appropriate. The strong association between a primary diagnosis of depression and lowered self-esteem was the basis for exclusion in paper II, where the main focus was upon self-esteem in psychotic disorder.

3.3. Measures

3.3.1. Diagnostic assessment

Diagnosis was based on the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995), modules A-E. The patients were interviewed by trained psychologists and psychiatrists who were regularly supervised during diagnostic consensus meetings led by Professor in Psychiatry Stein Opjordsmoen, a clinically well experienced investigator. Furthermore, all the interviewers had completed the general training- and reliability program in the TOP research study based on the training program at the UCLA (Ventura et al., 1998). For DSM-IV diagnostics, mean overall kappa with training videos was 0.77, and mean overall kappa for a randomly drawn subset of actual study patients was also 0.77 (95% CI 0.60-0.94).

3.3.2. Clinical assessment

Current psychotic symptom level was rated using the Structural Clinical Interview of the Positive And Negative Symptom Scale (SCI-PANSS) (Kay et al., 1987). Inter-rater reliability, measured by the intra class correlation coefficient (ICC 1.1), were for the PANSS positive subscale was 0.82 (95% CI 0.66–0.94), for the PANSS negative subscale 0.76 (95% CI 0.58–0.93), the PANSS general subscale 0.73 (95% CI 0.54–0.90). Current psychosis was defined as a score of 4 or higher on any of the following PANSS items: P1, P3, P5, P6 or G9.

Global symptoms and psychosocial functioning were measured by the Global Assessment of Functioning Scale (Jones et al., 1995). We applied the split version(Pedersen et al., 2007). It distinguishes between symptom level (GAF-S), the overall degree of present symptoms, and function level (GAF-F), which focus on the overall degree of social and occupational functioning. Inter-rater reliability, measured by the intra class correlation coefficient (ICC 1.1), for the GAF symptom scale was 0.86 (95% CI 0.77–0.92) and for the GAF functioning scale was 0.85 (95% CI 0.76–0.92). Higher scores indicate fewer symptoms and better functioning.

Premorbid adjustment was measured with the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). The premorbid phase is defined as the time from birth until 6 months

before onset of psychosis. It measures both social and academic functioning during four age ranges. We only included the age range of childhood (-11 years) and early adolescence (12–15 years) as the usual onset of schizophrenia spectrum disorders is in early adulthood. We thus tried to avoid 'contaminating' the premorbid period as it can be difficult to identify the exact time point of conversion to psychosis, especially in individuals with insidious onset. To make ratings on items regarding sociability and withdrawal, peer relationships, academic performance and adaptation to school, information was collected within each age range based on information from the patient, medical journal and significant family members, when appropriate. Increasing scores indicate poorer functioning. In paper I we used the mean score of the sub measures of the PAS, and in paper II and IV, we used the total sum score of the PAS sub measures.

Duration of untreated psychosis (DUP) was measured following the criteria described by Larsen et.al (Larsen et al., 1998); time from the first onset of positive psychotic symptoms (the first week with a PANSS score of 4 or above on at least one of the Positive Scale items 1, 3, 5, 6 or General scale item 9) to the start of first adequate treatment of psychosis.

Current severity of depressive symptoms was assessed using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990). Number of lifetime MDE was defined according to SCID-I. We registered MDE up until one year before the recorded onset of the first psychotic episode as MDE with onset before psychosis, and MDE with onset within the same year or after the onset of the first episode as MDE with simultaneous onset or onset after psychosis.

Self-esteem was assessed using the Rosenberg self-esteem scale (RSES) (Rosenberg, 1965). This is a 10-item self-administered questionnaire with a 4-point likert-type response set, ranging from strongly disagree to strongly agree.

Social phobia was assessed using the self-rating version of the Liebowitz Social Anxiety Scale (LSAS-SR). The LSAS comprise 24 items measuring fear and avoidance separately for 24 social situations over the past week. We chose the same way to instruct the patients abut how to fill in the questionnaire as described by Fresco et al. (Fresco et al., 2001).

Insight was measured by the Insight Scale (Birchwood et al., 1994) and includes three dimensions of insight; 'awareness of illness',' awareness of symptoms of psychotic illness' and 'belief in need for treatment'.

The Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) was used to screen for problem drinking , and use of illegal drugs was assessed with Drug Disorders Identification Test (DUDIT) (Berman et al., 2005).

3.4. Literature search

To get an overview of relevant literature, a thorough search was performed during the early phases of this PhD work. With assistance from librarians at the Medical Library at Oslo University Hospital-Ullevaal, searches were performed in databases such as PubMed, Medline and Psychinfo on the topics depression, self-esteem and social anxiety (and interchangeable expressions) in relation to psychosis or schizophrenia. During the research period, regularly searches have been performed to check up on recently published relevant publications. Bibliographies from important papers have been checked for relevant supplements. Hopefully, we have covered the most important literature concerning the topics discussed in this thesis.

3.5. Statistics

All data were analysed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA, version 16.0). Preliminary analyses were performed to examine the distribution of each variable which included inspection for skewness, linearity and outliers. Only the duration of untreated psychosis (DUP) required transformation to its natural logarithm (Ln(DUP+1)), due to skewed data distribution. The five factor model of the PANSS scale (Bentsen et al., 1996) was used in paper I, III and IV. Descriptive statistics for the whole sample were obtained using proportions, standard deviations, means, medians or range according to the measurement type and distribution. Independent sample t-tests were used to assess potential differences between groups on demographic and symptom variables. Pearson correlation coefficients were used to show how the variables were associated within the groups. Significance level was set to $p < .05$; all tests were two-tailed. Differences between multiple groups in normally distributed continuous variables were analyzed with

factorial One-Way Analysis of Variance (one-way ANOVA) with post-hoc Tukey tests. Hierarchical multiple linear regression analysis was performed to control for possible confounders and explore the proportion of variance explained for continuous variables. Psychometric properties of the LSAS-SR were analyzed using principal component factor analysis with Varimax rotation.

Further information about the analysis of the different sub studies has been thoroughly described in each paper, and the reader is referred to these for more detailed information.

3.6. Ethical aspects

3.6.1. The participants perspective

The TOP-protocol is an extensive and time-consuming protocol including diagnostic interviews, neurocognitive tests, blood/urine sampling, somatic testing and can include brain imaging. The total evaluation time was several hours and in most cases had to be divided over several days. Despite this, the time used for this thorough diagnostic evaluation was not considered much longer than what is common in a normal clinical setting, but resulted in a more extensive report than usual. The burden for each patient was therefore considered to be acceptable, which is very important for research including participants with severe mental disorders. To alleviate the stress following the extensive interviews and tests, the participants were frequently asked if they wanted a break or would like to continue another day. They were welcomed to bring someone with them to the tests and interviews if they felt more secure and less stressed by doing so. The final report was sent to the clinician who was in charge of the participants' treatment, if this was agreed upon. The participant could also ask the investigators to withhold certain information he/she did not want the clinician to know about regarding drug/alcohol abuse. This was to ensure that the participants felt free to admit if they had problems with drugs/alcohol that had been denied in treatment settings.

The impression was that most of the participants appreciated the long time the investigators had to talk with them about their problems compared to the time limited appointments in a normal clinical setting. Both normalization and psycho-education was extensively used

during the interview which often resulted in positive feed-back from the patients. There were, however, a few patients who expressed feeling disappointed after receiving their diagnosis, and argued that they were misunderstood etc. In such cases, an extra effort was made to thoroughly explain the basis for the conclusion. My personal opinion in these cases was that reactions like this were connected to the specific diagnosis of schizophrenia, and stigma surrounding this diagnosis. I found it helpful to discuss the continuum-hypothesis with these patients and be very careful to check out their specific beliefs about having a diagnosis of schizophrenia. Furthermore, they were once more informed about their right to have all data deleted and refuse to further participate in the study.

The project was approved by the Regional Ethics Committee (ref # 493-03-01179).

3.6.2. Data collection and handling

Written informed consent was obtained before entry to the study. Information about the study and the procedure was given both written and orally by a trained MD or psychologist well aware of the importance of doing this properly as some degree of cognitive difficulties can be present in some of these patients. Included in the information was the purpose of the study, extent of investigation and interviews, how and for how long personal information would be stored, and how confidentiality would be maintained. They were also informed about their right to see all data collected in their name, and have these deleted on any request. Furthermore, it was stressed that this was a voluntary project, and that refusal would *not* have any consequence for their future treatment or right to be diagnostically evaluated in their usual clinical setting.

The collecting and handling of data were approved by the Norwegian Data Protection Agency (ref # 2003/2052). The TOP database was inspected and approved by the Clinical Monitor at Oslo University Hospital (Ullevål) (Audit certificate 12.03.07). Personal information was handled following the same rules as applied within the EU countries medical system. The only persons with access to personal information will be health care professionals with a duty of confidentiality. A numerical code replaced all personal identifiers when handling the data. The key to this code was kept separate from the archive

and was stored at a similar security level as the ordinary patient data elsewhere in the hospital system.

4. RESULTS/SUMMARY OF PAPERS

Paper I: Depression and depressive symptoms in first episode psychosis.

Objective: The main aim of the present study was to examine the prevalence and pattern of lifetime DSM-IV Major Depressive Episodes (MDE), and the relationship between patient characteristics and current depressive symptoms in first episode psychosis patients.
Method: A total of 122 First episode psychosis patients were included. Current severity of depression was measured by the CDSS, psychotic symptoms were assessed by the PANSS and premorbid functioning was assessed by the PAS. Furthermore, assessment of alcohol and drug patterns was measured with the AUDIT and DUDIT and functioning by the GAF.

Results: A total of 58 patients (48 %) had experienced one or more MDE. Twenty-seven (22%) patients had experienced recurrent MDE. There were no differences between the groups having a lifetime history of MDE and the group who did not on demographic variables. On clinical variables such as GAF, PAS or PANSS the only difference was found in the depressive factor score of the PANSS. Twenty-five (21%) patients met the criteria for a MDE at the time of inclusion. Furthermore, 21 (17 %) patients had met the criteria for an MDE before onset of psychosis and 37 (30 %) during or after onset of psychosis, and significantly more females than males (13(30%) vs. 8(10%)) (p= 0.01) had experienced a MDE before onset of psychosis. Poor premorbid adjustment in childhood, substance abuse and excitative symptoms at start of treatment were significantly associated with higher current depressive symptoms. Gender, AUDIT and PANSS excitative symptoms explained a significant proportion of the variance in the CDSS scores for the total sample. Divided by gender, alcohol use predicted current depression in men, while excitative symptoms were predictive of current depression in women in the final model.

Conclusion: Depressive symptoms are frequent among patients with a first episode psychosis and in many cases; these symptoms seem to predate the first episode of psychosis. Furthermore, this study indicates that there may be gender specific factors associated with the development of depression in psychosis.

Paper II: Self-esteem is associated with premorbid adjustment and positive psychotic symptoms in first episode psychosis.

Objective: Self-esteem is often found to be compromised among persons with mental illness. Furthermore, low levels of self esteem have been implicated as both a cause and consequence of severe mental disorders. The main aims of the study were to examine whether poor premorbid adjustment was associated with lowered self-esteem and whether lowered self-esteem was found to contribute to the development and persistence of delusions and hallucinations in our model.

Method: A total of 113 patients were included at first treatment. The PANSS was used to assess present psychotic- and general symptoms. Premorbid adjustment was measured with the PAS and self-esteem by the RSES. Current depression was diagnosed according to the criteria for DSM-IV.

Results: Self-esteem was significantly associated with the four submeasures of PAS (childhood and early adolescence social and academic score), hallucinations, persecutory delusions and depression. Furthermore, females reported lower self-esteem than males. A hierarchical multiple regression analysis with self-esteem as the dependent variable revealed that gender and early adolescence premorbid social adjustment contributed significantly to the explained level of global self-esteem in the final model. They explained respectively 16% and 9% of the variance in self-esteem. A second set of hierarchical multiple regression analyses with positive psychotic symptoms as the dependent variables, revealed that self-esteem explained a significant amount of the variance in hallucination and persecutory delusions; respectively 11 % in hallucinations (p3) and 7 % in persecutory delusions (p6). This was after controlling for age, gender and depression.

Conclusion: The current study revealed a significant association between self-esteem and premorbid adjustment, especially social adjustment. Furthermore, we found an association between poor self-esteem and higher level of positive psychotic symptoms, namely hallucinations and persecutory delusions. Both main findings are of importance when evaluating possible treatment approaches. Firstly, if self-esteem is linked to poor premorbid

adjustment, a more active approach towards increasing self-esteem in adolescence would be of interest from a preventive point of view. Furthermore a more targeted treatment approach towards increasing self-esteem by therapeutic interventions in first episode patients may possibly reduce psychotic symptoms.

Paper III: Assessment of social anxiety in first episode psychosis using the Liebowitz social anxiety scale as a self-report measure.

Objective: Social anxiety is a common problem in psychotic disorders. The Liebowitz Social Anxiety Scale, Self-Rating version (LSAS-SR) is a widely used instrument to capture different aspects of social anxiety, but its psychometric properties has not been tested in this patient group. The aims of the present study were to evaluate the psychometric properties of the LSAS-SR in patients with first episode psychosis, to investigate whether it differentiated between active and passive social withdrawal and to test which clinical factors contributed to current level of social anxiety.

Method: A total of 144 patients were included at the time of first treatment. Psychotic and general symptoms were assessed by the PANSS, while depression additionally was measured by the CDSS. Self-esteem was assessed by the Rosenberg self-esteem scale and finally, social anxiety was measured by the LSAS-SR. To validate the psychometric properties of the LSAS-SR, a factor analysis was carried out and the relationship of social anxiety to psychotic and general symptomatology was evaluated. Possible predictors to social anxiety were analyzed using multiple hierarchic regression analysis.

Results: The Fear and Avoidance subscales turned out to be strongly correlated and loaded on the same factor. For the subsequent factor analysis, only the fear subscale was used. The factor analysis identified three subscales accounting for 56% of the variance; Public performance, Social interaction and Observation. All three subscales showed satisfactory psychometric properties, acceptable convergent and discriminate properties, and confirmed previous findings in social anxiety samples. The scale differentiated between active and passive social withdrawal. Lastly, self-esteem explained a significant amount of the variance

in social anxiety, even after controlling for delusions, suspiciousness and depression in the final model.

Conclusion: The study shows that the LSAS-SR can be used to assess social anxiety in first episode psychosis as it revealed satisfactory psychometric properties. Furthermore, it demonstrated that it was able to differentiate between active and passive social withdrawal and finally that self-esteem is a contributing factor to social anxiety. The results support the use of this measure in assessment of social anxiety in both clinical settings and in research.

Paper IV: Severe social anxiety in early psychosis: associated with poor premorbid functioning, depression and reduced quality of life.

Objective: The relationship between anxiety and other clinical characteristics and functioning is not yet fully understood. The main aims of the present study were to test whether first episode psychosis patients with severe social anxiety shows poorer premorbid functioning, higher level of current clinical symptoms, better insight, lower current functioning and reduced quality of life.

Method: A sample of 144 individuals was divided into three groups depending on current level of social anxiety symptoms measured by LSAS-SR; 1) no social anxiety (no-SaD), 2) clinically relevant symptoms of social anxiety (SaD) and 3) generalized social anxiety symptoms (G- SaD). Analysis of variance was performed including measures of demographic and clinical characteristics. Furthermore, a hierarchical regression analysis was performed to explore possible predictors of quality of life.

Results: Seventy-nine per cent of the sample had some clinical symptoms of social anxiety, and 68 (47%) met the criteria for G-SaD. There were no significant differences between the three groups for age, education or primary diagnosis. Being in the G-SaD group was associated with poorer premorbid adjustment, lower social functioning, lower self-esteem and higher levels of depression, while there were no group differences in level of psychotic symptoms. Furthermore, the G-SaD group revealed a higher awareness of illness more related to depression and low self-esteem, than to psychotic symptoms, and experienced

reduced quality of life. In the final hierarchic regression model we found that higher level of social anxiety predicted poorer quality of life even when adjusted for psychotic symptoms and depression.

Conclusion: The current study indicates that those mostly impaired by social anxiety, exhibit distinct clinical patterns and are more impaired on several measures as; poorer premorbid functioning, higher levels of depression and lower self-esteem, despite the fact that there were no significant differences between the groups on measures of psychotic symptoms. Furthermore, social anxiety is an important factor associated with poorer quality of life, an outcome measure of utmost importance

5. DISCUSSION

5.1. Discussion of main results

The current thesis has focused on emotional dysfunction in first episode psychotic disorders. It has explored relevant associations regarding possible pathways to emotional dysfunction as previously described. Pertaining the developmental pathway, paper I, II and IV are all concerned with the relationship between premorbid functioning and symptoms of emotional dysfunction in terms of depression (paper I), self-esteem (paper II) and social anxiety (paper IV). All papers (paper I-IV) discuss issues related to the second pathway, viewing emotional dysfunction as intrinsic to the psychotic episode, but only paper II specifically analyzes the role of emotional dysfunction in the formation of psychotic symptoms. In paper IV the third pathway is explored in relation to how insight into illness and subjective quality of life are related to emotional dysfunction.

The main findings of this thesis could be summarized as follows:

1) Depression, social anxiety and low self-esteem are prevalent in first episode psychotic disorder. Gender specific factors were associated with the development of depression in psychosis.

2) Depression, social anxiety and self-esteem are all significantly associated with poor premorbid adjustment.

3) Self-esteem was associated with both hallucinations and persecutory delusions.

4) The Liebowitz social anxiety scale as a self rated version revealed satisfactory psychometric properties and was able to differentiate between active and passive withdrawal.

5) The patients mostly impaired by symptoms of social anxiety were found to reveal poorer premorbid functioning, higher levels of depression and lower self-esteem than patients with mild or no symptoms of social anxiety despite no significant differences between the groups on measures of psychotic symptoms.

6) Social anxiety is an important predictor of quality of life.

5.1.1. Prevalence of emotional dysfunction

Overall, the findings presented support that depression, social anxiety and low self-esteem are prevalent in first episode psychosis. Close to 50 % of the patients had a lifetime history of one or more MDE, while 21 % met the criteria for a MDE at time of inclusion (paper I). Likewise, nearly half of the patients with a first episode psychosis experienced severe social anxiety problems when engaging in social interaction and performance (paper IV), and this group had significantly lower levels of self-esteem and more depression than those with no or minor problems with social anxiety.

There exists a substantial body of literature demonstrating the importance of emotional dysfunction in chronic samples. However, the findings in the current thesis indicate that symptoms of emotional dysfunction are prevalent from early on and that features of emotional dysfunction are associated with each other. After we finished the preparation of our four papers, two new publications supporting our findings were published. One study showed that from the prodromal phase and until one year after onset of psychosis 80 % FEP patients had experienced at least moderate levels of depression (Upthegrove et al., 2010). The other study found moderately low self-esteem among 167 FEP patients, and that self-esteem predicted functional out-come at six months (Vracotas et al., 2010).

5.1.2. Gender differences

Results presented in paper I revealed that females were three times more likely than males to have experienced a MDE before onset of the first psychotic episode. Additionally, we found that the PANSS excitative symptoms explained a significant amount of the variance in current severity of depressive symptoms for women, while drinking habits were associated with depression in men in the final regression model. Lastly, findings presented in paper II demonstrated that women with FEP had lower levels of self-esteem than men. These findings are important as gender differences in schizophrenia have received minimal attention over the last years, despite the fact that women with schizophrenia differ from men in several aspects besides being more depressed. Women, diagnosed with a psychotic

disorder, are characterized by symptoms of more irritability, hostility, inappropriate affect and impulsivity compared to men with a psychotic disorder (Leung and Chue, 2000).

The fact that women are more depressed than men mirrors the general population. Furthermore, substantial literature from studies in the general population indicates that women have significantly lower levels of self-esteem than men, even after correcting for level of depression (Accortt et al., 2008). Relevant explanations for these differences include the effect of genetic influence, neurotransmitter systems , brain asymmetry, hormones and stressful life events (Accortt et al., 2008).

Perhaps our findings of more excitative symptoms and depression among women with FEP are an expression of dysfunctional coping strategies due to previous adverse life events, such as trauma. Stressful life events are of significant importance when discussing psychotic disorder in general. Traumatisation, abuse and neglect have for a long time been linked to the development of impulsive and affective personality traits in the general population (Ball and Links, 2009;Alexander et al., 2007), and the same factors have been associated with subsequent development of psychosis (Read et al., 2001). A review by Goodman and coworkers states that among women with severe mental illness the prevalence rates of physical and sexual abuse range from 51-97% (Goodman et al., 1997). A previous review found a weighted average of child sexual and physical abuse in women to be 69%, compared to 60% in men exploring samples of psychiatric in-patients (Read, 2004). A considerably larger number of females compared to males had been victims of sexual abuse and incest (50% and 29% vs. 28% and 7%).

Our findings of lowered self-esteem in women could be a reflection of more previous negative life events in this group. However, another possibility is that men with schizophrenia, due to cognitive disabilities and an earlier onset of psychosis than women are less able to express their feeling of inferiority and low self-esteem, and consequently rates themselves as having a higher level of self-esteem. Also cultural tradition facilitates gender specific expectation which have an important influence both on behaviour and expression of pathology.

As for the male patients, the finding of a significant association between drinking habits in men and current severity of depressive symptoms supports previous studies (Verdoux et al., 1999) and could imply a more focused assessment and subsequently more active treatment approach to problem drinking. However, this finding should be interpreted with care regarding gender and clinical implications, as there are reasons to assume that alcohol abuse in women is also associated with depression, but the prevalence of alcohol abuse among women with psychosis is lower. A Swedish study found that male patients started to abuse alcohol at an earlier age than women (20.4 versus 28.0 years) (Cantor-Graae et al., 2001). This may explain the finding of gender differences concerning drinking habits obtained in the present thesis as this is both a FEP-study and has a skewed distribution with regard to gender.

5.1.3. Emotional dysfunction and the developmental pathway

We found that level of depression at start of treatment was significantly associated with poorer premorbid childhood social- and academic functioning (paper I). Furthermore, we found associations between premorbid adjustment and level of global self-esteem (paper II) and between premorbid adjustment and severe social anxiety (paper IV). We interpret our findings to be in line with the idea of a possibly disturbed developmental pathway to emotional dysfunction where premorbid adjustment mirrors developmental difficulties (Birchwood, 2003).

There are studies which suggest that patients with psychotic disorders inherit a premorbid vulnerability that might reduce their ability to achieve and maintain social competence with a subsequent effect on premorbid adjustment (Bentall et al., 2001;Freeman et al., 2002;Garety et al., 2001). A theoretical consequence of this vulnerability is the stress-diathesis model which propose that patients with a severe psychotic disorder are more sensitive to stress (Norman and Malla, 1993). This model views the vulnerability as mainly being of genetic or possible perinatal origin. However, premorbid adjustment might mirror a confluence of organic and psychosocial precipitating factors involved in the development of both emotional dysfunction and psychosis as described in a recent paper discussing environmental factors (van Os et al., 2010). It is tempting to discuss these psychological,

social and biological factors separately, but as they are intertwined, a more complex model including all three aspects has to be applied to comprehend the full picture.

A Swedish cohort-study found that psychological constructs of difficulties in achieving and maintaining close relationships were the variables that were most significantly associated with later development of schizophrenia (Malmberg et al., 1998). In line with this is a study suggesting a link between shyness, schizophrenia and social dysfunction from early childhood (Goldberg and Schmidt, 2001).

The results of the present thesis regarding premorbid adjustment are also of interest when discussing social and cognitive models expressed by social ranking theory (Gilbert and Allan, 1998). Studies of persons with auditory hallucinations have shown that voice hearers experience a subordinate relationship to their voices mirroring other social relationships and suggesting the existence of maladaptive interpersonal schemata serving both (Birchwood et al., 2000b). These schemata are not necessarily a result of the psychotic illness, but a result of premorbid poor social adjustment and might be seen in line with theories of how long term experience of social defeat, can be a risk factor for psychosis (Selten and Cantor-Graae, 2005). All studies demonstrate how psychological mechanisms are in play, but there are several other explanatory factors involved to be able to explain this. Biological and social factors are implicated. Previous studies have shown that general cognitive abilities, exposure to bullying, social marginalization and abuse/neglect are the strongest predictors of social adjustment in psychosis (Selten and Cantor-Graae, 2005;Gracie et al., 2007;Garety et al., 2007). Furthermore, there are studies demonstrating that early traumatic events can result in persistence of fear-related neurophysiological patterns affecting emotional, behavioral, cognitive, and social functioning (Heim et al., 2000;Perry and Pollard, 1998;Read et al., 2001). Others have found a link between reduced flexibility in abstract thought, flexibly shifting mind set and social anxiety (Lysaker and Hammersley, 2006;Lysaker et al., 2004) both in people with and without a severe mental disorder (Easter et al., 2005;Hariri et al., 2003). Hence, factors involved in cognition with presumable neurodevelopmetal correlates may be involved on several stages of the process. Furthermore, there are studies supporting the idea that childhood trauma and adverse life

events may act directly and mold the early brain development (Read et al., 2005;Bentall and Fernyhough, 2008).

To sum up, there is a large body of evidence supporting multiple pathways to poor premobid function including i.e. psychosocial factors as shyness, difficulties achieving friends, feeling subordinate in relation to others, marginalisation, abuse, trauma and neglect. Furthermore biological factors as genetic vulnerability or acquired neurological disabilities causing cognitive dysfunction may interact and cause not only a predisposition to poor premorbid functioning, but to emotional dysfunction in psychosis as well.

To explore this further, it might be necessary to look for subgroups. In paper IV we divided the group into three subgroups dependent upon level of social anxiety. Interestingly, the group mostly impaired by symptoms of social anxiety differed not only with regard to premorbid functioning, but on measures of self-esteem, depression and duration of untreated psychosis. As the group did not differ significantly on level of psychotic symptoms, this could imply that *level* of emotional dysfunction might be more related to aspects of premorbid functioning and indirectly reflects a higher load of precipitating pathoplastic factors which may be of psychosocial or biological origin.

5.1.4. Emotional dysfunction as intrinsic to the psychotic episode

In paper II we found self-esteem to be associated with both hallucinations and persecutory delusions in FEP. This is in line with previous studies (Bentall et al., 2008;Barrowclough et al., 2003;Smith et al., 2006;Thewissen et al., 2008). Garety's cognitive model of psychosis suggests that the experience of social adversity and lowered self-esteem eventually can lead to the development of psychotic symptoms (Garety et al., 2001). We would further argue that poor premorbid social adjustment with social withdrawal and subsequent marginalization will provide content to psychotic attribution by lack of correcting sources. This is supported by findings in studies of patients at high risk of developing psychosis (Cannon et al., 2008) and by findings in the general population, where negative ideas about oneself and others were found to predict paranoid thinking (Freeman et al., 2008b). In a Dutch population sample, premorbid neuroticism and low self-esteem were found to be associated with subsequent development of psychosis or psychosis-like symptoms at 3-year

follow-up (Krabbendam et al., 2002). If we take the continuum hypothesis of psychosis into consideration (Van Os et al., 2009), it is not surprising to find the same pattern in a FEP sample, such as the present one, which is less influenced by a long history of psychosis.

Depression has formerly been acknowledged to be the clearest example of an emotional disorder intrinsic to psychosis (Birchwood et al., 2000a). Nevertheless, the present study did not reveal any clear associations to positive psychotic symptoms in paper I. Nor did positive psychotic symptoms explain a significant part of the variance in depressive symptoms. However, our findings are in line with a more recent paper concluding that prodromal depression, not the severity of positive or negative symptoms, is predictive of depression in the early course (Upthegrove et al., 2010). Furthermore, the authors propose that there is a constant vulnerability to depression, which begins in adolescence, is manifest during the prodrome and can, depending on stressors, re-emerge at later time points. Considering the findings discussed previously, this repeats the question about whether at least aspects of emotional dysfunction in psychosis and psychosis per se, is the result of a common vulnerability of psychosocial and/or neurobiological origin.

In paper IV, the study revealed no significant difference between the three groups divided by level of social anxiety, on current level of neither positive nor negative psychotic symptoms. Symptoms of social anxiety and level of psychosis seemed to be present together, but as more independent pathological entities. This was supported by the follow-up analysis in paper III which revealed that social anxiety was closely related to active social avoidance and not passive withdrawal which is a core component of the negative psychotic symptoms. Active avoidance was neither solely mediated through behaviour based on suspiciousness, delusions or depression, even though this will be the case for some individuals. Furthermore, findings described in paper III demonstrated that the LSAS-SR showed good psychometric properties in a sample of first episode psychosis patients and that the three factors indicated by the factor analysis to a large extent corresponded to factors identified in other populations (Baker et al., 2002;Safren et al., 1999). This indicates that both the phenomenology and the severity of social anxiety in psychosis most probably are indistinguishable from non-psychotic social anxiety disorder. That these findings are based

on self-reports suggest that patients have insight into their maladaptive thoughts and behaviour, indicating that they may also be amenable to change.

To sum up, in the final regression model, only self-esteem was found to have a direct association and significantly predict level of psychotic symptoms (even though the contribution in itself was of modest size). It is noteworthy that both depression and social anxiety are associated with low self-esteem. This is exemplified by previous findings revealing that social anxiety in psychotic disorders is associated with shame and feeling inferior, and the notion that low self-esteem might underpin social anxiety in schizophrenia (Birchwood, 2003;Gumley et al., 2004a). However, it is possible that self-esteem acts as a key mediator of emotional dysfunction in general in psychotic disorders.

5.1.5. Emotional dysfunction as a reaction to the psychotic episode

Only paper IV verged on this last pathway to emotional dysfunction. We found that the group mostly impaired by social anxiety differed on several measures as depression and self-esteem. This could be part of a psychological reaction to psychosis as described in the 'social rank' or 'perceived stigma' theory (Iqbal et al., 2000;Gilbert, 2001). Implicit in this theory is the assumption that an awareness of diagnosis and symptoms might have an impact on perceived stigma and social role. As a result the individual experiences reduced hope in future opportunities with regard to both social relationship and functioning with a subsequent fall in self-esteem, depression and anxiety. In our study, the patients with severe social anxiety reported a significantly higher level of 'insight into illness' compared to the other two groups, but interestingly, there were no significant differences between the groups concerning 'insight into (psychotic) symptoms' or 'need for treatment'. A previous study of social anxiety with similar findings (positive association between social anxiety and insight into illness only) interpreted this as the patients' awareness of their psychotic illness (Birchwood et al., 2006). However, the underlying items constituting this factor could be interpreted as questions concerning the patient's general mental condition. The sub analysis in paper III testing this, failed to find any associations between psychotic symptoms and 'insight into illness', on the contrary, it confirmed a significant association between 'insight into illness' and depression and social anxiety. Hence, we concluded that the patients

actually were rating their level of social discomfort and/or depression rather than insight into having a psychotic illness. Furthermore, there were no significant differences between the three groups concerning positive and negative symptoms, but the G-SaD group differed both in GAF-s and GAF-f. This might reflect higher depression/social anxiety scores and/or reduced functioning due to depression and/or social anxiety with active withdrawal.

To sum up, emotional dysfunction might develop as a reaction to the psychotic episode, but there are indications in the present study, that emotional difficulties have a history dating backwards and possibly precede the first episode. This does not preclude the possibility that the episode per se, or the reaction to it, may further deteriorate the emotional dysfunction. Interesting in this regard is the finding of a continuously increasing DUP between the three social anxiety groups, even though the only significant difference was to be found between those with no social anxiety compared to the other two groups.

5.2. Methodology

5.2.1. Sample representativity and generalizability

The Norwegian Health Care system is catchment area based and publicly funded. This should diminish the possibility of sample recruitment bias based upon geographic or socioeconomic differences. However, there are reasons to be concerned whether this is the case. All patients described in paper I are recruited from the hospitals in Oslo county or the two nearby counties. The samples represented in paper II-IV included patients from Innlandet Hospital Trust with a catchment area representing mid-Norway, a more sparsely populated area. As displayed in Appendix 1, the duration of untreated psychosis is considerably longer in the late samples. Thus, it is possible that the patients recruited from Innlandet Hospital Trust has been ill for a longer period of time, and thereby could reduce the generalisablity of our results. However, there were only minor differences on the other demographic variables listed in Appendix 2. Furthermore, including patients from more sparsely populated areas will better reflect the source population and the distribution of patients in Norway. Overall, this might be a fairly good picture representing the general situation.

Norway does not have a public register where all diagnoses given at discharge from treatment are available. We were thus not able to gather data on subjects who either declined to participate or was not invited be their clinician. This made it impossible to accurately estimate the rate of participation. There are several reasons why this may have caused a selection bias. First, individuals not being able to make an informed consent were not asked to participate. We furthermore assume that individuals severely impaired by their psychotic symptoms, depression or cognitive deficits in many cases declined or was not asked to participate because their clinician found it unethical to expose them for several hours of assessment. On the other hand, it is possible that very well functioning patients with a first episode psychosis not wanting to identify with a socially stigmatised group, declined to participate. This would imply that we are generalising from a group representing the majority, but with a bias towards loss of information regarding patients with a very low or a very high level of functioning – as in all studies of patients with severe mental disorders.

The patients were referred to the project via the professional who was responsible for the main treatment. This could be a physician, psychologist, nurse or specialised social worker. Professionals' attitudes towards research vary considerably not only between departments, but also within departments, and probably between different professional groups. Different motives could lie behind a reluctance to refer patients as worry about the extra burden a thorough assessment would put on the patient. This would bias the sample towards better functioning patients. However, the opposite might be more relevant, that there was a tendency towards referral of those patients who constituted a problem with regard to diagnostic assessment because of a blurred or atypical history. This is based on the conviction that research has to give something back to the institution in form of diagnostic help. Ultimately, this would bias towards less of the more common pictures of the diagnostic subgroups. Others might have previously "disappointing" experiences with former patients who turned out to receive a different diagnosis after assessment in the project than was expected in the clinic, thereby imposing a suspicious feeling towards the project.

To avoid the above mentioned biases, great effort was put on providing both written and verbal information about the project to professionals and patients. Furthermore, the

research fellows, that were responsible for including patients, regularly participated in meetings at the different units to locate individuals suitable for recruitment. When patients had been assessed, time was set off to go through the written report together with both patient and clinician to be able to provide answers to questions about the report or the diagnosis. This is the same procedure as in the former early intervention in psychosis study (TIPS-study) which recruited from one of the catchment areas in the presents study found incidence rates over a four year period of 12-17/ 100 000 (Melle et al., 2005). The TIPS-study is comparable to the TOP-study that has found almost similar rate of referrals of patients to the first-episode studies over a two year period, albeit in the lower range compared to TIPS; 12-14/100 000 (Faerden, 2009), and resembles findings elsewhere in the literature (Goldner et al., 2002). Overall, we assume that satisfactory efforts were made to reduce the selection bias as much as possible, and thereby reduce threats to external validity (Shadish et al., 2002).

5.2.2. Validity and reliability of assessments

The diagnostic and clinical assessment tools applied in the current study are all widely used instruments. To secure reliable assessments, the TOP-study has included in their program a standardised procedure including supervised training in all parts of the protocol and all research fellows responsible for inclusion participated in an extensive training program in diagnostic assessment led by Professor Joseph Ventura from the UCLA. Furthermore, tests for inter-rater reliability for SCID, PANSS and GAF were regularly conducted (for more detailed information about test results, see Methods).

In addition to the clinician rated instruments, self-report instruments were employed to answer some of the research questions. There are several reasons why the use of self-report could be a potential bias in research on psychotic disorders as; denial, shame, cognitive difficulties or distrust as to how the project will administer the information gathered. These possible threats to the internal validity (Shadish et al., 2002) are not specific for self-report though, but could as well be in play when using clinician rated instruments. To minimize these, a considerable amount of time was spent to strengthen the alliance between the investigator and the patient to diminish distrust towards both the investigator and the

project. Psychoeducation was also applied both to inform, but also to initiate hope and reduce stigma. Furthermore, cultural and ethnic diversity might be of importance in self-report as there is less opportunity to gather additional information if you worry whether the person actually understood you correctly. To minimize this possible source of bias, great effort was put into explaining each participant that the main investigator would answer all questions necessary to understand and complete the forms. Besides, all instruments contained written information about procedure and how to rate it.

However, previous research on this issue has demonstrated that standardized self-administered questionnaires on clinical outcome measures in schizophrenia show relatively good agreement with clinician ratings (Burlingame et al., 2005;Hamera et al., 1996). All self-report instruments referred to in the present thesis are widely used in studies of psychotic disorders and have been extensively validated. Only the LSAS-SR had not been thoroughly validated in a psychosis sample. The findings in paper III documented that social anxiety reported via self-rating yielded both valid and reliable results and revealed dimensions comparable to what is found in a general sample of patients with social anxiety disorder. Hence, we conclude that even though we can not rule out the possibility of biases mentioned above, we find the preferred instruments to have satisfactory psychometric properties used as self-report in psychotic disorder and that threat to internal validity were properly handled.

5.2.3. Strengths and weaknesses of the study

There are some strengths and weaknesses in the present study that needs to be described. Importantly, the study was financially supported by public grants and was not confounded by economical interests. The naturalistic and catchment-area based design with a multi-site organisation combined with the effect of a well function public Health Service has a strong impact on the generalizability of this project. Furthermore, the organization of the TOP-study with its emphasis on reliability, regular supervision and organized training modules add to the reliability of the results.

There are several limitations to the present study. The cross-sectional design makes it impossible to conclude regarding the direction of the associations between depression and

course of illness. There are, as usual in FEP studies, relatively more men compared to women in the present study. The distribution is though similar to what is found in other first episode psychosis studies. The retrospective diagnosis of earlier MDE's and PAS might be confounded by the patients' ability to remember the details correctly. However, as psychotic disorders are rare, a prospective study is difficult to perform, and hence, the advantage of being able to study these features in a FEP sample might be considered a reasonable solution.

Studying self-esteem in this context is a difficult issue. There are still uncertainties about what kind of self-esteem that has the most pronounced impact on the individual's quality of life and functioning. As previously mentioned, we have only measured global self-esteem, while it might be that the ability to measure several aspects of self-esteem including self-esteem instability would have added more knowledge to this issue. There are limitations to how many measures and interventions you can add, as a single research fellow, to an extensive protocol when entering a large collaborative study as the TOP-study. The same problem is part of the studies in social anxiety. It would have been preferable to have a more extensive battery of instruments to measure social anxiety including clinician rated instruments to be able to compare. Furthermore, our findings of emotional dysfunction in first episode psychosis would have benefitted from a matched control group without psychotic disorder.

5.3. Clinical implications

Both depression and social anxiety were significant predictors of subjective QoL. The present study thus supports previous research pointing to the importance of incorporating targeted monitoring and treatment of affective and anxiety symptomatology in severe mental illness (Hansson, 2006). The importance of being aware of depression is obvious as it is prevalent in psychosis and acts as an important contributor to the increased risk of suicide (Melle et al., 2006;Barrett et al., 2010). Furthermore, both social anxiety and depression are rarely a target of targeted therapeutic treatment and are often not recognized in the clinic due to focus on the traditional positive and negative symptoms (Cosoff and Hafner, 1998;Schneier et al., 1992). Considering evidence for new therapeutic gains as CBT has been proven

effective as adjunctive treatment for social anxiety in psychosis (Kingsep et al., 2003;Halperin et al., 2000), a more active approach towards recognition and treatment of social anxiety should be applied, and interventions aiming to reduce depression should be tested. Furthermore, a more focused living skills training to enhance social functioning targeted towards self-care, occupational, leisure and recreation, friendship and intimacy skills would be particularly relevant (Falloon et al., 1998). In line with this, cognitive behavioural therapy aiming to improve self-esteem with focus on correcting misattributing tendencies has showed clinical benefits in terms of both increased self-esteem, reduced positive symptoms and improved social functioning (Hall and Tarrier, 2003). Validated instruments to capture these symptoms have to be applied and follow as a natural part of the assessments in psychotic disorders.

Lastly, these implications are in line with recently published hopes for future treatment development; treatment addressing both underlying neurobiological vulnerability and aiming to protect against environmental risks (van Os and Kapur, 2009).

5.4. Implications for future research

Future research would benefit from a more thorough exploration of premorbid functioning to reveal what factors implicit in this term do have a significant impact on development of emotional dysfunction. There are several studies confirming how trauma and abuse do predict anxiety and depression, but more studies are needed to explore the relation between cognition and emotional functioning and between neglect and emotional functioning in psychosis. Hypothetically, this could lead to a more targeted approach to intervention and would be useful in treatment of individuals in risk of developing psychosis.

Future research would benefit from a closer link between child and adult psychiatry to explore if developmental psychology could provide more information about the role of self-esteem and its formation during childhood and early adulthood in persons at risk of developing a severe mental disorder such as a psychotic disorder.

Furthermore, studies to clarify whether *level* of emotional dysfunction in general actually divide these patients into clinically meaningful subgroups with different needs regarding treatment and rehabilitation would be of interest.

Lastly, gender differences have been a neglected area of research within psychotic disorders during the last decade, even though we do know they exist. There are to our knowledge no studies on gender differences regarding social anxiety in psychosis, which would be of interest as one theory behind the fact that males tends to be more withdrawn than women has been linked to the later onset of psychosis in women. However, this might not be the only reason, another option is that men with psychosis do have more severe cognitive impairment related to social adjustment on the basis of developmental problems. This has not yet been explored. Furthermore, studies aiming to explore the effect of personality traits and gender with regard to symptoms, treatment and diagnosis, are warranted.

6. CONCLUSION

Depression, social anxiety and lowered self-esteem are features frequently encountered in first episode psychosis. The current findings lend support to previous theories of multiple, but not mutually exclusive pathways to emotional dysfunction in psychosis. The strong relationship between the various comorbid conditions and premorbid adjustment found in the present material, indicate that for a large subgroup, these difficulties may have a history preceding the onset of psychosis. Furthermore, findings related to differences between groups depending on *level* of social anxiety could indicate that high levels of emotional dysfunction might reflect vulnerability for mental disorders in general as a result of a more developmental pathway. Subsequently, these individuals will be more prone to developing depression and anxiety in addition to psychosis.

However, both depression and social anxiety exist as separate entities and are not clearly linked to positive psychotic symptoms, while self-esteem may significantly contribute to level of positive psychotic symptoms. Considering the strong associations between self-esteem and depression and social anxiety respectively, self-esteem could be a key to future intervention. Interesting in this respect, is our use and validation of a self-report questionnaire emphasising that self-reported symptoms of social anxiety in a sample of first episode psychosis patients yields similar factors as in samples of non-psychotic patients. This adds strongly to moderation and application of validated treatment procedures for emotional dysfunction used in non-psychotic populations.

Finally, the present results indicate that aspects of emotional dysfunction do have an impact on quality of life independent of psychotic symptoms. Thus, the current thesis supports a more active approach towards both recognition and treatment of emotional dysfunction in terms of depression, social anxiety and lowered self-esteem, as quality of life has to be considered an outcome measure of utmost importance.

7. APPENDIX

Appendix 1: Abbreviations

FEP	First Episode Psychosis
GAF-s	Global Assessment of Functioning scale - symptom
GAF-f	Global Assessment of Functioning scale - function
G-SaD	General Social anxiety disorder
ICD-10	Classification of Mental and Behavioural Disorders -10
IQ	Intelligence Quotient
LSAS-SR	Liebowitz Social Anxiety Scale - Self-rated version
MDE	Major Depressive Episode
SCI-PANSS	Structured Clinical Interview for the Positive And Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
RSES	Rosenberg Self-Esteem Scale
SaD	Social anxiety Disorder
SCID - I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	Standard Deviation
TOP study	Thematically Organized Psychosis research study

Appendix 2: Table 1: Demographic and clinical background of study samples

	Paper I	Paper II	Paper III	Paper IV
Inclusion	July 2004-July 2007	February 2007-Oct 2009	February 2007-Oct 2009	February 2007-Oct 2009
N	122	113	144	144
Age (mean) (SD)	28,3 (9,2)	25,8	26,3 (8,4)	26,3 (8,4)
Female (%)	36	32,7	36	36
Single (%)	78,7	72,6	78	78
Married/cohabiting (%)	13,1	21,2		
Divorced/separated (%)	8,2	6,3		
Education (mean years) (SD)	12,7 (2,8)	12,4	12,4 (2,6)	12,4 (2,6)
DUP* (median)(range)	38 (0-1040)	78 (0-1040)	77 (0-1040)	77 (0-1040)
Diagnosis (%)				
Schizophrenia	50,8	60,2	51,0	51,0
Schizophreniaform	9,0	6,2	8,0	8,0
Schizoaffective	4,9	9,7	9,0	9,0
Brief psychosis	4,9	0,9	0,0	0,0
Delusional disorder	4,1	6,2	0,0	0,0
Psychosis NOS**	26,2	16,8	26,0	26,0
Major depression with psychosis	0,0	0,0	6	6

*DUP: Duration of Untreated Psychosis

**Psychosis NOS: Psychosis Not Otherwise Specified

APPENDIX 3: The five factor model of the Positive and Negative Syndrome Scale (PANSS) for Schizophrenia:

Positive factor
P1 Delusions
P3 Hallucination
P5 Grandiosity
G9 Unusual thougt content
G12 Lack of insight

Negative factor
N1 Blunted affect
N2 Emotional withdrawal
N3 Poor rapport
N4 Apathetic social withdrawal
N6 Lack of flow
G5 Mannerism
G7 Motor retardation
G11 Poor attention
G13 Disturbance of volition
G16 Active social avoidance

Excitative factor
P4 Excitement
P7 Hostility
G4 Tension
G8 Uncooperativeness
G14 Poor impulse control

Depressive factor
G1 Somatic concern
G2 Anxiety
G3 Guilt feelings
G6 Depression
G15 Preoccupation

Cognitive factor
P2 Disorganized
N5 Abstract thinking
G10 Disorientation

(Bentsen et al. 1996)

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II

Self-esteem is associated with premorbid adjustment and positive psychotic symptoms in first episode psychosis.

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Abstract:

Objective: Low levels of self esteem have been implicated as both a cause and consequence of severe mental disorders. The main aims of the study were to examine whether premorbid adjustment has an impact on the person's self-esteem and whether lowered self-esteem contributes to the development and persistence of delusions and hallucinations.

Method: A total of 113 patients from the Thematically Organized Psychosis research study (TOP) were included at first treatment. The Positive and Negative Syndrome Scale (PANSS) were used to assess present symptoms, premorbid adjustment was measured with the Premorbid Adjustment Scale (PAS) and self-esteem by the Rosenberg Self-Esteem Rating Scale (RSES).

Results: Premorbid social adjustment was significantly related to lower self-esteem, and explained a significant proportion of the variance in self-esteem. Self-esteem was significantly associated with the level of persecutory delusions and hallucinations and explained a significant proportion of the variance regarding both symptoms, even after adjusting for depression in the final model.

Conclusion: Premorbid functioning is an important aspect in development of self- esteem. Self esteem appears to play a significant role in the development of delusions and hallucinations.

Keywords: Self-esteem, First episode psychosis, Schizophrenia, Premorbid adjustment, Delusions, Hallucinations

Introduction

Self-esteem is a global and complex concept, comprising appraisal of self- worth based on personal achievements and anticipation of evaluation by others [1,2]. Even though not uniformly low, self-esteem is often found to be compromised among persons with mental illnesses [3]. Here, low self-esteem is of considerable interest because it is both a possible consequence and a cause of psychiatric symptoms [4-6]. Concerning the first, studies not surprisingly show that stigmatization and self-stigmatization may lower self-esteem in persons with mental illness [7]. On the other hand, low self-esteem also appears to increase the risk of psychiatric disorders such as depression, eating disorders and substance abuse [8]. In psychotic disorders, low self-esteem has been implicated in both the development of delusions [9,10] and the maintenance of psychotic symptoms [11].

Recent models of global self-esteem suggest that it is both a trait and a state measure [12]. People have a typical, average or trait level of self-esteem, while their momentary or state judgments of self-esteem can fluctuate around this level dependent on social feed-back and self-judgment. Furthermore, it is the person's interpretation of the event or circumstance, and its relevance to his or her contingencies of self-worth, that determines both *if* and *how strongly* an event will affect state self-esteem [12,13]. How treatment failures, functional loss, demoralization and stigmatization may lower self-esteem in patients with severe mental illnesses appears evident. To what extent low levels of self-esteem in severe mental disorders could be based on underlying or trait levels of self-esteem, and how this in turn may increase vulnerability to more severe symptoms, is not thoroughly explored. This is of importance both for understanding the mechanisms behind

the development of psychotic symptoms, and also for improving treatment as self-esteem can be influenced by therapeutic interventions [14,15].

One would assume that people's trait levels of self-esteem would be affected by early childhood and adolescence experiences. In line with this, studies have suggested that difficult childhood experiences such as childhood loss and social marginalization contribute to a cognitive vulnerability accompanied by a negative view both towards the person himself and towards others [4,11,16]. Here one could hypothesize that individuals with a history of poor premorbid adjustment (both social and academic) could be more prone to negative self-evaluation and reduced global self-esteem. To our knowledge only one study has tried to examine the relationship between premorbid adjustment and self-esteem in patients with schizophrenia spectrum disorder [17]. They found no relationships between self-esteem and premorbid adjustment in recovered psychotic patients. Premorbid adjustment was however not captured with a specific instrument which may account for the negative results.

There is a relatively rich literature on the relationship between low self esteem and symptom formation in severe mental disorders. Bowins and Shugar found that the contents of patients' delusions were consistent with patients' global self esteem, and suggested that low self-esteem accounted for the persistence of delusions [18]. Barrowclough and colleagues found a significant correlations between negative self-evaluation and a wider variety of positive symptoms (hallucinations and delusions) in schizophrenia [10], while Smith and coworkers found that patients with a low level of self-esteem and more depressive symptoms had more intense auditory hallucinations with a more negative content [19].

Other studies have on the other hand, found higher levels of self-esteem in patients with delusional disorder compared to depressed patients [20]. However, they found that the group without depressive symptoms had significantly higher levels of grandiose ideation than the other groups, which may account for the elevated levels of self-esteem. The authors concluded that persecutory delusions may reflect an attributional style protecting the individual from low self-esteem. Other studies have found equal levels of self-esteem in patients with delusions and matched healthy controls with both groups demonstrating higher levels than depressed patients [21].

Previous studies on the relationship between premorbid adjustment, low self esteem and positive symptoms have all been done in patients with chronic psychotic disorders, where the effects of a long-term severe illness may significantly confound relationships.

To our knowledge, no previous studies have examined this in patients coming to their first treatment for a psychotic disorder with less prominent effects of treatment failures and subsequent disappointments. The aims of the current study are thus to investigate in a large and well characterized group of patients with first episode psychosis (FEP):

1) To what extent is premorbid adjustment (measured by the Premorbid Adjustment Scale (PAS)) related to self-esteem (measured by the Rosenberg Self- Esteem Scale (RSES)) in this patient group?

2) To what extent is self -esteem related to the level of hallucinations (measured by the Positive and Negative Syndrome Scale (PANSS))?

3) To what extent is self-esteem related to the level of delusions in general and persecutory delusions in particular (measured by the Positive and Negative Syndrome Scale (PANSS))?

2. Method

2.1 Subjects

From February 2007 through October 2009, 113 FEP patients from the main psychiatric treatment centres in Oslo and two neighbouring counties were consecutively included in the Thematically Organized Psychosis research study (TOP). The inclusion criteria were: 1) age 18 - 65 years and 2) coming to their first treatment for a non-affective psychosis according to DSM-IV. Exclusion criteria were a history of organic brain disorder, a significant co-morbid medical condition or an IQ of less than 70. The diagnostic distribution was as follows (N (%)): schizophrenia 68 (60.2%), schizophreniform disorder 7 (6.2%) schizoaffective disorder 11 (9.7%), brief psychosis 1 (0.9%) delusional disorder 7 (6.2%) and psychosis NOS 19 (16.8%).

Patients were eligible for inclusion up to 52 weeks after the start of first adequate treatment for their disorder and were not considered as FEP patients if they previously on any occasion had been treated with antipsychotic medication in adequate dosage for more than 12 weeks or until remission. Being psychotic was defined as having a rating of 4 or more on the PANSS items p1 (delusions), p2 (disorganisation), p3 (hallucinations), p5 (grandiosity), p6 (persecutory delusions) or g9 (unusual thought content) for more than one week. The mean age of the patients was 25.8 (SD 7.7), 37 (32.7%) were females, 82 (72.6%) were single, 24 (21.2%) were married/cohabiting, 7 (6.3%) were divorced/separated/widowed. Mean years of education were 12.4 (SD 2.72) and median duration of untreated psychosis (DUP) was 78 weeks (range 0-1040) (N=106). All patients gave written informed consent and the study was approved by the regional research ethics committee.

2.2 Assessments

2.2.1 Measures

Diagnosis was set according to the Structured Clinical Interview for Diagnostic and Structural Manual of Mental Disorders, fourth version (SCID I interview for the DSM -IV) [22]. Current severity of psychotic symptoms was measured with the Structural Clinical Interview of the Positive And Negative Syndrome Scale (SCI-PANSS) [23]. Self-esteem was measured using the Rosenberg Self-Esteem Scale (RSES) [24]. This is a 10-item self-administered questionnaire with a 4-point likert-type response set, ranging from strongly disagree to strongly agree. Depression was diagnosed according the criteria for DSM-IV. We only measured Major depression to avoid overlap with negative symptoms. DUP was measured according to previously published criteria [25]. Premorbid adjustment was measured with the Premorbid Adjustment Scale (PAS) [26]. The premorbid phase is defined as the time from birth until 6 months before onset of psychosis. It measures both social and academic functioning during four age ranges. We only included the age range of childhood (-11 years) and early adolescence (12–15 years) as the usual onset of schizophrenia spectrum disorders is in early adulthood. We thus tried to avoid 'contaminating' the premorbid period as it can be difficult to point out the exact time point of conversion to psychosis, especially in individuals with insidious onset. Information was collected within each age range from the patient, medical journal and from significant family members when appropriate, to make ratings on items regarding sociability and withdrawal, peer relationships, academic performance and adaptation to school.

2.2.2. Procedures

The patients were interviewed by trained psychologists and psychiatrists at the same time as the SCID-I was administered. The investigators had all completed the general training- and reliability program in the TOP research study. For DSM-IV diagnostics, mean overall kappa with training videos was 0.77, and mean overall kappa for a randomly drawn subset of actual study patients was also 0.77 (95% CI 0.60-0.94). Inter-rater reliability, measured by the intra class correlation coefficient (ICC 1.1), was for the PANSS positive subscale 0.82 (95% CI 0.66–0.94), for the PANSS negative subscale 0.76 (95% CI 0.58–0.93) and the PANSS general subscale 0.73 (95% CI 0.54–0.90).

3. Statistical analysis

Correlations between demographic/clinical characteristics and self-esteem were calculated as Pearson's product moment coefficients. To estimate how much of the variance in self-esteem was explained independently by premorbid functioning, we performed a blockwise hierarchical multiple regression analysis with age and gender entered in the first block and premorbid adjustment in the second block. As academic adjustment in childhood versus academic adjustment in early adolescence, and social adjustment in childhood versus social adjustment in early adolescence were strongly inter correlated (with r=0.66 and 0.77; respectively), only results for early adolescence were entered to represent PAS and avoid co-linearity problems. The associations between global self-esteem and hallucinations and delusions (general and persecutory) were analyzed similarly using Pearson's correlations and followed up with three block-wise hierarchical multiple regression analysis with hallucinations, delusions and persecutory delusions as the dependent variables; demographic information in the first block (as this must be considered as the most basic

ones), depression (whether the patient was in a major depressive episode or not) in the second and self-esteem in the third. By entering self-esteem in the third, we controlled for the amount of variance explained by the variables in the two first blocks.

4. Results

Table 1 shows the patient characteristics of the 113 included patients.

Insert table 1 about here.

As displayed in table 2, self-esteem was significantly correlated with several demographic and clinical characteristics, including the four subscale measures of premorbid adjustment and with the levels of symptoms (depression, persecutory delusions and hallucinations). Furthermore, females reported lower self-esteem.

Insert table 2 about here.

In the first hierarchical multiple regression analysis with self-esteem as the dependent variable the included variables explained 25 % of the variance in self-esteem (Table 3). Only gender and social adjustment in early adolescence contributed significantly to the explained level of global self-esteem. Gender explained 16 % of the variance while premorbid social adjustment explained additionally 9 %.

Insert table 3 about here.

In the second set of hierarchical multiple regression analyses with positive psychotic symptoms as dependent variables, self-esteem explained a significant amount of the variance; respectively 11 % in hallucinations (p3) and 7 % in persecutory delusions (p6). This was after adjusting for age, gender and depression,

Insert table 4 about here.

5. Discussion

The main findings of this study are the demonstration of statistically significant relationships between poor premorbid social adjustment and low levels of global self-esteem on the one hand, and between self-esteem and positive psychotic symptoms (hallucinations and persecutory delusions) on the other hand. The last finding remained significant even after adjusting for the presence of a major depressive episode indicating that this effect is not mediated by the presence of depressive symptoms.

The current study is thus the first to show a relationship between poor premorbid social adjustment and level of global self-esteem in psychotic disorders. The only other study exploring this relationship [17] did not apply a specific validated measure of premorbid

adjustment (i.e. as the PAS), but did instead dichotomize collections of information based on the Diagnostic interview for Psychosis (DIP) as 'yes' versus 'no' poor premorbid adjustment, which implies both a less validated measure and a subsequent loss of variance in statistical analyses. In addition their sample consisted of older participants with a longer duration of illness, and thus a higher risk for recall bias. Premorbid social adjustment as a concept incorporates issues ranging from how you interact with your schoolmates, adjust to groups and friends and the presence of age-relevant sexual interest. Previous studies have shown that general cognitive abilities, exposure to bullying, social marginalization, abuse/neglect or the presence of neurodevelopmental factors are the strongest predictors of social adjustment [27-29]. Patients with psychotic disorder most probably have a premorbid vulnerability that might reduce their ability to achieve and maintain social competence and thus affects premorbid social adjustment [9,11,30]. This will in turn affect the individuals schematic beliefs about self and others that are dependent upon how we experience ourselves in relation to the world and thus lead to social adversity and a feeling of low self-esteem [16]. This is not contradictory to Bentall et al.'s model as attributional style will be affected by these same factors, whether it is an expression of genetic vulnerability, neurodevelopmental factors or the result of environmental effects [9]. The present study gives empirical support to these considerations.

The findings regarding premorbid adjustment are also of interest for social and cognitive models expressed by social ranking theory [31]. Studies of persons with auditory hallucinations have shown that voice hearers experiences a subordinate relationship to their voices mirroring other social relationships and suggesting the existence of maladaptive interpersonal schemata serving both [32]. These schemata are not necessarily a result of the

psychotic illness, but a result of premorbid poor social adjustment and might be seen in line with theories of how long term experience of social defeat, can be a risk factor for psychosis [27].

Furthermore, we found self-esteem to be a predictor of both hallucinations and persecutory delusions in FEP. This is in line with previous studies [10,19,33,34]. Garety's cognitive model of psychosis [11] suggests that the experience of social adversity and lowered self-esteem eventually can lead to the development of psychotic symptoms through an increased vulnerability for psychotic disorders. We would further argue that poor premorbid social adjustment with social withdrawal and subsequent marginalization will provide content to psychotic attribution by lack of correcting sources. This is supported by findings in studies of patients at high risk of developing psychosis [35]. In line with this, cognitive behavioral therapy aiming to improve self-esteem with focus on correcting misattributing tendencies has showed clinical benefits in terms of both increased self-esteem, reduced positive symptoms and improved social functioning [14].

This is also supported by findings in the general population. Negative ideas about oneself and others have been found to predict paranoid thinking in the general population [36]. Furthermore, premorbid neuroticism and low self-esteem were associated with subsequent development of psychosis or psychosis like symptoms at 3-year follow-up in a Dutch population sample [37]. If we take the continuum hypothesis of psychosis into consideration [38], it is not surprising to find the same pattern in a FEP sample as the present. On the other hand, there are studies showing that patients self-stigma tends to be most affected during the early course of the disease, and that self-stigma and self-esteem are closely related [39]. It might be different subgroups within the psychosis spectrum that

differs with regard to both stability in self-esteem and which factors (long-term/short-term) that constitutes the most potent impact on the individuals' self-esteem level. Further research into these complex mechanisms needs to be explored further in longitudinal studies.

Gender turned out to be a significant predictor of self-esteem in this FEP sample, even after correction for differences in levels of depression, with women having significantly lower levels of self-esteem than men. A vast body of literature from the general population indicate a small but significant gender difference in the same direction [40]. There is surprisingly little research on gender-differences regarding self-esteem in psychosis, but the present study is supported by findings from the Danish Opus trial [41], and suggests that gender differences is a factor which warrants further investigation.

The present study has some limitations. This is a cross-sectional study where conclusions about directions of relationships cannot be ascertained, and where data on premorbid adjustment necessarily are gathered retrospectively. There might be a recall bias regarding the scores for premorbid adjustment. To what degree self-esteem is affected before the development of psychosis is thus not possible to test directly using the current design.

Conclusion: The current study revealed both a significant association between premorbid adjustment and self-esteem and between self-esteem and positive psychotic symptoms (persecutory delusions and hallucinations). Future studies in self-esteem should consider looking into how self-esteem changes over time from the prodromal phase and over the course of illness.

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Contributors

All authors contributed to and have approved of the manuscript.

Conflict of interest

None of the authors has any conflicts of interest.

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Table 1. Demographics, n = 113.

	Mean	±SD (%)
Age	25.79	±7.7
Female (N/%)	37	(32.7)
Years of education	12.4	±2.72
DUP (mean/median) (N=106)	78	(0-1040)
PANSS:		
Positive score	17.4	±4.21
Negative score	16.28	±6.03
General score	36.74	±8.03
Total score	69.99	±15.14
RSES	22.81	±6.16
Depression MDE (N/%)	24	(21.24)
Diagnosis (N/%)		
Schizophrenia	68	(60.18)
Schizoaffective disorder	11	(9.73)
Schizophreniform disorder	7	(6.19)
Delusional disorder	7	(6.19)
Psychosis NOS	19	(16.81)
Brief psychosis	1	(0.88)

Abbreviations:
DUP; Duration of Untreated Psychosis
PANSS; Positive and negative syndrome scale
RSES; Rosenberg self-esteem scale
MDE; Major Depressive Episode

Table 2. Clinical characteristics and their correlations with self esteem

	Mean	±SD	RSES (r)
RSES	22.81	±6.14	1.00
Age	25.79	±7.70	0.08
Gender (Female) (N/%)	37	32,7	- 0.41**
PAS			
Childhood social	2.76	±3.22	-0.27**
Childhood academic	3.96	±2.93	-0.19*
Early adolescence social	3.56	±3.30	-0.30**
Early adolescence academic	4.93	±2.90	-0.22*
PANSS			
Hallucination	3.24	±1.65	-0.29**
Delusions	3.85	±1.32	-0.17
Persecutory delusions	3.33	±1.50	-0.30**
Depression MDE	1.79	±0.41	0.28**

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Abbreviations:
RSES; Rosenberg self-esteem scale
PAS; Premorbid adjustment scale
PANSS; Positive and negative syndrome scale
MDE; Major Depressive Episode

Table 3. Multiple hierarchical regression analysis with self-esteem as the dependent variable.

Model	Unstand-ardized Coef-ficients		Standard-ized Coefficients	t	Sig.	95% Confidence Interval for B		Adjusted R Square
	B	Std. Error	Beta			Lower Bound	Upper Bound	
Age	0.04	0.07	0.05	0.67	0.507	-0.09	0.17	
Gender	-5.35	1.07	-0.41	-5.00	0.001	-7.47	-3.23	0.16
Early adolescence social (PAS)	-0.43	0.17	-0.23	-2.55	0.012	-0.77	-0.10	
Early adolescence academic (PAS)	-0.29	0.19	-0.14	-1.51	0.133	-0.67	0.09	0.25

Explained variance for final model: R^2=0.25, F=10.19, p<0.001
Dependent Variable: Rosenberg self-esteem scale (RSES)

Abbreviations:
PAS; Premorbid adjustment scale

Table 4. Multiple hierarchical regression analysis with hallucinations and delusions and persecutory delusions as the dependent variables.

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B		Adjusted R Square
	B	Std. Error	Beta			Lower Bound	Upper Bound	
Age	-0.05	0.02	-0.21	-2.39	0.018	-0.08	-0.01	
Gender	0.31	0.34	0.09	0.91	0.364	-0.36	0.99	0.08
Depression MDE	-0.36	0.37	-0.09	-0.97	0.334	-1.10	0.38	0.09
RSES	-0.06	0.03	-0.21	-2.11	0.037	-0.11	0.00	0.12
Explained variance for final model: R^2=0.12, F=4.65, p=0.002								
a. Dependent Variable: Hallucinations (PANSS p3)								
Age	0.01	0.02	0.05	0.49	0.622	-0.02	0.04	
Gender	-0.48	0.29	-0.17	-1.68	0.097	-1.05	0.09	-0.01
Depression MDE	0.16	0.31	0.05	0.51	0.613	-0.46	0.78	-0.02
RSES	-0.05	0.02	-0.25	-2.39	0.019	-0.10	-0.01	0.02
Explained variance for final model: R^2=0.02, F=1.63, p= n.s.								
a. Dependent Variable: Delusions (PANSS p1)								
Age	0.03	0.02	0.14	1.54	0.127	-0.01	0.06	
Gender	-0.08	0.32	-0.03	-0.25	0.802	-0.71	0.55	0.01
Depression MDE	0.25	0.34	0.07	0.71	0.477	-0.44	0.93	0.00
RSES	-0.08	0.03	-0.34	-3.30	0.001	-0.13	-0.03	0.08
Explained variance for final model: R^2=0.08, F=3.46, p=0.01								
a. Dependent Variable: Persecutory delusions (PANSS p6)								

Abbreviations:
MDE; Major Depressive Episode
RSES; Rosenberg self-esteem scale,
PANSS; Positive and negative syndrome scale

III

IV

Severe social anxiety in early psychosis: associated with poor premorbid functioning, depression and reduced quality of life

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Abstract:

Objective: Social anxiety is a frequent feature of psychotic disorders. The relationship between anxiety and other clinical characteristics and functioning is not yet fully understood. The main aims of the present study were to examine whether first episode psychosis patients with severe social anxiety shows poorer premorbid functioning, higher level of current clinical symptoms, better insight, lower current functioning and reduced quality of life.

Method: A sample of 144 individuals with a first episode psychosis was divided into three groups dependent upon current level of social anxiety symptoms measured by the Liebowitz social anxiety scale, self-rated version; 1) no social anxiety (no-SaD), 2) clinically relevant symptoms of social anxiety (SaD) and 3) generalized social anxiety symptoms (G- SaD). Analysis of variance was performed including measures of demographic and clinical characteristics. Furthermore, a hierarchical regression analysis was performed to explore possible predictors of quality of life.

Results: Being in the G-SaD group was associated with poorer premorbid adjustment, lower social functioning and higher levels of depression, while there were no group differences in level of psychotic symptoms. Furthermore, the G-SaD group revealed a higher awareness of illness and experienced reduced quality of life. Social anxiety predicted quality of life even when adjusted for psychotic symptoms and depression.

Conclusion: Severe social anxiety in first episode psychosis is to a larger extent associated with poor premorbid functioning and depression than to current level of psychotic symptoms, and is furthermore, an important predictor of quality of life.

Keywords: First episode psychosis, Schizophrenia, Social phobia, Social anxiety, Premorbid adjustment, Quality of life

1. Introduction

Social anxiety disorder has lately received increased interest, as it is the most prevalent form of anxiety disorder in schizophrenia. A meta-analysis (Achim et al., 2009) showed pooled overall prevalence rates for social anxiety disorder in schizophrenia to be approximately 15% with a variation from 14 % to 39 % between the different studies (Bermanzohn et al., 2000;Cassano et al., 1999;Cosoff and Hafner, 1998;Pallanti et al., 2004).

Three possible pathways are described to explain the association between social anxiety and psychosis (Birchwood et al., 2006;Voges and Addington, 2005); 1) Social anxiety disorder explained as a premorbid developmental disorder and perceived as a vulnerability marker for psychosis 2) Social anxiety disorder emerging concurrently with and constituting a core component of the psychotic syndrome, and 3) Social anxiety disorder emerging as a psychological reaction to the psychotic episode.

Concerning the first possible pathway, that social anxiety disorder may evolve as part of a premorbid developmental disorder, Birchwood and coworkers did not find any differences in premorbid peer-relations in a group of first episode patients with social anxiety disorder compared to first episode patients without social anxiety disorder (Birchwood et al., 2006). This is in contrast to the Edinburgh High-Risk Study that found early "situational anxiety" to be one of the best predictors of conversion to psychosis (Johnstone et al., 2005;Owens et al., 2005). If social anxiety disorder in patients with psychosis represents a pre-morbid disorder with interpersonal difficulties we would expect that patients with severe social anxiety symptoms would show poorer premorbid functioning, specifically reduced social adjustment, when compared to patients without social anxiety disorder.

Concerning the second possible pathway, there are some support for the view that social anxiety is a core component of the psychotic syndrome, or at least a co-occurring process that might both initiate and exacerbate positive psychotic symptoms (Freeman et al., 2008). However, Michail and coworkers (Michail and Birchwood, 2009) did not find any relationship between positive symptoms and social anxiety. This is in line with a study by Pallanti and colleagues (Pallanti et al., 2004) who found no relationship between neither positive nor negative symptoms and social anxiety. Others again have found social anxiety to be related to negative symptoms only, and not to positive symptoms (Voges and Addington, 2005). If social anxiety disorder is a core component of the psychotic syndrome, we would expect a close relationship between social anxiety symptoms and current severity of psychotic symptoms.

The third pathway perceives social anxiety as a result of the psychotic episode. Embedded in this theory lies the patients appraisals of psychosis involving perceived stigma, shame, loss of social role and enforced low status (Iqbal et al., 2000). This is followed by reduced self-esteem and development of social anxiety (Gumley et al., 2004). Implicit in this theory lies the assumption that insight into illness to some extent has an impact on self-esteem. Self-esteem is after all dependent upon how we view ourselves in relation to others.

Quality of life (QoL) measures are considered as an important part of outcome assessment in psychosis (Melle et al., 2005). Only few studies have focused on the relationship between social anxiety and QoL in patients with psychosis and more studies have been asked for (Huppert et al., 2001). Two studies, including patients with chronic psychosis, have revealed a close relationship between social anxiety and reduced QoL (Pallanti et al., 2004;Halperin et al., 2000). Furthermore, one study found that QoL to a larger extent were related to depression than to current psychotic symptoms (Fitzgerald et al., 2001;Kusel et al., 2007) while another

study revealed that QoL was strongly related to negative symptoms only (Kusel, 2007). Few studies have investigated social anxiety in patients with first episode psychosis (Birchwood et al., 2006;Voges and Addington, 2005;Michail and Birchwood, 2009). Studying patients in early phases is associated with a reduced recall bias with regard to premorbid functioning and less risk of blending of psychotic symptoms such as persecutory delusions and social anxiety (Michail and Birchwood, 2009). Overall, to study phenomena proximal to early development of psychosis is important as this period has shown to be very important for later course and important outcome measures (Fenton, 2000;Birchwood et al., 1998). No previous study have examined to what extent social anxiety predict subjective QoL in first episode psychosis patients, controlling for important clinical variables such as depression, positive and negative symptoms.

To sum up, there might exist several and possibly overlapping pathways to social anxiety in psychosis. These are not yet fully understood, and only few studies are performed in samples of patients with a first episode psychosis. The purpose of the current study was to investigate further the different pathways of social anxiety in first episode psychosis and the impact of social anxiety on QoL. As we assumed that most of the patients would display some degree of social anxiety, we decided to look specifically into the group most affected. More specifically we aimed to answer the following research questions: Do patients with high levels of current social anxiety symptoms reveal 1) poorer premorbid functioning, 2) stronger associations to clinical correlates such as current psychotic symptoms, depression and functioning and 3) better insight and lower self-esteem. Finally, we wanted to explore if social anxiety per se acts as an independent predictor of QoL.

Methods

2.1 Subjects

From February 2007 through October 2009, 144 FEP patients from the main psychiatric treatment centres in Oslo and two neighbouring counties were consecutively included in the ongoing Thematically Organized Psychosis (TOP) research study. The inclusion criteria were: 1) age 18 - 65 years and 2) coming to their first treatment for a non-affective psychosis according to DSM-IV. Exclusion criteria were a history of organic brain disorder, a significant co-morbid medical condition or an IQ of less than 70. The diagnostic distribution was as follows: Schizophrenia 74 (51%), schizophreniform disorder 11 (8 %) schizoaffective disorder 13 (9 %), major depression with mood incongruent psychotic symptoms 8 (6%), psychosis NOS 38 (26%).

Patients were eligible for inclusion up to 52 weeks after the start of first adequate treatment for their psychotic disorder, but were not considered as FEP patients if they previously on any occasion had been treated with antipsychotic medication in adequate dosage for more than 12 weeks or until remission. The mean age of the patients were 26.3 (SD 8.4), 92 (64 %) were males and 112 (78%) were single. Mean years of education were 12.4 (SD 2.6) and median duration of untreated psychosis (DUP) was 77 weeks (range 0-1040) (N=143). The study was approved by the regional research ethics committee. All patients gave written informed consent upon entry to the study.

2.2 Assessments

2.2.1 Measures

Diagnosis was set according to the Structured Clinical Interview for Diagnostic and Structural Manual of Mental Disorders, fourth version (SCID I interview for the DSM -IV)(American

Psychiatric Association, 1994). Positive symptoms, negative symptoms and general psychopathology were assessed by the Structural Clinical Interview of the Positive and Negative Syndrome Scale (SCI-PANSS)(Kay et al., 1987) and divided into a five-factor model reflecting Positive, Negative, Excitative, Depressive and Cognitive Components (Bentsen et al., 1996) .

Social anxiety was measured by the self-rating version of the Liebowitz Social Anxiety Scale (LSAS-SR). The Liebowitz Social anxiety scale (LSAS) (Liebowitz, 1987) is a widely used instrument, and comprises 24 items measuring fear and avoidance separately for 24 social situations over the past week. The self-report version has recently been satisfactorily validated in a first episode psychosis sample (Romm et al., 2010b). The scale was administered in connection with an interview session, and the patients had ample opportunity to ask questions. We chose the same way to instruct the patients about how to complete the questionnaire as described by Fresco et al. (Fresco et al., 2001).

Insight was measured by the Insight Scale (IS) (Birchwood et al., 1994) and includes three dimensions of insight; 'insight into illness',' insight into (psychotic) symptoms' and 'insight into need for treatment'.

Self-esteem was measured using the Rosenberg self-esteem scale (RSES) (Rosenberg, 1965). This is a 10-item self-administered questionnaire with a 4-point likert-type response set, ranging from strongly disagree to strongly agree, with low total score pointing towards low self-esteem. Premorbid adjustment was measured with the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). The premorbid phase is defined as the time from birth until 6 months before onset of psychosis. It measures both social and academic functioning during four age ranges. We only included the age ranges of childhood (-11 years) and early adolescence (12–15 years) as the usual onset of schizophrenia spectrum disorders is in early

adulthood. In this manner we tried to avoid 'contaminating' the premorbid period as it can be difficult to point out the exact time point of conversion to psychosis, especially in individuals with insidious onset. Information was collected within each age range from the patient, medical journal and from significant family members when appropriate, to make ratings on items regarding sociability and withdrawal, peer relationships, academic performance and adaptation to school. Global functioning was measured by the split version of the Global assessment of functioning scale (GAF)(Endicott et al., 1976), which measures both symptoms and functioning per se (Pedersen et al., 2007). QoL was measured by one of the items, 'Satisfaction with life in general', in the Lehman Quality of Life Interview (Lehman, 1988). This has a 7-point likert-type response set, ranging from "Terrible" to "Delighted". A previous psychometric study has found statistically significant association between the "satisfaction with life in general" scale and all nine indices constituting the full-length version of the interview (Melle et al., 2005).

2.2.2. Procedures

The patients were interviewed by trained psychologists and psychiatrists at the same time as the SCID-I was administered. The investigators had all completed the general training- and reliability program in the TOP research study. For DSM-IV diagnostics, mean overall kappa with training videos was 0.77, and mean overall kappa for a randomly drawn subset of actual study patients was also 0.77 (95% CI 0.60-0.94). Inter-rater reliability, measured by the intra class correlation coefficient (ICC 1.1), was for the PANSS positive subscale 0.82 (95% CI 0.66–0.94), for the PANSS negative subscale 0.76 (95% CI 0.58–0.93) and the PANSS general subscale 0.73 (95% CI 0.54–0.90).

3. Statistics

All analysis was carried out using SPSS Version 16.0. All hypothesis testing were two-tailed. Duration of untreated psychosis (DUP) was substituted in the multivariate analysis with ln(DUP+1) due to skewed data. Twenty-one of the 144 patients did not complete the Rosenberg self-esteem questionnaire as this was added to the study protocol at a later stage. Thus, the analysis concerning self-esteem is performed with fewer participants, but this sub-group was not different from the whole group.

We divided the sample according to Mennin et al. (Mennin et al., 2002) into three groups depending upon the LSAS-SR total score as we assumed there would be group differences according to severity of social anxiety symptoms; Total score < 30: no social anxiety (No-SaD), 31-60: clinically relevant social anxiety symptoms (SaD), >60: Generalized social anxiety (G-SaD). Analysis of variance (ANOVA) was carried out to compare group differences on demographic and clinical characteristics. Post-Hoc Tukey Honestly significant test was used to adjust for multiple comparisons. Effect sizes were calculated according to Cohen's classification; 0.01 = small effect size, 0.06= medium effect and 0.14 = large effect (Cohen, 1988).

A subanalysis was carried out using Pearson's correlation to test whether 'insight into illness' was associated to psychotic symptoms in particular or other clinical symptoms such as depression and social anxiety.

Finally, a hierarchical multiple regression analysis was carried out to assess the independent contribution of social anxiety on quality of life when adjusting for variables presumed to have an impact on quality of life, i.e. a theoretically driven regression analysis. Self-esteem was not

included in the analysis as it was intra correlated with both depression (r=-0.55) and social anxiety (r=-0.64).

4. Results

Demographic characteristics are shown in Table 1.

Insert Table 1 about here.

According to the criteria of Mennin and colleagues (Mennin et al., 2002), 79% of the patients had some clinical symptoms that were associated with social anxiety disorder. A total of 68 patients (47%) met the criteria for G-SaD. No significant differences were detected for age, gender, education or primary diagnosis between Non-SaD, SaD and the G-SaD group.
The ANOVA revealed that the most pronounced group differences were found between the G-SaD group and the other two, the SaD and Non-SaD group.

Insert table 2 about here.

The G-SaD group performed poorer in both academic and social premorbid functioning. The partial Eta square confirmed moderate to large effect sizes in differences in social functioning both in childhood and early adolescence. Furthermore, a difference in DUP was revealed primarily between the G-SaD/SaD groups and the Non-SaD group. The trend was though that heightened level of SaD was running along with an increase in DUP.
We did not find any differences between the groups with regard to neither positive- nor negative symptoms. The only significant findings concerning the different PANSS components were, as expected, for the depressive component. The G-SaD group differed

significantly from the two other groups with regard to GAF-symptoms, while GAF-functioning revealed only a significant difference between the G-SaD and the Non-SaD group.

The G-SaD group showed a significant lower level of self-esteem with a large effect size. The same pattern was obtained concerning the item 'insight into illness' where the effect size was likewise large. Neither 'insight into symptoms' nor 'insight into need for treatment' revealed any significant differences between the three groups.

The subanalysis, to explore the associations between 'insight into illness' and clinical symptoms, revealed that 'insight into illness' was related to the depressive component of the PANSS ($r=0.37$, $p<0.05$) and self-esteem ($r=-0.37$, $p<0.05$) while no significant associations were found between 'insight into illness' and psychotic symptoms.

To explore whether social anxiety symptoms predicted subjective quality of life adjusting for other important clinical variables, we performed a blockwise multiple hierarchical regression analysis.

Insert table 3 about here.

Table 3 shows that in the final model, only depression and social anxiety had a statistically significantly contribution, with depression having a higher beta value (beta = 0.35, $p<0.001$) than social anxiety (beta = 0.23, $p<0.05$). Neither positive psychotic symptoms nor negative symptoms contributed significantly.

5. Discussion

The main finding of the current study was that nearly half of the patients with a first episode psychosis experienced severe social anxiety problems when engaging in social interaction and performance. Patients with severe symptoms of social anxiety disorder revealed poorer premorbid and current functioning, more insight and lower self-esteem compared to patients with less- or no social anxiety symptoms. Furthermore social anxiety was a significant predictor of subjective quality of life. The study revealed no significant relationship between psychotic symptoms and social anxiety.

We did not explore whether patients with severe social anxiety disorder met the DSM-IV criteria, but our findings are comparable to other studies. Voges and Addington (Voges and Addington, 2005) found 50-60 % of their sample of first episode patients to fall in the range of 'a probable diagnosis of social phobia', while 31 % actually met the criteria. Mazeh and coworkers (Mazeh et al., 2009) reported LSAS subscale mean scores (fear; 38.5, and avoidance; 37.7) in a sample of long term ill schizophrenia patients to be somewhat higher than in the current study (fear; 30 and avoidance; 29), but still comparable.

The G-SaD group differed significantly on measures of premorbid functioning, specifically with regard to social adjustment. This is in line with previous findings (Johnstone et al., 2005;Owens et al., 2005), but contrary to Birchwood and colleagues (Birchwood et al., 2006). We find it plausible to conclude that this might be a reflection of a possible neuro-developmental pathway even though we have to underline that this is a cross-sectional study and as such do not allow us to draw any firm conclusion other than causative assumptions. However, there are other studies suggesting a link among shyness, schizophrenia and social dysfunction from early childhood (Goldberg and Schmidt, 2001). Others have found a link between reduced flexibility in abstract thought, flexibly shifting mind set and social anxiety (Lysaker and Hammersley, 2006;Lysaker et al., 2004) both in people with and without a

severe mental disorder(Easter et al., 2005;Hariri et al., 2003). Thus, a confluence of organic and psychological precipitating factors might be involved. This finding is also supported by the fact that the group with G-SaD had a significantly longer DUP than those with only minor or no problems with social anxiety. Overall, there was a trend towards longer DUP with rising level of anxiety. One possible explanation consistent with the findings in the Edinburgh high-risk study as well, would be that some of these children have been actively withdrawn and to some degree deviant from an early age. The transition into psychosis might have been less pronounced and therefore not detected and treated properly at an earlier time point. Another option is that social anxiety inhibits the seeking of psychiatric care in general which would be in line with previous findings concluding that social anxiety disorder inhibits the seeking of psychiatric care for depressed patients (Pilkonis et al., 1980). This would inevitably prolong the DUP.

The present study revealed no difference between the groups on current level of positive and negative symptoms. Symptoms of social anxiety and level of psychosis seems to be present together, but as more independent pathological entities. However, despite the lack of group differences concerning psychotic symptoms, we found that the G-SaD group revealed significant more depressive symptoms than the other two groups. This is in line with previous studies supporting a clear link between social anxiety and mood-symptoms (Kessler et al., 1999) in the general population, and the conceptualisation of social anxiety as part of an emotional dysfunction complex in psychotic disorders (Birchwood, 2003).

As expected the G-SaD group exhibited significantly lower levels of self-esteem than the other two groups. This could be part of a psychological reaction to psychosis as described in the 'social rank' or 'perceived stigma' theory (Iqbal et al., 2000;Gilbert, 2001), and should then be mirrored in the insight scores. Patients with G-SaD did report a significant higher

level of ‘insight into illness’ compared to the other two groups, but there were no significant differences between the groups concerning ‘insight into (psychotic) symptoms’ or ‘need for treatment’. A previous study of social anxiety with similar findings (positive association between social anxiety and insight into illness only) has interpreted this as the patients awareness of their psychotic illness (Birchwood et al., 2006). However, the underlying items making up this factor consist of the following statements: 1) I am mentally well, 2) If someone said I have a nervous or mental illness they would be right. Another option could be that patients with severe concurrent disorders as G-SaD or depression are misinterpreting the questions and are reporting level of social discomfort and/or depression rather than insight into having a psychotic illness. This was supported by the sub analysis that failed to find any associations between psychotic symptoms and ‘insight into illness’, but found significant associations to depression and social anxiety. Furthermore, despite the fact that the three groups are almost identical regarding positive and negative symptoms, the G-SaD group differ both in GAF-s and GAF-f. This might reflect higher depression/social anxiety scores and/or reduced functioning due to depression and/or social anxiety with active withdrawal.

To our knowledge, this is the first study to examine whether social anxiety is an important predictor of QoL even after adjusting for depression and psychotic symptoms. Both depression and social anxiety were significant predictors of subjective QoL. The present study support previous research that has pointed to the importance of incorporating targeted monitoring and treatment of affective and anxiety symptomatology in severe mental illness (Hansson, 2006). The importance of being aware of depression is obvious as it is prevalent in psychosis (Romm et al., 2010a) and acts as an important contributor to the increased risk of suicide (Melle et al., 2006;Barrett et al., 2010). Furthermore, this is of especially importance, since both social anxiety and depression rarely are the target of treatment and are often not

recognized in the clinic due to focus on the traditional positive and negative symptoms (Cosoff and Hafner, 1998;Schneier et al., 1992). Considering evidence for new therapeutic gains as CBT has been proven effective as adjunctive treatment for social anxiety and depression in psychosis (Kingsep et al., 2003;Halperin et al., 2000), a more active approach towards recognition and treatment of social anxiety should be applied. Furthermore, a more focused living skills training to enhance social functioning targeted towards self-care, occupational, leisure and recreation, friendship and intimacy skills would be particularly relevant (Falloon et al., 1998).

Limitations:

Besides the cross sectional design, the skewed group sizes is a limitation. There are twice as many men as women; this is though comparable with other first episode studies. Furthermore, assessment and description of the diagnostic distribution with regard to a DSM-IV diagnosis of social anxiety disorder would be preferable, but not possible within the limits of this study. Future research would profit from exploring whether there exist an association between social anxiety disorders and reduced cognitive functioning in psychosis, as this may be a sign of a more developmental disorder, and would help explain why the most severly impaired group seem to differ on several clinical aspect compared to those with no or minor social anxiety symptoms.

Conclusions:

While symptoms of social anxiety are prevalent in first episode psychosis, those mostly impaired by social anxiety, exhibit distinct clinical characteristics and are more impaired on several measures. Furthermore, social anxiety is a significant predictor of subjective quality

of life. Hence, a more active approach towards treatment of social anxiety during early phases of psychotic illness should be applied.

Conflict of interest: None.

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Table 1.

Demographic and clinical characteristics (N=144)

	All patients		Non-SaD N=30		SaD N=46		G-SaD N=68	
Age (years)(mean/SD)	26.27	8.45	25.47	8.91	28.67	10.78	25.00	5.83
Male gender	92.00	63.90	21.00	70.00	31.00	67.39	40.00	58.82
Education (years)(mean/SD)	12.38	2.63	12.30	2.88	13.03	2.86	11.99	2.29
DIAGNOSIS:								
Schizophrenia	74.00	51.40	14.00	46.67	20.00	43.48	40.00	58.82
Schizophreniform	11.00	7.60	5.00	16.67	5.00	10.87	1.00	1.47
Schizoaffective	13.00	9.00	2.00	6.67	4.00	8.70	7.00	10.29
Affective psychosis*	8.00	5.60	3.00	10.00	2.00	4.35	3.00	4.41
Psychosis NOS	38.00	26.40	6.00	20.00	15.00	32.61	17.00	25.00

N and % are given except when noted.

*Major depression with mood incongruent psychotic symptoms

NOS: Not Otherwise Spesified

SaD: Social anxiety Disorder

G-SaD: Generalized Social anxiety Disorder

Table 2.
Clinical characteristics (N=144)

	Non SaD N=30		SaD N=46		G-SaD N=68		F	Sig.	Partial Eta Square
PAS									
Childhood social	1.23	(2.22)	1.89	(2.20)	3.79	(3.60)	9.99 **	3>2.1	0.12
Childhood academic	2.70	(2.04)	3.24	(2.40)	4.84	(3.10)	8.41 **	3>2.1	0.11
Early adolescense social	1.33	(2.80)	2.57	(2.48)	4.71	(3.37)	15.13 **	3>2.1	0.18
Early adolescense academic	3.77	(2.70)	4.11	(2.60)	5.80	(2.99)	7.62 **	3>2.1	0.10
DUP* (weeks) (median-range)	22.00	(1-383)	72.00	(1-1040)	104.00	(0-1040)	5.99 **	3.2>1	0.08
GAF									
symptom	43.50	(10.03)	41.39	(10.18)	34.85	(7.60)	12.51 **	3>2.1	0.15
function	45.27	(11.42)	43.13	(12.01)	38.69	(8.28)	5.14 **	3>1	0.07
PANSS									
Positive	13.10	(3.99)	14.04	(4.52)	14.84	(4.15)	1.81	n.s.	0.03
Negative	19.07	(7.79)	23.00	(7.67)	23.49	(9.35)	2.95	n.s.	0.04
Excitative	8.00	(2.96)	8.78	(2.63)	9.53	(3.29)	2.79	n.s.	0.04
Depressive	11.33	(3.53)	12.85	(3.52)	15.24	(3.62)	14.20 **	3>2.1	0.17
Cognitive	5.30	(1.91)	5.76	(2.20)	6.34	(3.08)	1.80	n.s.	0.02
Quality of life	3.77	(1.55)	4.23	(1.40)	5.14	(1.41)	10.91 **	3>2.1	0.16
Self-esteem	27.82	(5.47)	25.79	(4.92)	18.46	(4.85)	40.39 **	3>2.1	0.41
IS									
Insight into symptoms	2.45	(0.97)	2.36	(0.81)	2.33	(0.82)	0.19	n.s.	<0.01
Insight into illness	1.88	(1.17)	2.50	(0.85)	2.77	(0.87)	9.17 **	3.2>1	0.12
Insight into need for treatment	2.47	(0.99)	2.63	(0.76)	2.67	(0.89)	0.50	n.s.	0.01

* p<0.05. **p<0.001. Mean and SD are given except when noted.

*Duration of untreated psychosis

**Positive and Negative Syndrome Scale

***Major depression with mood incongruent psychotic symptoms

Table 3: Hierarchical regression analysis with Quality of life as dependent variable

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B		Adjusted R Square
	B	Std. Error	Beta			Lower Bound	Upper Bound	
Age	-0.003	0.016	-0.018	-0.210	0.834	-0.035	0.028	
Gender	0.007	0.268	0.002	0.027	0.979	-0.523	0.537	-0.003
DUP	-0.068	0.076	-0.078	-0.900	0.370	-0.218	0.082	-0.011
PANSS								
positive component	-0.016	0.032	-0.045	-0.491	0.624	-0.080	0.048	
negative component	-0.018	0.017	-0.103	-1.062	0.290	-0.052	0.016	
excitative component	0.013	0.044	0.027	0.303	0.762	-0.074	0.101	
depressive component	0.139	0.037	0.352	3.740	0.000	0.066	0.213	
cognitive component	0.024	0.056	0.042	0.437	0.663	-0.086	0.134	0.136
LSAS-SR	0.011	0.004	0.226	2.447	0.016	0.002	0.020	0.170

Explained variance for final model: R^2=0.17, F=3.97, p<0.001

a. Dependent Variable: Quality of life

DUP: Duration of untreated psychosis

PANSS: Positive And Negative Syndrome Scale

LSAS-SR: Liebowitz Social Anxiety Scale - Self Rated