Symptom profiles in first episode psychosis

A 10 year follow-up study

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Scientific environment

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Abbreviations

AES	**Apathy Evaluation Scale**
AES-C	**Clinician version of AES**
AES-S-Apathy	**Abridged self-rater version of AES**
AUDIT	**Alcohol Use Disorders Identification Test**
CDSS	**Calgary Depression Scale for Schizophrenia**
Schizophrenia spectrum diagnosis	**Schizophrenia, schizophreniform disorder and schizoaffective disorder**
DSM	**Diagnostic and Statistical Manual of Mental Disorders**
DDD	**Defined Daily Dose (WHO criteria)**
DUDIT	**Drug Use Disorders Identification Test**
DUP	**Duration of Untreated Psychosis**
D	**Delusion only group**
ED	**Early Detection**
FA	**Flat Affect**
FEP	**First Episode Psychosis**
GAF	**Global Assessment of Functioning**
H	**Hallucination only group**
ICD	**International Classification of Diseases**
L-QoLI	**Lehman's Quality of Life Interview**
MDE	**Major depressive disorder and bipolar disorder with mood incongruent psychotic symptoms**
N.S.	**Non significant**
PAS	**Premorbid Assessment of functioning Scale**
PANSS	**Positive and Negative Syndrome Scale**
SCID	**The Structured Clinical Interview for the DSM-IV Axis I Disorders**
SCLFS	**Strauss Carpenter Level of Functioning Scale**
SD	**Standard deviation**
TIPS	**Early Treatment and Intervention in Psychosis**
QoL	**Quality of Life**

Summary

Objectives:

This thesis explores different symptom profiles found in First Episode Psychosis (FEP) patients assessed at several points of time over a ten year period. Earlier studies have focused predominantly on groups of symptoms rather than individual symptoms when describing course of illness and outcome, and long-term studies of symptom development in epidemiological FEP samples assessed multiples times are lacking. By studying individual symptoms longitudinally from the onset of illness we aimed to gain more knowledge about symptom development and the relationship between symptoms and outcome variables that are known to be affected in psychotic disorders. The aim of the study was threefold: 1) to identify a group of patients with delusions only and a group with hallucinations only, and examine if the groups differed with regard to demographics, clinical variables and outcome measures, and in particular suicidality, 2) to assess the prevalence of apathy ten years after the first psychotic episode, and to explore the association between apathy and general functioning, and between apathy and quality of life, and 3) to identify different flat affect (FA) symptom profiles based on longitudinal symptom trajectories and assess the prevalence and correlates of these trajectories, to assess predictors of enduring FA, and to explore the longitudinal relationship between FA and social functioning.

Methods:

Three-hundred-and-one first episode, non organic psychosis patients were included in the TIPS Study (Early Treatment and Intervention in Psychosis) and followed over a ten year period. Patients were assessed at baseline, three months, and one, two, five and ten year

follow-up with an extensive battery of instruments including measures of demographics, duration of untreated psychosis (DUP), premorbid function (PAS), diagnosis (SCID), symptom measures (PANSS, AES, CDSS), measures of functioning (GAF, SCLFS), suicidality and quality of life (L-QoLI). The relationship of the symptoms of interest, namely hallucinations and delusions (PANSS P1 and P3, respectively), apathy (AES-S-Apathy and PANSS N2+N4) and flat affect (PANSS N1), to the above measures were assessed with t-test, correlation and regression analyses.

Results:

Sub-groups of patients with hallucinations only and delusions only can be identified in a five year follow-up study, and the groups differed on multiple variables. Most importantly, the hallucination only group scored higher on measures of suicidality, and insight might be a possible mediator of suicidality in this group.

Apathy was found to be a common symptom ten years after the first psychotic episode, affecting 30 % of the sample. Proxy-measures of apathy indicated that this symptom declined in the follow-up period. Clinical apathy was strongly related to poorer functioning and to poorer subjective quality of life in patients ten years after the first psychotic episode.

Five different FA trajectory groups were identified. FA was more fluctuant than expected, and only 5 % of the sample experienced enduring FA. Furthermore, FA was related to poorer functional outcome measures, in particular to objective social functioning, both premorbidly and throughout the ten year follow-up period.

Conclusions:

By looking at individual symptoms rather than groups of symptoms it was possible to shed light on patients with symptom profiles that previously have received limited attention, and to learn more about the long-term development of the individual symptoms. Combined, the findings highlight the importance of looking at symptoms separately in order to both better understand the longitudinal association between symptoms, and to gain knowledge of how individual symptom profiles affect outcome measures including suicidality, quality of life, and social functioning.

List of publications

Paper I

Contrasting Mono-symptomatic Patients with Hallucinations and Delusions in First-Episode Psychosis Patients: A Five-Year Longitudinal Follow-Up Study. Julie Evensen, Jan Ivar Røssberg , Helene Barder , Ulrik Haahr, Wenche ten Velden Hegelstad, Inge Joa , Jan Olav Johannessen, T.K. Larsen, Ingrid Melle, Stein Opjordsmoen,
Bjørn Rishovd Rund, Erik Simonsen, Kjetil Sundet, Per Vaglum, Svein Friis (PI), Thomas McGlashan (PI), 2011. Psychopathology. 44, 90–97.

Paper II

Apathy in first episode psychosis patients: A ten year longitudinal follow-up study. Julie Evensen, Jan Ivar Røssberg , Helene Barder , Ulrik Haahr, Wenche ten Velden Hegelstad, Inge Joa , Jan Olav Johannessen, T.K. Larsen, Ingrid Melle, Stein Opjordsmoen,
Bjørn Rishovd Rund, Erik Simonsen, Kjetil Sundet, Per Vaglum, Svein Friis (PI), Thomas McGlashan (PI), 2012. Schizophrenia Research. 136 (1-3) 19-24.

Paper III

Flat affect and social functioning: a ten year follow-up study of first episode psychosis patients. Julie Evensen; Jan Ivar Røssberg; Helene Barder; Ulrik Haahr; Wenche ten Velden Hegelstad; Inge Joa; Jan Olav Johannessen; T.K. Larsen; Ingrid Melle; Stein Opjordsmoen; Bjørn Rishovd Rund; Erik Simonsen; Per Vaglum; Thomas McGlashan (PI); Svein Friis (PI**).** Schizophrenia Research, May 22 (Epub ahead of print).

1. Introduction

1.1 Psychosis and psychotic disorders

The term “psychosis” was coined in 1841 by the German physician Karl Friedrich Canstatt, from the Greek "psyche", meaning mind/soul, and "-osis", meaning abnormal condition (Canstatt, 1841). Several definitions of psychosis exists, uniting them is a loss of contact with reality and reality distorting phenomena like hallucinations and delusions. Broader definitions include disordered thought and emotion that influences functioning. The term psychosis came to substitute and formalize the older term “insanity”, and separated the more serious conditions of the mind from the milder “neurosis”. Another German physician, Emil Kraepelin, divided psychosis into manic depressive insanity (now bipolar disorder, an affective psychosis) and dementia praecox (now schizophrenia, a non-affective psychosis) (Kraepelin, 1919). In his description of dementia praecox he focused not only on hallucinations and delusions, symptoms we now refer to as “positive symptoms” of psychotic illness, he also described “...emotional dullness...loss of mastery over volition, of endeavor, and of ability for independent action”, similar to apathy or amotivation that we now group as a negative symptom of psychotic illness.

Positive psychotic symptoms, like hallucinations and delusions, and also negative symptoms, like apathy and flat affect (FA), occur in a variety of neuropsychiatric conditions and as a consequence of substance abuse and as side-effects of prescribed medication. The focus of this thesis is on patients with non-affective psychotic disorders and affective psychotic disorders with mood incongruent psychotic symptoms followed from their first psychotic episode. The most studied psychotic illness is schizophrenia.

1.1.1 Schizophrenia

Schizophrenia is regarded as the most serious of the psychotic disorders. It has a lifetime prevalence of about 1 % of the population (Mueser and McGurk, 2004). The onset of illness is usually in late adolescence or early adulthood (Jablensky, 1992), and it is more common in men than women (Abel et al., 2010).

The Diagnostic Statistical Manual of Mental Disorders' (DSM-IV) criteria for schizophrenia require two of the following characteristic symptoms: 1) delusions, 2) hallucinations, 3) disorganized speech, 4) grossly disorganized or catatonic behaviour, and/or 5) negative symptoms, like apathy or FA. These need to be present for a period of one month or longer, as a part of a total illness duration of a minimum of six months, which may include a prodromal and a residual phase of illness. Furthermore, disrupted occupational or social functioning and/or poor self-care are required to fulfil the diagnostic criteria.

The precise aetiology and pathophysiological mechanisms of schizophrenia remains uncertain despite more than a century of scientific investigation (Tandon et al., 2008). Both environmental and genetic factors have been found to contribute to the development of the disorder. Studies comparing monozygotic to dizygotic twins estimate the heritability of the disorder to be about 80% (Cardno et al., 1999, Sullivan et al., 2003), and a number of susceptibility genes have been linked to the disorder (Craddock et al., 2009, Williams et al., 2011, Ripke et al., 2011, Shayevitz et al., 2012). Environmental factors like high paternal age, obstetric complications, cannabis use (Matheson et al., 2011), urbanicity (Kelly et al., 2010), and migration (Veling and Susser, 2011) also

increase susceptibility. However, none of these genetic or environmental factors alone have more than a modest contribution to the risk of developing schizophrenia.

1.1.2 Other psychotic disorders

The DSM-IV diagnostic criteria for other non-affective psychotic illnesses are similar to that of schizophrenia. The most common psychotic disorders are described below.

Schizophreniform disorder includes the same symptom clusters that are required for schizophrenia, but the total illness duration is shorter, between 1 and 6 months.

Schizoaffective disorder includes fulfilling the symptom criteria for schizophrenia, and the presence of affective symptoms for a significant period of the total illness duration, but with a minimum two weeks period of having psychotic symptoms in the absence of prominent mood symptoms.

In the current study *Schizophrenia, schizophreniform disorder and schizoaffective disorder* are described together as *schizophrenia spectrum disorder.*

Brief psychotic disorder includes the symptom cluster described in schizophrenia, with the total illness duration of more than one day and less than one month.

Delusional disorder is described as non-bizarre delusions of a minimum one month duration. Other active phase symptoms, like hallucinations or pronounced negative symptoms, are not permitted.

Psychosis NOS includes non-organic psychotic syndromes and states that do not meet the diagnostic criteria for any specific psychotic disorder, or where inadequate or contradictory information makes it impossible to reach a conclusive diagnosis.

Affective psychosis is similar in symptomatology to non-affective psychosis, however the clinical symptom picture is weighted towards the affective component of the illness and therefore is described in the affective/mood section in the DSM-IV. Included in this thesis are affective psychoses with mood incongruent psychotic symptoms only.

Major depressive disorder and bipolar disorder with mood incongruent psychotic symptoms (MDE) are characterized by primary depressive or manic and depressive episodes, with co-occurring hallucinations or delusions whose content have no apparent relationship to the affective symptoms.

Major depressive disorder and bipolar disorder with mood congruent psychotic symptoms are characterized by primary depressive or manic and depressive episodes, with co-occurring hallucinations or delusions whose content is related to the affective symptoms.

1.1.3 Symptom components of psychotic disorders

The various symptoms seen in psychotic disorders are commonly grouped together and described as symptom components of the disorders. Most factor analyses of the main symptom rating scales, the Positive and Negative Symptom Scale (PANSS) and Scale for the Assessment of negative/positive Symptoms (SANS) / (SAPS), have identified three to five separate factors (Kay et al., 1987, Kay and Sevy, 1990, Blanchard and Cohen 2006, Lehoux et al., 2009). The most consistently reported components are listed below:

Positive symptoms include hallucinations and delusions, and represent the reality distortion component of psychotic illness. These symptoms are often the most noticeable aspects of the illness. Patients may talk to themselves and express beliefs and ideas that are implausible or even incomprehensible.

Negative symptoms include apathy/amotivation, asociality, anhedonia, alogia and flat affect (FA). Patients with these symptoms show decreased initiative, poor self care, social withdrawal, and/or reduced expressivity.

Symptoms within the positive and negative symptom components are the focus of this thesis and are thoroughly described in separate sections (1.2 and 1.3).

Cognitive symptoms include impairment of concentration, attention, memory and executive function, as well as social cognition, which is the ability to process and apply social information. The cognitive component of rating scales like the PANSS may provide a rough clinical estimation of possible cognitive deficits. The component has limited psychometric properties, however, and cognitive function is better measured by neurocognitive test batteries (Nuechterlein and Green, 2006). The decline in cognitive function often predates the onset of clinical symptoms (Brewer et al., 2005), and generally is found to be stable in the long-term course of illness (Heinrichs et al, 1997, Hoff et al., 2005, Bonner-Jackson et al., 2010). Attenuated forms of cognitive impairment are also seen in siblings of patients with schizophrenia (Szoke et al., 2005, Snitz et al., 2006). Cognitive impairment may be evident across the range of psychotic illnesses (Zanelli et al., 2010), with the highest rate occurring in schizophrenia, where pervasive cognitive dysfunction has been reported in more than 50% of patients (Heinrichs et al, 1997). Impairment in social cognition is well documented in schizophrenia spectrum disorders (Kohler et al., 2010), and is also seen in bipolar disorder and major depressive disorder (Kohler et al., 2011).

Affective symptoms range from mania to major depression. Depression is common in FEP, affecting approximately 50 % of patients during the first year of illness (Romm et al., 2010). Depression in FEP patients are associated with female gender, poorer

premorbid function, poorer self-esteem, higher levels of insight into own condition and an elevated risk of suicide (Romm et al., 2010, 2011, Melle and Barrett, 2012), as well as reduced level of social functioning and quality of life (Sim et al., 2004).

Excitative symptoms include agitation, hostility and impulsivity. Baseline excitative symptoms have been found to predict non-remission at three month follow-up (Simonsen et al., 2010), and to contribute significantly in explaining service engagement in patients with early phase schizophrenia spectrum diagnosis (Johansen et al., 2011).

None of the symptom components or the symptoms within the components are pathognomonic for any of the psychotic disorders. Patients with the diagnoses described above may experience symptoms from all five symptom groups, though negative and cognitive symptoms are more pronounced and/or longer lasting in schizophrenia and schizoaffective disorder (Gerebaldo et al., 1995a,b, Hebener and Harrow, 2001, Malla et al., 2004, Simonsen et al., 2011).

1.1.4 Why study first episode psychosis patients?

Psychotic disorders develop through phases. The period before the onset of symptoms is called the premorbid phase. It is followed by the prodromal phase, when symptoms start to develop. When the symptoms have developed over a given threshold, and are sustained, it is termed the first psychotic episode. Studies of patients with psychotic disorders conducted over the last two decades have focused on patients in the early stage of illness. A seminal study by Johnstone and colleagues was the first prospective study to report Duration of Untreated Psychosis (DUP) as an important predictor of outcome (Johnstone et al., 1986). This finding inspired further research and shifted the focused

towards early intervention and detection of psychosis (Falloon, 1992). A main focus of the ensuing research has been to examine to what extent identification and treatment can modify and improve course and outcome, as well as relieve suffering. A benefit of studying First Episode Psychosis (FEP) samples is that by following the course of illness from as early as possible the effects of recall bias, chronicity, medication and institutionalisation are minimized. Also, by comparing patients at a similar stage of illness the heterogeneity in the sample is reduced.

FEP studies often include a broad spectrum of diagnoses within the psychosis spectrum both because of initial diagnostic instability (Baldwin et al., 2005, Haahr et al., 2008), and because affective and non-affective psychosis share many characteristics including symptomatology. Studying symptoms and symptom components in a broad spectrum of psychotic disorders allows for larger samples and may illuminate how core symptoms in psychotic disorders are related to each other and how they affect functioning and outcome.

1.1.5 Longitudinal studies of psychotic disorders

Longitudinal studies provide us with important data on illness course and outcome. Results from the earliest longitudinal studies of patients with psychotic disorders were reviewed in a seminal study by Shepherd and colleagues. These studies reported a deteriorating course in 62 % of patients with schizophrenia assessed between1900-1929 (Shepherd et al., 1989). This almost uniformly pessimistic view was nuanced by a later study that described schizophrenia as a heterogeneous disorder with eight different courses of illness and end states ranging from recovery to severe illness (Bleuler, 1978). The clinical data in this study was reassessed using today's diagnostic criteria (DSM-IV),

and it was found that 61 of the original 189 schizophrenia patients were better described as having a psychotic disorder other than schizophrenia (Modestin et al., 2003). In a study published in 1980, Ciompi and colleagues retrospectively assessed 289 patients with schizophrenia for an average of 37 years after their first admission. They reported that about three fifths of the patients had a favourable outcome. The results further challenged the earlier view of schizophrenia as an illness with globally poor prognosis. The study had several limitations, however. The median age at onset of illness was high, all participants were inpatients at the time of inclusion, and diagnosis was made without reference to any international diagnostic classification system. Later studies have improved methodology by having a prospective design, using standardized diagnostic criteria and using epidemiological and more representative patient samples that are followed from earlier in the course of illness. To better compare the results in different studies, criteria for remission have been standardized (Andreassen et al., 2005), and now include not only the absence of positive symptoms but also a low score, or the absence, of significant negative symptoms. Using these criteria the Australian FEP study, EPPIC, found that 36.8 % of patients were in remission at seven year follow-up. This rate is similar to results from shorter duration studies, also applying the Andreassen's remission criteria that were reviewed in the same paper (Henry et al., 2010).

Even if the earlier studies report a better outcome, with a significant proportion of the patients reaching recovery, many patients with psychotic disorders still experience a chronic course of illness. Poor outcome has been found to be predicted by male gender, early onset, insidious onset, long DUP and the severity of negative and cognitive symptoms (Ho et al., 1998, Perkins et al., 2005, Milev et al., 2007, White et al., 2009, Bertelsen et al., 2009). The Danish FEP study, OPUS, reported that 13 % of their 265 patient were institutionalised at five year follow-up. They further reported that 18 % of

the patients were in recovery. A large proportion of the sample thus experiences a relapsing remitting course of illness.

Longitudinal studies from the early eighties onwards widened their scope to focus more closely on symptom development. The Chestnut Lodge follow-up study described symptom development retrospectively in an inpatient population followed over five years after the first admission using the SAPS/SANS (McGlashan, 1984). The natural history of schizophrenia was summarized as follows: "In first or early episodes positive symptoms are frequent, negative symptoms are infrequent, and both types are unstable fluctuating, and usually treatment responsive. In sub-acute/chronic stages of the illness negative symptoms increase in prevalence, are at least as common as positive symptoms, and fluctuate less. In the latter stages of the illness, negative symptoms are quite stable and usually dominate the clinical picture" (McGlashan and Fenton, 1992). Later studies of symptom development have strengthened methodology by being prospective and following epidemiologic samples from the first psychotic episode. These studies have also often included a wider diagnostic group of psychotic disorders. However, the studies that focus on symptom development have two main limitations. Firstly, most studies focus on symptom components rather than specific symptoms (Eaton et al., 1995, Breier et al., 1991, Milev et al., 2005, Siegel et al., 2006, Bertelsen et al., 2009, White et al., 2009). With regard to positive symptoms this implies that patients with hallucinations and delusions are not looked at separately. With regard to negative symptoms this method makes data especially difficult to interpret as the negative symptom construct consists of several symptoms, and different negative symptom assessment scales include and emphasize different symptoms. The second main limitation is that most studies that do follow individual symptoms (McGlashan et al., 1992, Arnt et al., 1996) report mean prevalence of a given symptom at each point of follow-up rather than following

individual patients and looking for clusters of patients with similar symptom development. A reason why earlier studies have reported on mean values could be a lingering notion that symptoms in psychotic disorders are stable, especially with regard to negative symptoms. As described, the above studies show that schizophrenia and other psychotic disorders are mostly relapsing remitting disorders, and that only a minority of patients follow a chronic course. Studies that have reported stable mean values for symptoms over time in psychotic disorders appear to have overlooked the relapsing and remitting nature of the disorders, as patients with fluctuating symptoms may have equalled each-other out, giving the appearance of higher symptom stability in the total sample. Longitudinal studies of specific positive and negative symptoms where different symptom trajectories and profiles are documented may thus further inform this field of research.

1.2 Positive symptoms of psychotic disorders

The term positive symptoms describe the reality distortion component of psychotic illnesses including hallucinations and delusions. Since the advent of neuroleptic treatment this symptom group has been the most extensively studied component of psychotic disorders. Positive symptoms are thought to result in part from prefrontal-limbic dopamine imbalance (Howes and Kapur, 2009, Heinz and Schalgenhauf, 2010), and dopaminergic models are supported by the effect of antipsychotic medication through the blockade of dopamine receptors. These models only partly explain the symptoms, and an ongoing work is progressing to map out the role of other neurotransmitter systems as well as structural changes to the pathogenesis of positive symptoms.

Hallucinations and delusions are commonly described together. However, it is recognized that these symptoms often occur separately, and possibly give a separate contribution to outcome measures. A number of studies have recorded the presence of both hallucinations and delusions in patient samples over time and related individual symptoms to associated symptoms and outcome factors (Fenton and McGlashan, 1991, 1992, Addington et al., 1993, Harrow et al., 2004). A 20 year follow-up study found that hallucinations and delusions correlated strongly at two year follow-up (r=.85), but that the correlation weakened during the follow-up period (r=.53 at 20 years). Continuous delusional activity was present in both patients with schizophrenia and other psychotic disorders, including affective psychosis), and persistent delusional activity strongly predicted work disability (Harrow and Jobe, 2010).

1.2.1 Delusions

Delusions are erroneous beliefs that usually involve a misinterpretation of perceptions or experiences, and are described in the DSM-IV as "A false belief based on incorrect inference about external reality that is firmly sustained despite what almost everyone else believes and despite what constitutes the convertible and obvious proof or evidence to the contrary. The belief is not ordinarily accepted by the members of the persons culture and subculture (e.g. is not an article of the persons faith)" (APA, 2000). The delusionary content may include a variety of themes (persecutory, referential, somatic, religious or grandiose), and persecutory delusions are the most common. Delusions are suggested to arise from anomalies in reasoning processes, and studies have shown that patients with delusions show: 1) jumping to conclusion bias, 2) attributional bias, and 3) difficulties appreciating other peoples' perspectives on theory of mind tasks (Langdon et al., 2010).

1.2.2 Delusions without hallucinations

Clinical studies that recognize a group of patients who experience delusional ideation without also suffering from hallucinations, usually focus on delusional disorder (Munro, 1995, Opjordsmoen, 1988, 1989a). This diagnosis is associated with later onset of illness and better outcome (Opjordsmoen, 1989b), including less hospitalizations and higher rate of employment, compared to a schizophrenia sample (Marneros et al., 2012). Patients from other diagnostic categories who experience delusions only have received little specific attention.

1.2.3 Hallucinations

A hallucination is a percept-like experience occurring in the absence of an external stimulus. The percept-like experience has the full force and impact of a real perception, and is unwilled and cannot be readily controlled (Slade, 1976). Unlike illusions, hallucinations arise de novo and occur alongside normal perceptions (Jaspers, 1969). Hallucinations may arise from a variety of sensory systems, giving rise to auditory, visual, somatosensory and olfactory hallucinations. Auditory hallucinations are the commonest form, and these may range from elementary noises to fully formed voices. It has been suggested that auditory hallucinations arise from a deficit in source monitoring, whereby inner speech is misidentified as external voices (Firth et al., 1987, Bentall et al., 1990). Studies using manipulated auditory feedback of patients' own voices have reported that patients with schizophrenia tended to misidentify their own distorted voice as someone else's (Cahill, 1996, Johns et al., 2001). Johns and colleagues furthermore reported similar, but less marked, misattribution deficits in patients with schizophrenia without a history of hallucinations, and that patients with affective psychosis tended to report that they were "unsure" about the origin of the voice rather than to misattribute

(Johns et al., 2006). Deficit in source monitoring thus seem to be a mechanism shared between diagnoses and also in patients with delusions both with and without hallucinations.

1.2.4 Hallucinations without delusions

Like delusions, hallucinations can occur mono-symptomatically, without coexisting delusions. The number of studies describing patients who experience hallucinations, but not delusions is limited, but the symptom-profile has been described in non-clinical samples. A study comparing a group of voice-hearers without additional psychopathology to a normal (non-voice-hearing) control group, found that the voice-hearing group had poorer global functioning (Sommer et al., 2010). Another study, comparing a similar group of voice-hearers to a schizophrenia patient group, found that while the form of hallucinations was similar between patient and non-patient groups, other differences existed between the groups in terms of hallucinatory content, emotional quality and locus of control of the voices, with the non-clinical group experiencing the voices as less threatening and more controllable than the patient group (Honig et al., 1998). Mauri and colleagues have described a patient group where hallucinations, rather than delusions, were the dominating symptom (Mauri et al., 2006, 2008). The group was labeled "Hallucinatory Disorder" and the patients were found to be older, have higher academic achievement, score better on insight measures, and to have higher suicidality compared to a schizophrenia patient group.

1.2.5 Positive symptoms and suicidality

Suicide is one of the major contributors to the excess mortality reported in psychotic disorders (Pompili et al., 2011). Approximately 2-5% of deaths in FEP patients, as

reported in long-term follow-up studies, are a result of suicide (Palmer et al., 2005, Dutta et al., 2011). Suicidal acts and suicide are most common in the early stage of illness (Nordentoft et al., 2002, Dutta et al., 2010, Bertelsen et al., 2007, Barrett et al., 2010), and most completed suicides occur in the first decade of illness, and 50 % of these occur in the first two years after illness onset (Montross et al., 2005). Several studies have related delusions and hallucinations to suicidality. A study investigating the relationship between delusions and suicidality found no evidence of a significant correlation between delusions at admission, and a history of suicidal ideation or suicide attempts. The study reviewed the existing literature, and concluded against delusions as a separate predictor of suicidality (Grunebaum et al., 2001). A small number of studies have showed that hallucinations is a risk factor for suicidality (Fialko et al., 2006, Kaplan and Harrow, 1996), but a clear association between hallucination and suicidality is not established (Harkavy –Friedman et al., 2003). The OPUS study found that hallucinations at two year follow-up predicted suicidality (plans and attempts) in FEP (Bertlesen et al., 2007). The above studies, however, looked at data cross-sectionally and recorded the number of patients suffering from any one symptom at a particular time rather than showing longitudinal symptom profiles and their separate correlates. Prior to our study patients with hallucinations only and delusions only had not been compared on measures of suicidality.

1.3 Negative symptoms of psychotic disorders

The negative symptoms construct include apathy/avolition, asociality, anhedonia, inattention, alogia and flat affect (FA). The etiology of these symptoms is still poorly understood, with findings implying multiple and complex neurophysiological

mechanisms underlying symptom expression (Linscott and van Os, 2011, Howes and Kapur, 2009). The negative symptom group has been found to be cross-sectionally and longitudinally independent from the positive symptom group (Kirkpatrick et al., 2001, Drake et al., 2003), and factor analytic studies confirm the negative symptom component as being separate from the cognitive, affective as well as excitative symptom components (Kay and Sevy, 1990, Emsley et al., 2003, Blanchard and Cohen, 2006, Foussias and Remington, 2010). Negative symptoms are often the first symptoms to develop in patients with psychotic illness (Hafner et al., 1999). These symptoms adversely influence functioning and outcome (Ho et al., 1998, Bowie et al., 2006, White et al., 2009, Ventura et al., 2009, Bottlender et al., 2010), and are associated with slower recovery and longer periods of hospitalization (Hwu et al., 2002). The symptoms are treatment resistant (Kirkpatrick et al., 2006, Makinen et al., 2008), and often persist after positive psychotic symptoms have been successfully treated.

Most long-term follow-up studies of negative symptoms report mean levels cross-sectionally rather than investigating longitudinal symptom trajectories. Harrow and colleagues, however, followed 42 young patients with schizophrenia and schizoaffective disorder and found that 19 % had enduring, 41 % episodic, and 40 % no negative symptoms over a ten year follow-up period. Enduring symptoms were defined as being above threshold level (score of >1 on at least one item of the Pogue-Geile and Harrow's Negative Symptom Scale) at three follow-up assessments (Herbener and Harrow, 2001). These patients were also compared to a group with affective psychosis and a group with non-psychotic depression. Enduring negative symptoms had lower prevalence in non-schizophrenic illness, but similar level of severity, persistence and relation to symptom correlates (medication, positive symptoms and depression) was observed (Herbener and Harrow, 2001, 2004). A recent study of FE schizophrenia patients found that 24% of

patients had persistent negative symptoms at ten year follow up. This study also reported that 41% of their participants had negative symptoms at baseline (Makinen et al., 2010). The study did not have more than one point of follow up, however, and neither this nor Herbener and Harrow's study examined individual negative symptoms.

Most studies that report symptom stability over time emphasize the stability of negative symptoms over positive symptoms (Pougue-Geile and Harrow, 1985, Fenton and McGlashan, 1992, Drake et al., 2003, Makinen, 2008). However, some studies indicate a more fluid symptom picture also for negative symptoms. Edwards and colleagues examined negative symptoms in a FEP sample followed three times over a one year period. Persistent negative symptoms was found in 4- 41 % of the sample, depending on the criteria used to define enduring symptoms (Edwards et al., 1999).

Negative symptoms are often studied together, with studies reporting negative component sum scores rather than scores on individual symptoms (Edwards et al., 1999, Hebener and Harrow, 2001, Makinenen al., 2010, Chang et al., 2011). However, the negative symptom construct represents a heterogeneous symptom group. Different symptom scales, like the PANSS, SANS and the Schedule for the Deficit Syndrome (SDS) differ on how they define the individual negative symptoms and what negative symptoms that are focused on and measured, and no clear consensus exists on how to best measure this group of symptoms. Factor analyses of the negative symptom component of assessment batteries like the PANSS and the SANS have indicated that alogia is better explained as part of the cognitive component, and that the remaining negative symptoms should be seen as two separate factors: an experiential factor where apathy/amotivation is the main feature, and an expressive factor where FA is the main feature (Blanchard and Cohen, 2006, Messinger et al., 2011). The finding has been

replicated in factor analyses of two new negative symptom measures, the Clinical Assessment Interview for Negative Symptoms (CAINS) and the Brief Negative Symptom Scale (BNSS) (Horan et al., 2011, Kirkpatrick et al., 2011).

In 2005 the National Institute for Mental Health (NIMH) organized the Consensus Development Conference on Negative Symptoms to further the study of negative symptoms. An expert group was assembled with the aim of improving our understanding of negative symptoms so as to facilitate treatment development. The group defined the key negative symptoms described above and released a consensus statement that encouraged the longitudinal study of individual negative symptoms (Kirkpatrick et al., 2006). Previous literature is lacking in prospective long-tem studies of well described epidemiological FEP samples that follow the symptom development of individual negative symptoms. Following the incentive from the NIMH consensus statement on negative symptoms, and the conclusion from factor analytic studies of negative symptoms, we chose to focus on the longitudinal symptom development of apathy and FA in our patient sample.

1.3.1 Apathy

Apathy is described as a neuropsychiatric symptom associated with dysfunction of the prefrontal cortex and its subcortical connections (Marin et al., 1991b, Stuss et al., 2002, Tekin et al., 2002). It is highly prevalent in neuropsychiatric conditions such as Alzheimer's Disease and Parkinson's Disease, in which it has been associated with functional decline (Starkstein et al., 2006), worse course and outcome (Starkstein et al., 2006, 2009), and poor executive function (McPherson et al. 2002, Pluck et al., 2002, Tsoi et al. 2008).

Apathy is also well documented in psychotic disorders (Barch, 2008, Foussias and Remington, 2010, Messinger et al., 2011), and the terms apathy, avolition and amotivation are used interchangeably in the literature (Foussias and Remington, 2010). Apathy in psychotic disorders was first described by Kraepelin in 1919. It was later defined by Marin as "the lack of motivation not attributed to diminished levels of consciousness, cognitive impairment or emotional distress" (Marin, 1991a). This definition forms the basis for the commonly used assessment tool Apathy Evaluation Scale (AES) (Marin et al., 1991b). Studies of apathy in both neuropsychiatric and psychotic disorders have found apathy to be a primary symptom, with only a small percent of the variance in the apathy score being explained by depression, side-effects of medication or psychotic withdrawal (Faerden et al., 2009a, Kiang et al., 2003).

Studies of apathy in psychotic disorders have found an association between apathy and longer DUP (Malla et al., 2002), poorer general functioning (Kiang et al., 2003, Foussias et al., 2009, 2011), aberrant executive function (Roth et al., 2004), and reduced prefrontal cortical volume (Roth et al., 2004). The generalizability of these findings is limited by cross-sectional designs, small sample sizes, and inclusion of patients with long illness durations.

Faerden and colleagues used the clinician version of the AES (AES-C) to examine apathy in FEP. They investigated 103 patients at baseline and 84 patients at one year follow-up, and found that 51 % of patients at baseline, and 40 % at one year follow-up, were clinically apathetic (AES-C score $\geq$ 27). They also found that apathy at one year follow-up was predicted by male gender, long DUP, a diagnosis within the schizophrenia spectrum, and baseline apathy. They further provided evidence for the association between apathy and poorer functioning, as apathy was found to be significantly and

independently related to functioning at both baseline and follow-up (Faerden et al., 2009b, 2010).

1.3.2 Apathy and subjective quality of life

Quality of life (QoL) is an important outcome variable in psychotic disorders. Studies often differentiate objective from subjective QoL. Objective QoL refers to role fulfillment, financial situation, social functioning and daily activities, whereas subjective QoL focuses on patients' self-reported satisfaction with life and over-all sense of wellbeing. Subjective QoL has been reported to be lower in patients with psychotic disorders (Malla and Payne, 2005), and also lower in patients with first episode schizophrenia and schizoaffective disorder compared to a chronic patient sample (Priebe et al., 2000). Studies of FEP patients have found that lower subjective QoL is associated with depression (Malla and Payne, 2005, Renwick et al., 2011), longer DUP, and younger age at onset (Malla and Payne, 2004). While Gorna and colleagues reported a significant association between subjective QoL and both positive and negative symptoms in first episode schizophrenia (Gorna et al., 2008), Melle and colleagues failed to find such relationships in the two year follow-up study of the TIPS sample using the three factor model of PANSS to measure symptom components (Melle et al., 2010).

The association between apathy and patient rated, subjective QoL is contested. In Alzheimer's disease patient's careers, but not patients themselves, rated quality of life as poorer in those with high apathy levels (Karttunen et al., 2010). In Parkinson' disease patient's own rating of QoL has been associated with higher apathy scores (Barone et al., 2009; Benito-León et al., 2011). In psychotic disorders apathy has been viewed as an ego-syntonic symptom in patients indifferent to their own state and surroundings (Bleuler, 1950). A further study found apathy to be the negative symptom causing the

most distress (Selten et al., 2000). In our study we sought to further explore the relationship between apathy and subjective quality of life.

1.3.3 Flat affect

Flat affect is described as unchanging facial expression, paucity of gestures, and affective non-responsiveness (Kay et al., 1987). A study comparing patients with schizophrenia and with depression to healthy controls found that the patient groups had similar deficits in spontaneous and posed emotional expressiveness, smiling and co-verbal gestures (Tremeau et al., 2005). FA is also documented in neuropsychiatric disorders like Parkinson's Disease and right hemisphere brain damage (Borod et al., 1989). In patients with schizophrenia FA has been reported to be present at the onset of illness (Shtasel et al., 1992), and associated with earlier onset, poorer premorbid adjustment and poorer verbal memory (Gur et al., 2006). Malla and colleagues found that FA was predicted by male gender, younger age of onset, a diagnosis of schizophrenia and length of prodromal period in an FEP population. The same mean level of FA was reported for patients with schizophrenia compared to a broad spectrum of other psychotic disorders (Malla et al., 2002). At one year follow-up Malla and colleagues found that FA was an indicator of poor response to treatment, and a predictor of the development of persistent negative symptoms (Malla et al., 2004). These findings have been replicated in a recent one year follow-up study (Gladerisi et al., 2012) that additionally found FA to be the most persistant negative symptom. Kelley and colleagues investigated FA, avolition, alogia and anhedonia separately using the SANS at baseline and four points of follow-up over one year in both a chronic and a first episode schizophrenia sample (Kelley et al., 2008). The study concluded that levels of FA were largely stable over one year, in contrast with the other negative symptoms that followed a more fluctuating course.

Laboratory studies of patients with schizophrenia have reported reduced facial expressions during social interaction (Krause et al., 1989), and watching emotional films (Berenbaum and Oltmanns, 1992) and cartoons (Dworkin, 1992). FA, the deficit in expression of emotion, has been shown to be a separate factor to anhedonia, the deficit in experiencing pleasure (Foussias and Remington, 2010). Kring and colleagues found that when watching both positive and negative emotional films, patients with schizophrenia were less facially expressive than normal subjects, yet they reported experiencing as much, or more, emotion than did the normal controls (Kring et al., 1993). FA may thus be a failure to express emotional states rather than a genuine lack of emotionality. Other studies contest these findings and describe FA as incorporating both an affective and a neuromotor deficit (Dworkin et al., 1996).

1.3.4 Flat affect and social functioning

Deficits in social functioning are common in psychotic disorders and have been found to precede the first psychotic episode (Hafner et al., 1995, Woods et al., 2009). In the Israeli draft board study of patients who later developed schizophrenia, asymptomatic future patients were found to have poorer social functioning at the age of 16 (Reichenberg et al., 2002).

Studies of negative symptoms have found a significant association between this symptom group and reduced social functioning over time (Ho et al., 1998, Shatsel et al., 1992, Lysaker and Davis 2004). The lack of observable expressive behavior seen in patients with FA is likely to have detrimental interpersonal consequences. A study found that healthy individuals were less expressive when they interacted with a patient with schizophrenia than with healthy subjects (Krause et al., 1992). A one year follow-up study of patients with schizophrenia found that patients with FA had poorer social

outcome compared to patients without FA (Gur et al., 2006). The relationship between FA and social functioning beyond one year had not been described prior to our study.

1.4 Diagnostic categories versus dimensions

How to best describe psychiatric illness has been an ongoing debate since the first diagnostic systems were constructed. The two main classification systems, the International Classification of Diseases (ICD) and the DSM divide non organic psychosis into affective/mood disorders and non-affective/schizophrenia disorders. Schizoaffective disorder, where both schizophrenia- type symptoms and affective symptoms are equally pronounced, is categorized under the schizophrenia spectrum disorders. The division into affective and non-affective psychosis may not, however, reflect the difference in aetiology, disease processes and prognosis that we assume when we describe two conditions as separate entities. Non-affective psychotic disorders, affective psychotic disorders and purely affective disorders share many of the same risk factors and symptomatology. Studies show that schizophrenia and bipolar illness have similar heritability rates (Chicon et al., 2009), and share affected neurotransmitter systems (dopamine, serotonin, Gamma-aminobutyric acid, and glutamate) (Freedman et al., 2003, Ackenheil et al., 2001, Cherlyn et al., 2010), as well as symptom response to the same psychoactive medication (Citrome et al., 2005). In the last two decades new tools have been developed to study neurobiological vulnerability markers, or endophenotypes, that bridge genotype and clinical phenotype. These tools have revealed that affective and non affective psychotic disorders share many of the same biological correlates. Studies using MRI imaging have found similar type, but quantitatively different, structural brain

changes in schizophrenia and bipolar disorder (Strakowski et al., 2005, Strasser et al., 2005, Morgan et al., 2007). Similarly, recent cross diagnostic studies have found little or no difference between psychotic disorders on neurocognitive functioning (Simonsen et al. 2011, Lewandowski, 2011). The conditions furthermore share several susceptibility genes (Craddock et al., 2009, Williams et al., 2011, Skal et al., 2011).

Studies of symptomatology in healthy populations have shown attenuated positive and negative symptoms in non-clinical populations (Van Os et al., 2009). The same symptoms have also been found in neuropsychiatric conditions like Parkinson's disease and Alzheimer's disease (Barone et al, 2009, Kartuunen et al., 2010). These findings, together with the data that describes the similarities between affective and non affective psychosis, suggest that psychotic symptoms are experienced on a continuum, stretching from the well, non clinical population to the severely ill, and over several diagnostic categories. The "psychosis-proneness-persistence-impairment model" of psychotic disorder details this psychosis continuum (Van Os et al., 2009), and describes how the usually transitory psychotic experiences can become more persistent psychotic experiences with a need for clinical care due to environmental and psychological risk factors such as psychological trauma, cannabis and urbanicity.

These findings seems to imply that the disease processes we describe as schizophrenia, schizoaffective disorder and bipolar disorder could be better described dimensionally, as syndromes with shared symptom components, and that the disorders differ from each other quantitatively rather than qualitatively. Longitudinal studies of patients from different diagnostic categories, but with overlapping phenotype and genotype, may further illuminate the pathogenesis of symptoms and syndromes in psychotic illness, and help us learn more about these symptoms and how they are related to each other. Following patients with similar symptoms profiles over time give us the possibility of

uncovering relationships between these symptom profiles and functional and outcome variables.

2. Aims

This thesis aims to explore individual positive and negative symptoms in a large, epidemiologic sample of FEP patients. By studying single symptoms longitudinally and identifying distinct longitudinal symptom profiles, we aimed to increase our understanding of how these symptoms develop over time, their relation to other symptoms, and to outcome variables known to be affected in psychotic disorders. The thesis focuses on a broad group of FEP patients with shared symptomatology, followed for ten years from the onset of illness, with up to six assessments.

In paper I the main aim was to examine if it was possible to identify subgroups of patients who, during a five year follow-up period, had suffered either from hallucinations only or delusions only, and to examine if these groups differed on baseline variables (demographic characteristics, DUP, premorbid functioning) and clinical measures, including insight. Furthermore, we wanted to explore if hallucinations, to a greater extent than delusions, were related to suicidality and completed suicides.

In paper II the main aim was to assess the prevalence of self-reported apathy at ten years follow-up, and to explore symptom development through a longitudinal clinician rated proxy-measures of apathy (PANSS N2+N4). Furthermore, we wanted to investigate if apathy had a significant independent contribution to global functioning and to subjective quality of life scores ten years after the first psychotic episode.

In paper III the main aim was to identify groups of patients with different flat affect (FA) trajectories and to examine the prevalence and stability of FA over a ten year period. We also wanted to examine if the FA trajectory groups differed in outcome measure at ten years follow-up, and in social functioning over the ten year follow-up period.

3. Method

3.1 Design

The TIPS (Early Treatment and Intervention in Psychosis) project is a large, longitudinal study of an epidemiologic sample of FEP patients. The study protocol was planned and initiated from 1995 by the study research committee; Thomas McGlashan (Chair), Ulrik Haahr, Jan Olav Johannessen, T.K. Larsen, Ingrid Melle, Stein Opjordsmoen, Bjørn R. Rund, Erik Simonsen, Per Vaglum, and Svein Friis. The study was designed to identify and follow consecutively admitted FEP patients from four Scandinavian health care sectors (North and South sector, Rogaland County, Norway, Ullevaal Sector, Oslo, Norway, and Fjorden mid-sector, Roskilde, Denmark). Patients received publicly funded, catchment based, specialist psychiatric care. Patients were included between 1997-2000, after equivalent treatment programs for FEP patients had been established in the health care sectors involved. The TIPS project is an early intervention in psychosis study. The primary aim of the original study was to answer the following research questions:

- Is it possible to reduce the duration of untreated psychosis (DUP) through an early detection program?
- Would a reduction in DUP be followed by a difference in the course of illness, and can this difference be explained by the reduction of DUP?

In order to answer these questions patients from the two healthcare sectors in Rogaland County (ED group) were exposed to an early detection and compared to patients from the Oslo and Roskilde healthcare sector (no-ED group) who engaged with the services as previously done. The early detection program consisted of public information campaigns, education of teachers, social workers and GPs, a telephone "hotline" and an offer of

assessment within 24 hours of service contact. The early detection campaign successfully reduced DUP (Melle et al., 2004), answering the first main research question of the study. Patients in the ED and the no-ED regions were compared with regard to clinical severity, function, suicidality and other outcome measures. At baseline, ED patients were found to have lower symptom load (positive, negative and general symptoms), better social functioning, and lower suicidality (Melle et al., 2004, 2005, 2006), answering the second main research question. For the ED / no-ED comparison part of the study the design was quasi-experimental parallel control.

The study described in this thesis did not distinguish between the ED and no-ED patients, but followed the whole patient sample. The design of the described studies is hence prospective and longitudinal.

The overall study design, samples, assessment instruments, and results of previous assessments are carefully detailed in several reports (Larsen et al., 2001, Melle et al., 2004).

3.2 Procedure

3.2.1 Inclusion and treatment

Patients were recruited to the study as they presented to the services. As described above, this process was different in the ED region compared to the no-ED, however once recruited to the study the same inclusion criteria and assessment protocol applied. Patients in the four healthcare sectors were offered the same basic treatment after inclusion to the project:

1. Defined treatment algorithms for antipsychotic medication (low dose second-generation antipsychotic medication).
2. Individual psychosocial treatment (a trained therapist offering weekly sessions).
3. Psycho-educational family work (multifamily groups).

We chose to define inclusion/start of project as the start of first adequate treatment. Adequate treatment was defined as the start of structured treatment with antipsychotic medication, or the start of hospitalization in highly staffed psychiatric wards organized to manage disturbing psychotic symptoms.

3.2.2 Follow-up assessments

Following the initial inclusion in the study and baseline assessment, patients were reassessed at three months, and one, two, five and ten years.

3.3 Participants

3.3.1 Participants at baseline

Inclusion and exclusion criteria for the TIPS study are listed below:

1) A first episode psychosis (PANSS score ≥4 on one or more of positive subscale items P1, 3, 5 or 6 or on general subscale G9 for ≥ 7days).
2) Meeting the DSM-IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic episode, delusional disorder, affective psychosis with mood-incongruent psychotic features or psychotic disorder not otherwise specified.

3) Age 18–65 years (15-65 in Rogaland).

4) IQ >70.

5) Living in the catchment area of one of the four healthcare sectors.

6) Understanding/speaking a Scandinavian language.

7) Ability to give written, informed consent.

The exclusion criteria were:

1) Having received adequate prior antipsychotic treatment (antipsychotic medication > 3.5 haloperidol equivalents for >12 weeks or until psychotic symptoms remission) and an organic- or substance-induced psychosis.
2) Having a neurological or endocrine disorder related to psychosis.

Both inpatients and outpatients were included in the study. Altogether 301 patients were included from 1997 through 2000.

3.3.2 Participants in the papers included in this thesis

The three papers included in this thesis all use patients drawn from the TIPS sample described above. The different studies, however, focused on different subgroups of patients and followed them for different lengths of time.

The table below describes the number of patients and length of follow-up in the three studies.

	Paper I	Paper II	Paper III
Length of follow-up	≤ 5 yrs.	10 yrs.	10 yrs.
Number of participants	301	178	184
Use of data	All points of measure (baseline -5 yrs.)	Baseline + 10 yrs. (N2 and N4 used at all points of measure)	All points of measure (baseline -10 yrs)

3.3.3 Drop out analyses at ten years

		Included		Not included	
		Total	**N, %**	**Total**	**N, %**
Gender (males)		186	104 (56)	115	72 (63)
Marital status		186		113	
	Single		131 (73)		34 (61)
	Living together/married		31 (17)		13 (23)
Ethnicity	Scandinavian	186	178 (96)	115	102 (89)
Diagnosis	Core schizophrenia at baseline	186	116 (62)	115	72 (63)
Abuse	Alcohol	186	23 (12)	115	26 (21)
	Drugs	186	41 (22)	115	29 (25)
		N	**Median(min-max)**	**N**	**Median (min-max)**
Age		186	25 (15-61)	115	24 (15-63)
Years of education		175	12 (7-22)	110	11 (8-20)
Premorbid Adjustment Scale					
	Social level childhood	183	0.5 (0-5)	110	1 (0-5)
	Academic level childhood	183	1.5 (0-6)	110	1.75 (0-5)
	Social level last score	183	1.5 (0-6)	110	2.0 (0-6)
	Academic level last score	183	2.0 (0-6)	110	2.5 (0-6)
Duration of untreated psychosis in weeks)		186	6 (0-520)	115	17 (0-1196)
Baseline psychopathology (median, min-max)					
	PANSS positive component	186	15 (5-28)	114	15 (8-26)
	PANSS negative component	186	18 (10-50)	112	19 (10-64)
	PANSS cognitive component	186	7 (3-17)	111	7 (3-20)
	PANSS depressive component	186	12 (5-23)	112	13 (5-24)
	PANSS excitative component	186	8 (5-31)	112	9 (5-27)
	GAF-f	186	30 (10-70)	113	30 (14-63)
Level of functioning (Strauss-Carpenter scale)					
	Working last year	169	2 (0-4)	103	1 (0-4)
	Meeting friends last year	180	3 (0-4)	111	3 (0-4)

The above drop out analyses show few significant differences between the participant at baseline and the remaining participants at ten years follow-up. The non-participant group had a significantly higher percentage of non-Scandinavian patients (p=0.020), higher rate of alcohol abuse (p=0.05), shorter education (p=0.035), a longer DUP (p=0.002) and lower rate of employment in the year before inclusion (p=0.006).The analyses were repeated comparing only the patients included in paper II (N=178) and in paper III (N=184) without finding additional differences between participants at ten years and baseline participants. These analyses included baseline levels of proxy measures of apathy (PANSS N2 and N4) and of FA (PANSS N1).

3.4 Measurements

3.4.1 Main assessment instruments

Measures conducted at baseline only: Duration of untreated psychosis (DUP) was measured as the time in weeks from the first positive psychotic symptoms (PANSS score of four or more on Positive scale items one, three, five or six or General scale item nine) to the start of the first adequate treatment of psychosis (i.e., admission to the study). Premorbid functioning was measured by the Premorbid Assessment of Functioning Scale (PAS). A previous analysis identified two premorbid dimensions: *social* consisting of PAS items social isolation and peer relationships and *academic* which comprised school performance and school adaptation (Larsen et al., 2004).

Diagnostic assessment: The structured clinical interview for the DSM-IV (SCID) was used for diagnostic purposes (Spitzer et al., 1992).

Symptoms: Symptom levels were measured by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and symptom domains were represented by the corresponding PANSS components (positive, negative, excitative, cognitive and

depressive) (Kay and Sevy, 1990, Bentsen et al., 1996). Individual items were used to follow specific symptoms (see table below).

Depression was assessed by the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992). Apathy was measured with the self report version of the Apathy Evaluation Scale (AES-S) (see further details, 3.4.4).

Function and quality of life: Global functioning was measured by the Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976), and split into symptom [GAFs] and function scores [GAFf] to improve psychometric properties (Pedersen et al., 2007).

Employment and ability to live independently was measured with the Strauss Carpenter Level of Functioning Scale (SCLFS) (Strauss and Carpenter, 1974).

Objective social functioning was measured using Lehman's Quality of Life Interview (L-QoLI) items, brief version (Lehman et al., 1988). It consists of three items: 1. How often do you visit friends? 2. How often do you telephone someone who does not live with you? 3. How often do you do something with a friend that you have planned ahead of time?

Quality of life was measured by Lehman's Quality of Life Interview (L-QoLI), brief version (Lehman et al., 1988). The item "Satisfaction with life in general" was used.

Medication: Antipsychotic medication, Defined Daily Dose (DDD), was measured using the World Health Organization Collaborating Center for Drugs statistics methodology (WHO Collaborating Center for Drug Statistics Methodology, 2008).

Substance abuse: Drug and alcohol abuse were assessed with AUDIT (Alcohol Use Disorders Identification Test) (Saunders et al., 1993) and DUDIT (Drug Use Disorders Identification Test) (Berman et al., 2005).

Suicidality: Suicidality was assessed by asking the patients at the baseline diagnostic interview whether they had experienced any suicidal thoughts, plans or attempts in the preceding month (suicidality at baseline), or whether they had experienced any suicidal thoughts, plans or attempts earlier in their lifetime (suicidality before baseline). The questions were repeated in the follow up interviews and suicidal thoughts, plans and attempts since last follow up were recorded. Completed suicides were recorded at follow-up assessments.

Symptom remission: Symptom remission at five year follow-up was defined as a period of at least one week without positive psychotic symptoms corresponding to a PANSS score >3 on positive subscale items 1, 3, 5 and 6 and on general subscale 9. Time to remission was defined as the time from when adequate treatment was initiated to remission of symptoms as described above.

Symptom remission criteria were changed at the ten year follow up to comply with the international standardized criteria (Andreasen et al., 2005), and included PANSS scores of 3 or less on items P1. Delusions**,** G9. Unusual thoughts**,** P3. Hallucinatory behaviour**,** P2. Conceptual disorganization**,** G5. Mannerism/posturing**,** N1. Blunted affect**,** N4. Passive/apathetic social withdrawal and N6. Lack of spontaneity and flow of conversation for at least six months. Recovery was also reported at ten years follow up and was operationalized as a combination of symptom remission and three functional dimensions based on the SCLFS: Day-to-day living (independent living), Role functioning (work, academic, or full-time home-making) and Social Interaction. A score of 0 indicated very poor functioning, and a score of 4 indicated good functioning. Patients in recovery had, during the previous 12 months, fulfilled the symptom remission criteria above and scored four on all three functional dimensions.

Most of the above test-battery was used at baseline and repeated at one, two, five and ten years. DUP and PAS were only assessed at baseline, at three months only PANSS and GAF were used, and at ten years AES and CDSS were added to the test battery.

Information was collected by interviewing patients, and gathering information from family, school and social workers when available. Information was cross checked with the medical charts.

Table 1. Instruments specific to individual studies

Paper I	**Paper II**	**Paper III**
PANSS items P1 (delusion) and P3 (hallucination)	AES-S-Apathy (Clinical apathy)	PANSS item N1 (flat affect)
PANSS items G12 (insight)	PANSS item N2 (emotional withdrawal) and N4 (Passive/apathetic social withdrawal) =proxy measures of apathy)	Objective social functioning (L-QoLI)
Suicidality (thoughts, plans or attempts)	Subjective quality of life (L-QoLI)	Symptom remission
Time to remission	Calgary Depression Scale for Schizophrenia (CDSS)	Recovery
	Alcohol and substance abuse (AUDIT and DUDIT)	

3.4.2 Reliability testing of the main instruments

Assessments at ten years were conducted by one psychiatrist, one clinical psychologist, and one psychiatric resident. The raters were trained in using the study instruments by rating previously prepared case notes and audiotapes/videotapes before entering the study. Good reliability for major variables (GAF, DUP and diagnosis) has been documented for earlier raters (Friis et al., 2003). During the early phase of the ten year data collection the site coordinators videotaped two PANSS interviews that were rated by all three site coordinators. The Intraclass Correlation Coefficients (ICC) two way mixed

model was used, as the three raters made all the evaluations. We used the absolute agreement option, as this is sensitive to systematic differences between raters. For the five PANSS components the ICC ranged from 0.61 to 0.82 with a median of 0.67. Twenty eight patients gave informed consent for video-recording of PANSS interviews for reliability testing. Based on the interviews the GAFs/GAFf measure was also tested. The videotaped patients were not significantly different to those who were not videotaped on any of the PANSS subscales, or on GAFs/GAFf. Two tapes could not be rated due to technical problems. The remaining 26 interviews were rated by an experienced psychologist who was not involved in the project and was blind to all ratings. The ICC two way mixed model was used, with the consistency option as consistency between the site scores and the independent rate's scores was the point of interest. For the five PANSS components the ICCs ranged from 0.61 to 0.82 with a median of 0.67. See table below for further details.

Variable	ICC	95% CI
PANSS total sum	0.90	0.80 - 0.96
Positive component	0.87	0.72 - 0.94
Negative component	0.81	0.61 - 0.91
Cognitive component	0.82	0.63 - 0.91
Depressive component	0.74	0.50 - 0.88
Excitative component	0.66	0.37 - 0.83
GAF symptoms	0.83	0.65 - 0.92
GAF function	0.88	3.3 - 0.94

3.4.3 Assessment of hallucinations and delusions

In paper I PANSS items P1, delusions, and P3, hallucinations, were used to identify the two mono-symptomatic groups. Having hallucinations or delusions was defined as a score of ≥ 4.

The hallucinations only group (H): This group experienced hallucinations (rated as PANSS score item P3, hallucinations, of ≥ 4), but not delusions (PANSS score P1,

delusions, of ≤ 3). Patients who were found to experience delusions (PANSS score P1, delusions, of ≥ 4) on follow up interviews, up to and including five years, were removed from the group.

The delusions only group (D): This group experienced delusions (rated as PANSS score item P1, delusions, of ≥ 4), but not hallucinations (PANSS score P3, hallucinations, of ≤ 3). Patients who were found to experience hallucinations (PANSS score P3, hallucinations, of ≥ 4) on follow up interviews, up to and including five years, were removed from the group.

3.4.4 Assessment of apathy

In paper II apathy was assessed using the abridged self-report Apathy Evaluation Scale (AES-S-Apathy). The Apathy Evaluation Scales has three versions; a clinician rated (AES-C), an informant rated (AES-I) and a self-rated (AES-S) version. The scales have been translated to Norwegian (Andersson et al., 1999). In this thesis we used an abridged version of the AES-S, the AES-S-Apathy. This version has been found to have better psychometric properties compared to the 18 item non-abridged version (Faerden et al., 2008). It consists of 12 questions that are answered on a Likert scale ranging from 1 to 4 (1=not at all, 4=very much). Patients with scores of 27 or above were considered to be clinically apathic. This score was two standard deviations (2SD=8.6) above the mean sum scores (mean=18.0+/-4.3) of a healthy control group in a study of the AES assessment tool in a FEP sample (Faerden et al., 2008). Examples of items in the AES are “Getting things done is important to me”, “I spend time doing things that interest me”, and “Someone has to tell me what to do each day”. The clinician version of this instrument (AES-C-Apathy) has been found to assess apathy in a FEP sample with

reliability (Faerden et al., 2008). Good internal consistency was found for AES-S-Apathy in the present study (Cronbach's α=.89).

3.4.5 Assessment of flat affect

In paper III the PANSS negative component item N1 was used to assess and follow the development of FA. Only patients who participated at the ten year follow-up were described in this paper (N=186). Two patients were excluded as they lacked more than two assessments. For patients who lacked two or less scores a mean score was calculated. This score was calculated from the score immediately preceding and following the missing score of the patient concerned. We used a PANSS score of ≥3 as threshold for clinically significant FA. A score of 3 is described as changes in facial expression and communicative gestures that seems to be stilted, forced artificial or lacking in modulation (Kay et al., 1987). Patients were grouped according to FA symptom trajectory:

1. Never-present (item score ≤2 on all assessments).
2. Improving (starts ≥3, ends ≤2).
3. Deteriorating (starts ≤2, ends ≥3).
4. Fluctuating (≥2 fluctuations across threshold for FA).
5. Enduring (item scores ≥3 on all assessments, a separate score of 2, but not 1, allowed).

Reliability testing of the single item flat affect measure (PANSS item N1) at the ten year follow-up came out favorably (ICC= .76.).

3.5 Statistics

The analysis was performed with the SPSS Statistical Program (version 16: SPSS Inc., Chicago, IL, USA). Analyses were performed with a significance level of <0.05 and a confidence level of 95%. Mean and standard deviations are reported for continuous variables and percentages for categorical variables. DUP had a markedly left skewed distribution and was transformed to its natural logarithm (lnDUP + 1) which is normally distributed, before t-test was performed.

The symptom profile groups in the three papers were compared using conventional descriptive methods and t-tests. For non-parametric data, and data of skewed distribution, Chi-Square and Mann-Whitney tests were performed. In situations where one or more expected cell frequencies were below 5, Fisher's exact test was used. When comparing more than two groups one way ANOVA was used for parametric data (including the Tukey post hoc test). For non-parametric and unevenly distributed data the Kruskal-Wallis test was used.

In paper II correlations between baseline variables, clinical and functional characteristics and AES-S-Apathy, GAF-F, and s-QoL were calculated as Pearson's product moment coefficients. A general linear model with repeated measurement was used to test the longitudinal development of the proxy score for apathy (mean score of PANSS items N2 and N4).

To examine whether apathy explained an independent amount of the variance in functioning and subjective quality of life adjusting for other important variables, a blockwise multiple hierarchical regression analysis was performed. Baseline variables were entered into the first and second blocks, AUDIT/DUDIT in the third, PANSS positive, cognitive and excitative components in the fourth (PANSS negative component

was excluded to avoid problems with colinearity), and CDSS in the fifth block. In the sixth block, AES-S-Apathy was entered. By entering apathy last, we could examine if apathy explained an additional amount of the variance in functioning and quality of life even when controlling for other important variables.

In paper III binary logistic regression was performed to assess possible baseline predictors of enduring flat FA. The model contained three independent variables: 1. PANSS baseline positive, depressive, cognitive and excitative components, 2. Baseline GAF-F, 3. PAS last social function. The variables were chosen as the FA groups showed statistically significant differences on these measures at baseline. Independent sample t-test was used to compare the enduring group to the other groups on objective social functioning from baseline to the ten year follow-up.

3.6 Ethics

The TIPS study was approved by the Regional Committee for Medical Research Ethics Health Region II (# S-95189), the Regional Committee for Medical Research Ethics Health Region East (# 1.2007.2177) and the Data Inspectorate (Licence # 96/3017-2 and # 2003/2052). Biological data collection approved by Norwegian Directory of Health (#200403453 and the Regional Committee for Medical Research Ethics Health Region East (# 493-03-01179). The Regional Committee for Science Ethics region Sjælland, Denmark (#1-01-83-0002-07).

Written informed consent was obtained from all participants included in the study. Only patients that could understand the study protocol and were able to give informed consent were included in the study. Participants were informed of their right to withdraw from the study at any time during baseline assessment and throughout the follow-up period.

Written informed consent was renewed at five year follow-up. Only patients who had agreed to participate in the ten year follow-up were contacted directly. Patients who had not participated at the previous follow-up interview but had given earlier consent were contacted through mail. The remaining patients (refuser group) were not contacted for follow-up interview.

Results from the TIPS study was made available to patients and the public through a website run from the Rogaland site; www.tips-info.com. The website includes links to articles printed in national and international journals.

4. Results and summary of papers

4.1 Paper I

Objective: Hallucinations and delusions are often described together, but are known to occur separately, and may have different relations to outcome variables. The aim of this study was twofold: 1) to identify subgroups of patients characterized by having hallucinations only or delusions only during a five year follow-up period, and 2) to examine if these groups differed with regard to demographic characteristics, clinical characteristics and outcome factors, including suicidality.

Methods: From the 301 FEP patients included at baseline, individuals with delusions only (D) and hallucinations only (H) were identified based on PANSS items P1 (delusions) and P3 (hallucinations) scores at baseline and through four follow-up interviews over five years. The subgroups were compared with regards to demographic data, diagnosis, premorbid functioning (PAS), duration of untreated psychosis (DUP), time to remission (TTR), clinical variables (PANSS components, PANSS G12 insight) , global functioning (GAF), suicidality (thoughts, plans and attempts) and completed suicides.

Results: Two mono-symptomatic groups of patients were identified, the H (n=16) and the D (n=106) group. 179 patients experienced both hallucinations and delusions (dual-symptom group). The mono-symptomatic groups differed on several baseline variables, and also with regard to outcome. The H group was significantly younger, had longer DUP, and poorer premorbid function. The H group also scored better on the cognitive component (statistically significant at two and five years) and, importantly, had better

insight at all time points (statistically significant at baseline and five years). Notably, the H group scored higher on measures of suicidality. Suicidality before admission was significantly higher in the H than the D group. At the five year interview four patients from the H group were dead (three from suicide, one from overdose), while in the five times larger D group, five patients were dead (two from suicide, one from overdose and two from unclear cause). Analyses showed a significantly higher rate of completed suicides in the H group (Fisher exact test; p=0.016).

Conclusion: Patients with hallucinations only can be separated from patients with delusions only. The subgroups differed with regards to demographical data, clinical variables, and most notably with regards to insight and suicidality. These findings suggest distinctions in the underlying biological and psychological processes involved in hallucinations and in delusions, and alert us to a vulnerable patient group with a clinical picture dominated by hallucinations which has received little attention in the earlier literature.

4.2 Paper II

Objective*:* Studies have shown that apathy is an important part of the negative symptomatology in psychotic disorders. It is a common symptom early in the course of illness, and has been associated with poor general functioning. The aim of this study was twofold:1) to examine the prevalence and predictors of self-reported apathy at ten years, and to assess the development of apathy, using a proxy-measure, prior to the ten year follow-up, 2) to explore the relationship between apathy at ten years and concurrent symptoms, functioning and outcome, with a particular focus on subjective quality of life.

Methods*:* Of the 301 FEP included at baseline, 186 participated in the ten year follow-up. Of these, 178 patients completed the Apathy Evaluation Scale (AES-S-Apathy). Patients were classified as having apathy (AES-S-Apathy≥27) or not at ten year follow-up. A proxy measure of apathy (PANSS items N2+N4) was used to assess apathy at assessments prior to the ten year follow-up. The relationship between apathy and baseline variables (Demographics, Diagnosis, DUP), measures of symptomatology (PANSS, Calgary Depression Scale for Schizophrenia), functioning (GAF, Strauss Carpenter Level of Functioning Scale) and subjective quality of life (Lehman's Quality of Life Interview) were estimated through correlation analyses and blockwise multiple hierarchical regression analysis.

Results: Nearly 30% of patients were clinically apathetic at ten year follow-up. No baseline measure was found to significantly predict apathy at ten years. Self-rated apathy was associated with all measures of psychopathology, as well as with poorer general functioning, less contact with friends, and lower level of employment. Proxy measures of apathy indicated that the level of apathy declined over the follow-up period. Apathy was found to contribute independently to global functioning. Notably, apathy was found to independently explain more than 10 % of the variance in subjective quality of life, even when other significant correlates were controlled for.

Conclusions: Apathy at ten years follow-up was associated with higher levels of psychopathology, poorer general functioning, and poorer subjective quality of life. Even though apathy was a common symptom at ten years, the levels appeared to be declining during the ten years follow-up period. The finding that apathy was independently related to both functioning and subjective quality of life at ten year follow-up confirms apathy as a core component of the negative symptom construct. Apathy could thus prove to be an important target symptom of rehabilitation programs for patients with psychotic illness.

4.3 Paper III

Objective*:* Flat affect (FA) has been described as enduring, but long term follow-up studies of FEP patients are lacking. The aim of this study was to study the symptom development of FA over a ten year follow-up period, with a focus on prevalence, predictors and outcome factors including social functioning.

Methods: Different FA trajectories were identified using the PANSS item N1 (FA) in the 186 patients followed from baseline through five follow-up assessments over ten years. A cut off of ≥3 was used to identify patients with clinically significant FA. Patients were classified as having never-present, improving, deteriorating, fluctuating, or enduring FA. Groups were compared on baseline variables (Diagnosis, PAS, DUP, demographics, PANSS components and global functioning (GAF)) and variables at ten year follow-up (reassessed diagnosis, PANSS components, GAF, remission and recovery), as well as social functioning throughout the follow-up period.

Results: Twenty nine percent of patients never displayed FA, 10 % had improving FA, 18 % deteriorating FA, 40% fluctuating FA, and 5 % had enduring FA. The patients with enduring, fluctuating and deteriorating FA did poorer on all outcome variables, including GAF, employment, and objective social functioning. The deteriorating FA group was similar to the best performing never-present group on symptom and functional measures at baseline. By ten year follow-up, however, the deteriorating group was the most symptom burdened group with regards to positive, depressive and excitative symptoms, and had functional levels close to those of the poorest functioning enduring FA group. The enduring FA group did significantly poorer with regard to social functioning at all assessments during the ten year period, and premorbid social function predicted enduring FA.

Conclusions: FA was expressed at some point of time in the majority of FEP patients in the ten year follow-up period, and appeared more fluctuant than expected from the relevant literature. FA was associated with poorer outcome at ten year follow-up, and enduring FA was associated with poorer social functioning both premorbidly, and at all points of assessment.

4.4 Comparing papers I-III: supplementary analyses

Papers I, II and III use the same patient sample, therefore some patients who are described as having apathy in paper II may also have clinically significant FA as described in paper III. Furthermore, patients with apathy or FA may also be a part of either the H or the D group. The below analyses have not been reported in the papers, but are reported in this thesis as a supplement in order to better compare the three papers.

4.4.1 Comparing the H and D groups with regard to apathy and FA

Seven of the 16 patients with Hallucinations only were assessed at ten year follow-up. One (14%) out of these seven scored as having clinical apathy, and 3 (42 %) had FA.

Of the delusion only group 64 out of the original 106 participated in the ten year follow-up. Of these 15 (14%) scored as having clinical apathy, while 18 (28%) scored as having FA. As reported in paper I there was no significant difference between the H and the D group with regard to subjective quality of life or social functioning throughout the follow-up period.

4.4.2 Comparing patients with apathy and flat affect

Of the 178 patients that filled out the AES-S-Apathy, 84 (47%) had neither apathy nor FA at ten year follow-up, while 33 (19%) patients had both symptoms. Twenty (11%) patients had apathy but not FA, and 41 (23%) patients had FA, but not apathy.

No statistically significant difference between the patients with and without apathy at ten years was found with regard to measures of suicidality at ten years, and no statistically significant differences between the FA groups with regard to suicidality or subjective quality of life at ten years were found.

5. Discussion

5.1 Discussion of the main findings

Paper I explores symptoms within the positive symptom component, while paper II and III explore symptoms within the negative symptom component. The main findings were:

1. Patients with hallucinations only and delusions only can be identified and differ especially with regard to suicidality**.**

2. Suicidality may be related to insight in the hallucination only group.

3. The findings suggest distinctions in the underlying processes involved in hallucinations and delusions.

4. The level of apathy appears to decline in the follow-up period.

5. Apathy is associated with higher levels of psychopathology and poorer functioning.

6. Apathy is independently related to subjective quality of life.

7. Flat affect is more fluctuant than anticipated.

8. Flat affect is associated with poorer social functioning both premorbidly and throughout the follow-up period.

9. Prevalence rates, symptom development and associations to outcome measures support apathy and flat affect as separate factors.

10. Symptoms within the positive and negative symptom constructs are separate from each other in prevalence and in relation to outcome measures.

5.1.1 Patients with hallucinations only and delusions only can be identified and differ especially with regard to suicidality

In paper I we identified two subgroups of FEP patients with a longitudinal symptom profile defined by the presence of either delusions or hallucinations. In a sample of 301 patients we found a smaller group of 16 patients with hallucinations only, while 105 patients had delusions only. The majority of the sample, 179 patients, experienced both hallucinations and delusions in the follow-up period.

We found that the H group were younger and had completed fewer years of education compared to the D group. These results differ from the results of studies by Mauri and colleagues (Mauri et al., 2006, 2008). They found a group of patients with a clinical picture dominated by hallucinations. These patients were older at onset of illness and had higher academic achievement compared to a schizophrenia patient group. Our findings, however, are similar to results from a study of non-clinical voice hearers that reported that this group was younger than a schizophrenia patient group at the age of onset of hallucinations (Honig et al., 1998). A likely reason for the difference between our finding and the findings of Mauri and colleagues is that while we studied FEP patients, Mauri and colleagues studied patients with chronic psychosis.

The most notable finding in this study is the association between symptom profile and suicidality. The H group scored as being significantly more suicidal than the D group at baseline. Later in the follow-up period the difference between the groups leveled out, possibly due to loss of the most suicidal patients in the H group. At five year follow-up 25 % of the H group was deceased. This is in contrast to the D group, where the mortality rate was only 5 %.

The high level of suicidality and suicide in the H group may be related to the clinical picture itself. Hallucinations tend to be experienced as frightening, intrusive and

imperative, and might themselves lead to suicidal thoughts and acts. In a review of schizophrenia and suicidality, the association between command hallucinations and suicidality was explored (Pompili et al., 2007). The results were conflicting; three out of five studies reviewed found that command hallucinations did not correlate significantly with suicidal ideation and attempts, and it is plausible that hallucinations in themselves are not the sole explanation of the increased suicidality found in our study.

DUP and premorbid function could be potential mediators of suicidality. Earlier studies have found that poor premorbid function may be both a risk factor (Clarke et al., 2006, Bakst et al., 2010), and a protective factor (Opjordsmoen et al., 2009, Melle et al., 2006) for suicidality. While some studies have found long DUP to be associated with suicidality in FEP (Nordentoft et al., 2002, Westermeyer et al., 1999), other studies have failed to find this association (Nordentoft et al., 2002, Bertelsen et al., 2007, Preti et al., 2009). Furthermore, while longer DUP could explain some of the differences in suicidality between the groups before baseline, it is less certain how much it might contribute to the higher suicide rate in the H group at five year follow-up. Though findings have been inconsistent, many studies have found an association between longer DUP and higher levels of negative symptoms (Perkins et al., 2005, Schmitz, 2007, Chang et al., 2012), and a recent review of suicidality in FEP suggested that high levels of negative symptoms at the time of the first psychotic breakthrough and at relapse could be a risk factor (Pompili et al., 2011). The H group had higher levels of negative symptoms than the D group at the first two assessments, but the differences did not reach statistical significance, and the mean level of negative symptoms in the H group was not very high, hence a difference in negative symptoms levels is unlikely to be an explanation for the difference in suicidality between the groups.

5.1.2 Suicidality may be related to insight in the hallucination only group

The H group had consistently better insight scores than the D group at all points of measure. This indicates that insight could be a potential mediator between hallucinations and suicidality in this group. Insight is a well documented risk factor for suicidality in schizophrenia (Bourgeouis et al., 2004, Crumlish et al., 2005, Barrett et al., 2010, Pompili et al., 2011). Mauri and colleagues reported that the patient group described as having Hallucinatory Disorder displayed better insight (Mauri et al., 2006). In addition, a recent study found that patients with hallucinations, but without concurrent delusions, had better cognitive insight than patients with delusions only (Engh et al., 2010).

We also found that the H group scored consistently better than the D group on the cognitive component of the PANSS. Two recent meta-analyses have found that cognitive deficits and poor insight may be linked (Aleman et al., 2006, Raffard et al., 2008).

The patients with both hallucinations and delusions were similar to the D group with regard to suicidality and suicide rate. This could imply that it is not hallucinations per se that increase suicidality. A possible hypothesis is that, in the absence of delusions, a very obvious symptom like hallucinations could result in better insight in patients that have the cognitive capacity to interpret hallucinations as pathological and self-originating, and therefore the high level of suicidality seen in the H group is secondary to the higher level of insight in this group.

5.1.3 The findings suggest distinctions in the underlying processes involved in hallucinations and delusions

The combined findings in paper I support a distinction in the underlying biological and psychological processes involved in hallucinations and in delusions. However, psychological models of delusion and hallucination formation use overlapping concepts, such as attribution bias and deficits in self-monitoring, when they describe how delusions and hallucinations arise. Larøi and Woodward have suggested that a two-step process is implicated in hallucination formation; the first step being an inability to identify self-generated mental events, and the second step being a misattribution, whereby these self-generated mental events are misattributed as coming from another (non-self, alien) source (Larøi and Woodward, 2007, Larøi 2012). This model may also be used to explain how hallucinations and delusions both overlap and exist as separate phenomena. Patients who experience hallucinations mono-symptomatically may undergo only the first step of the process, i.e. they are unable to identify self-generated events, but they do not misattribute the events and attach delusional content to them. Patients with delusions only may undergo only the second step of the process, i.e. misattribution. They are able to identify a mental event as self-generated, and thus do not experience hallucinations. These patients, however, engage the mental processes, including misattribution, involved in delusion formation, and attach delusional content to external/non self-generated events. The two-step process of hallucination formation, thus, only occurs in patients with both hallucinations and delusions, i.e. in patients that are both unable to identify self-generated mental events, and that form delusions around these events.

In the majority of our sample hallucinations and delusions co-occured, but we were also able to identify patients who experienced hallucinations and delusions mono-

symptomatically. In these patients the symptoms had different associations with demographics, insight, cognition, and suicidality, supporting a degree of difference in etiology between the two symptoms.

5.1.4 The level of apathy appears to decline in the follow-up period

In paper II we found that nearly 30 % of the patients showed clinical levels of apathy at ten year follow-up. The prevalence rate of apathy is lower than that found at one year follow-up in another broad spectrum FEP sample (Faerden et al., 2010). The TIPS study managed, through an early detection strategy, to significantly reduce the DUP. Faerden et al.'s sample had a more than five times longer median DUP than ours, but as we found no relationship between DUP and apathy in our study, it is unlikely that this could explain the difference in the mean score between the samples. Another possible explanation could be that we used AES-S-Apathy, while Faerden and colleagues used AES-C-Apathy. Clarke et al. (2007) found different cut off scores for AES-C and AES-S. However, Faerden and colleagues found about the same mean apathy score for the two instruments, and when comparing the AES-S-apathy and the AES-C-apathy at baseline they found near similar prevalence rates (54% and 53% respectively) (Faerden et al., 2009a). Furthermore, the proxy-measures of apathy in our sample show a decrease over the follow-up period. Even the patients with AES rated apathy at ten years did not show an overall increase on proxy measures of apathy in the follow-up period.

Earlier studies have documented increasing levels of negative symptoms in schizophrenia over the course of follow-up (Crow et al., 1980, Fenton and McGlashan, 1991, 1992, Breier et al., 1991), and possible decreasing brain grey matter volume associated with illness progression (Pantelis et al., 2005, Buckley, 2005), supporting the Kraepelinian description of a degenerative process manifested by increasing symptoms and reduced

function over time. Our proxy data on the development of apathy, and our prevalence rate at ten years, seen in combination with Faerden et al.'s prevalence rates at baseline and one year, imply that, for the majority of patients with FEP, apathy is a symptom that decreases in severity during the ten years after the first psychotic episode. Our results, therefore, do not support a neurodegenerative disease model.

5.1.5 Apathy is associated with higher levels of psychopathology and poorer functioning

Our study found that apathy at ten year follow-up was associated with higher levels of positive, depressive, cognitive and excitative symptoms, poorer general functioning, and less social contacts and employment. We found that apathy gave an independent contribution to functioning even when controlling for multiple factors including positive and depressive symptoms. This finding is in accordance with previous studies both in psychotic disorders (Foussias et al., 2009, Faerden et al., 2010,), and other brain disorders (Van Rekum et al, 2005). These findings validate apathy as an important symptom within the negative symptom construct, and as a central part of the symptomatology that leads to functional loss in psychotic illness.

This study does not explore how apathy leads to poor functioning. Previous studies have found an association between apathy and reduced executive function (Roth et al., 2004, Faerden et al., 2009a). There is evidence that dysfunction in frontal-subcortical circuits, especially those linking prefrontal cortex to striatum, might be involved in both apathy (Barch and Dowd, 2010) and executive functioning (Eisenberg and Berman, 2010), and that the same neural correlates are found in schizophrenia and other neuropsychiatric disorders (Bonelli and Cummings, 2007). This association might suggest a shared neural

substrate, and a bidirectional relationship between apathy and poor executive functioning could explain some of the functional loss found in patients with apathy.

5.1.6 Apathy is independently related to subjective quality of life

We found that apathy at ten years, measured by both AES-S-Apathy and PANSS items N2 and N4, was significantly related to subjective QoL. This finding was strengthened by the fact that apathy remained an important independent predictor of QoL even when depressive symptomatology was controlled for. As we used the self-report version of the AES, our findings suggest that patients with psychotic illnesses realize their lack of motivation, and that amotivation, or apathy, causes them to rate their life situation less favorably. Apathy, reframed as a symptom that patients actively experience, and that causes distress, could prove an important target for rehabilitative treatment programs. Talking to patients about how they experience motivational difficulties and the consequences of apathy in their daily life may prove an important ingredient in rehabilitative treatment of patients with poor functioning.

5.1.7 Flat affect is more fluctuant than anticipated

A surprising finding in paper III is that FA had a much more fluctuant course than expected from studies found in the literature which report negative symptoms as more stable than positive symptoms (Pougue-Geile and Harrow, 1985, Johnstone et al., 1987, Fenton and McGlashan, 1991, McGlashan and Fenton, 1992, Drake et al., 2003), and FA as more stable than apathy (Malla et al., 2004, Kelley et al., 2009, Galderisi et al., 2012). Seventy-one percent of the patients had FA at one or more assessments, but only 5 % had

enduring FA, and the largest group of patients, 40% of the sample, had a fluctuating course.

The low rate of enduring FA contrasts with previous studies, particularly those that describe deficit pathology (Kirkpatrick, 2001, Kirkpatrick and Galderisi, 2008), where FA is a key symptom. Our results also differ from two other ten year long follow-up studies that reported that 19-24 % of schizophrenia/schizoaffective patients had enduring negative symptoms (Herbener and Harrow, 2001, Makinen et al., 2010). Our sample consisted of a broader range of diagnoses, and this could contribute to the low prevalence of enduring FA. In contrast to the study by Herbener and Harrow our study followed patients from very early in the course of illness. Our study also followed the sample closely, with six assessments in the follow up period. A recent longitudinal FEP study of three years duration, found enduring negative symptoms in 23.7% in the last year of the follow-up period, but only in 6.5 % of patients in the first year of follow-up (Chang et al., 2011). Increasing symptom stability over time have been reported for the negative symptoms domain in a ten year follow-up study that conducted monthly assessments over a ten year period following first hospitalization (Eaton et al., 1995). When, in the course of illness, assessments are commenced, and how many assessments are conducted in the follow-up period, probably influence results on prevalence, and these differences in study design could explain why earlier studies have found a higher prevalence of enduring negative symptoms.

We found that somewhat more patients developed FA (deteriorating group) than improved from it (improving group) in the follow-up period. Forty-one percent of the sample had clinically significant FA at ten year follow-up, and the overall level of FA was largely unchanged in the follow-up period. We did not find a reduction in levels of

FA like we did for apathy, however, similar to the results on apathy, our results on FA do not support a degenerative process, as even the patients with enduring FA did not show an ongoing deterioration in the follow-up period. The deteriorating FA group could represent a part of the sample that developed chronic negative symptoms similar to what has been described as deficit psychopathology (Kirkpatrick, 2001, Kirkpatrick and Galderisi, 2008). This group differed from patients with deficit psychopathology in that it included patients with diagnoses other than schizophrenia. The deteriorating group also had premorbid function similar to the never-present FA group. Furthermore, the level of chronicity of FA in this group is debatable as FA seemed to develop in the latter part of the follow-up period and did not necessarily present as stable. We did not assess to what degree apathy fluctuated in our sample. An earlier study found that FA, measured four times over a one year period, had a more stable course compared to apathy (Kelley et al., 2009). This may imply that apathy fluctuates to an equal or greater extent than FA as measured in this study. Consequently our consideration of negative symptoms as chronic and enduring may need to be revised.

5.1.8 Flat affect is associated with poorer social functioning premorbidly and throughout the follow-up period.

We found a pronounced association between FA and poor objective social functioning, particularly in patients with enduring FA. FA may be viewed as an expressive deficit with a specific impact on social communication and interaction. A failure to respond to social stimuli could reduce the likelihood of establishing and maintaining friendships and other relationships. FA could also reflect poor social cognition. Social cognition is defined as the ability to process and apply social information, and is not regarded as a

part of the negative symptom construct (Kirckpatrick et al., 2006). Social cognition includes the ability to recognize facial expressions of emotion. Impaired performance on affect perception tasks is an established finding in patients with schizophrenia, where it has been inconsistently associated with negative symptoms (Kohler et al., 2010). Impaired social cognition has also been reported in affective psychosis (Kohler et al., 2011), and in FEP patients (Addington et al., 2006). Furthermore, facial expression recognition and unfamiliar face matching has been found to be poorer in schizophrenia patients with FA compared to patients without FA (Gur et al., 2006). Studies comparing patients with and without FA on emotion processing tasks using fMRI have identified increased amygdala activity as a neuronal correlate of FA in schizophrenia (Gur et al., 2007, Lepage et al., 2011). It has been suggested that increased amygdala activation in patients with schizophrenia triggers reduced function of the cortical regions necessary for the correct identification and labeling of facial expressions (Gur et al., 2007). Such a failure to respond to, and interpret, verbal and nonverbal stimuli is likely to affect social abilities and contacts over time. We also found that poor premorbid social function was the strongest predictor of enduring FA. A study of home videos of children that later developed schizophrenia compared these to videos of their siblings that remained healthy (Walker et al., 1993). The videos reveal that the patients who later developed schizophrenia had significantly more affective flattening than their siblings, even from a very early age. Thus, it may be that the failure to develop adequate social competency is associated with a similar failure to develop an ability to send social signals including facial expressions and gestures.

5.1.9 Prevalence rates, symptom development and associations to outcome measures support apathy and flat affect as separate factors

We found that apathy and FA differ in prevalence at ten year follow- up. The symptoms also seem to develop differently in our sample, as apathy appears to decrease over time, while the mean level of FA remains about the same. Our results further indicate that apathy and FA have different associations to outcome measures, including functioning. We found that apathy had a strong and independent relation to general functioning and to subjective quality of life, and that the correlation between apathy and general functioning was stronger than that between apathy and social functioning. FA, on the other hand, showed a strong relationship to social functioning throughout the follow-up period, but not to quality of life. Combined, our results from paper II and paper III support earlier factor analyses that report apathy and FA to be separate factors within the negative symptom construct (Blanchard and Cohen, 2005, Foussias and Remington, 2010). The different association to functioning could possibly be partly explained by the symptoms having different neurocognitive correlates. Earlier studies have reported an association between apathy and executive functioning (Roth et al., 2004, Faerden et al., 2009, Konstantakopoulos et al., 2011). Few studies have looked at the relationship between FA and neurocognition. A study by Gur et al. found a significant association between FA and verbal memory (Gur et al., 2006). The study did not adequately examine executive function. As previously described, a possible association between FA and poor social cognition has been reported (Gur et al., 2006), a similar association has not been reported between apathy and social cognition. This area requires further exploration, and the possibly different neurocognitive correlates of individual negative symptoms ought to be mapped out.

5.1.10 Symptoms within the positive and negative symptom constructs are separate from each other in prevalence and in relation to outcome measures

As apathy and FA are factors within the same symptom construct of negative symptoms we expect to find patients with overlapping symptom profiles. When comparing patients with apathy to patients with FA at ten years we found that more patients had clinically significant FA than apathy at ten years and that only a small proportion of the sample had overlapping symptoms. These results further supports factor analyses that show apathy and FA to be separate factors within the negative symptom construct. The additional supplementary analyses and results also support this conclusion as the association between apathy and subjective quality of life was not found between FA and subjective quality of life. Neither apathy nor FA showed an association to suicidality. Earlier literature concludes that the positive and negative dimensions are largely independent of each other both cross-sectionally and longitudinally (Fenton an McGlashan, 1991, Arndt et al., 1995, Bentsen et al., 1996,Blanchard and Cohen, 2006). Supporting this we found a low degree of overlap between the mono-symptomatic positive symptom groups with regard to apathy and FA. Both groups scored as having half as many patients with apathy as the total patient sample, and while the H group scored as having somewhat higher prevalence of FA than the D group, the group had similar prevalence to that of the total sample.

5.2 Methodological issues

The TIPS study is a longitudinal study of a large, epidemiological sample. It is one of the first studies to follow a FEP sample prospectively, and with several assessments, over a ten year follow-up period. The study kept a close focus on developing and maintaining the reliability of measurements used. A range of outcome variables were used throughout the follow-up period, and new and relevant instruments, like the AES-S-Apathy, were added to the battery of instruments. Limitations of the study related to representativity of the sample and the reliability and validity of the instruments used are discussed below.

5.2.1 Representativity of the sample

The institutions in the four sites included in the study had responsibility for all patients in their catchment areas. Consequently our patients sample should be an epidemiological one. A total of 874 persons with psychosis-like symptoms underwent screening by the study's assessment teams. Three hundred and ninety-seven fulfilled inclusion criteria. Of these, 23% refused to participate in the study, leaving a total of 301 participants at baseline. The patients who refused to participate had a significantly longer DUP than the participants (32 vs. 10 weeks), and the refusal rate increased with increasing DUP (Friis et al., 2003). As a result the study sample is to some degree biased towards a shorter DUP. However, many studies ignore the question of refusers, and the few who address this issue report refusal rates very close to ours for studies that have a comparatively shorter duration of follow-up (Bertelsen et al., 2009, Henry et al., 2010). Thus, it is reasonable to believe that the TIPS study sample has a high degree of representativity. The representativity of the sample at ten year follow-up is investigated in drop-out analyses (3.3.3). These analyses showed that the patients who dropped out had

significantly longer DUP, shorter education, higher rate of alcohol abuse, were more likely to be of non-Scandinavian ethnicity and were less likely to be employed in the year prior to inclusion. Longer DUP have been associated with higher levels of negative symptoms in some, but not all, studies exploring this relationship (Schmitz, 2007, Chang et al., 2011). There were, however, no difference between the included and the dropped-out patients with regard to the negative symptoms score or levels of proxy measures of apathy (PANSS N2 and N4) and measures of FA (PANSS N1) at baseline.

5.2.2 Limitations of the assessment instruments

5.2.2.1 The assessment of hallucinations and delusions

Using the PANSS items P1 and P3 to measure delusions and hallucinations respectively, provided a measure of the individual patients' symptoms at the different assessment points rather than a recording of life time prevalence of hallucinations and delusions. As our patient group was assessed from very early on in their illness, and reassessed two times in the year after inclusion, we have most likely recorded symptoms in the period where most patients in the sample were acutely ill. It is, however, possible that patients who relapsed later in the follow-up period experienced hallucinations or delusions for the first time, but that this was not discovered. It is also possible that patients who dropped out during the follow-up period did so because they developed new symptoms, like hallucinations and delusions. The small size of the H group makes it particularly sensitive to drop-out. However, most patients in this group dropped out after the two year assessment, and the symptom profile is therefore well described for most patients in this group. At two year follow-up 13 out of 16 patients participated. Two of the non-participants died between the three month and one year follow-up. The third non-

participant scored three on the PANSS P1 delusion item at the three month follow-up and it could be that this patient dropped out because he or she had developed delusions. Furthermore, the PANSS P3 item does not differentiate between different modalities of hallucinations. Auditory hallucinations, however, are estimated to be the more frequently occurring hallucinations in schizophrenia (APA, 2000), and it is thus feasible to use the PANSS score as a proxy for auditory hallucinations.

5.2.2.2 The assessment of insight

In paper I we used the PANSS G12 item to assess insight. The PANSS G12 item has shown good correlations with more specialized insight measures including the Beck Cognitive Insight scale, the Birchwood self rating scale, and the Schedule of Assessment of Insight-Expanded version (Engh et al., 2007, Jonsdottir et al., 2008). However, a more comprehensive insight measure would have improved our study by better describing insight in our sample.

5.2.2.3 The assessment of apathy

The abridged self-report version of the apathy evaluation scale (AES-S-apathy) used in our study has been used in fewer studies compared to clinician version of AES (AES-C). Clarke and colleagues (2007) reported that AES-S had poorer validity than AEC-C for evaluation of apathy in dementia. However, in studies of patients with psychotic disorders more favorable results have been found (Kiang et al., 2003, Faerden et al., 2008). Both studies indicate that the AES-S discriminates well between controls and patients. Kiang found that the self-rater and clinician rated versions of AES correlated strongly (r=.75), while Faerden and colleagues found an inter-correlation between AES-S-apathy and AES-C-apathy of 0.63, but that the patients sample had about the same

mean apathy score, and the same baseline prevalence rate of apathy using the two instruments (Faerden et al., 2008).

As the AES-S-apathy was only added to our test battery at the ten year follow-up, we used PANSS items N2 and N4 as proxy measures to assess the longitudinal development of apathy. In a small sample (N=28) Kiang and colleagues found a non-significant correlation between AES-C and PANSS items N2 and N4 of r= 0.27 and 0.02 respectively (Kiang et al., 2003). However, in a larger sample of FEP patients, Faerden and colleagues found the two items to correlate moderately with apathy scores (AES-C-apathy rated) (N2, r=.62, N4, r=.52). We found a correlation between AES-S and N2 of r=.49 and N4 of r=.48. These results indicate that apathy measured by PANSS differs from apathy measured by the AES. While the PANSS items N2 and N4 assess functioning both in relation to social contact and level of activity and grooming/self care, the AES taps into patients' ability to initiate contact and activities and experienced interest in being sociable, managing day to day living, hobbies, and learning new things. It is likely that the AES measure is more specific and rates apathy as a primary symptom, rather than measuring a functional consequence of being ill, as PANSS seem to do. The AES seems thus to be less likely to measure apathy secondary to depression, positive symptoms or as side-effect of medication.

5.2.2.4 The assessment of flat affect

The main limitation of paper III is the single item measure of flat affect. Single item measures are sensitive to poor reliability. A strength of the TIPS study, however, is that intense reliability testing has taken place from baseline and throughout the follow-up period. The assessment of PANSS item N1 (FA) came out favorably with an ICC score of .76 at the ten year follow-up.

Ideally a more sophisticated measure of FA should have been used. At the start of this study no validated instrument specifically assessing flat affect existed. However, since the start of the TIPS-study promising computerized FA assessment programs have been developed (Hamm et al., 2011). These techniques are however still in their infancy, and were considered outside the scope of our study.

5.2.2.5 Primary versus secondary negative symptoms

Primary negative symptoms are symptoms that are part of the disease process itself, while secondary negative symptoms arise as a result of depression, side effects of antipsychotic medication, or psychotic withdrawal (Carpenter et al., 1988). In epidemiological studies of patients with schizophrenia primary negative symptoms are estimated to be found in 15–20% of the samples (Kirkpatrick et al., 2001). Pathophysiological differences between primary and secondary negative symptoms have been found (Kirkpatrick et al., 2001). Mapping out secondary negative symptoms are of clinical importance as secondary symptoms could be treated with anti-depressive treatment if caused by depression, or with adjustment of antipsychotic medication if drug induced, or representing social withdrawal secondary to paranoid delusions. Differentiating primary from secondary negative symptoms, however, is not easy, and assessment tools like the PANSS were not created to make this differentiation. Previous research has, however, found (AES-C rated) apathy to be a primary symptom in FEP patients with depression, antipsychotic medication and positive symptoms having low or insignificant contributions to the apathy score (Faerden et al., 2009b). Our study on apathy found no significant correlation between apathy and DDD, and a low but significant correlation between apathy and positive symptoms. The correlation between apathy and depression was slightly higher (PANSS depressive component; r =0.38, and

CDSS; r=0.40). It could be that the self-rater version of the AES used in our study recruits some patients with a clinical picture closer to depression than primary apathy. However, our correlations between apathy and the PANSS depressive component are similar to those found by Faerden and colleagues at one year follow-up of a similar FEP sample using the clinician version of the AES. Regression analyses, furthermore, confirmed that apathy had a significant and independent contribution to quality of life and global functioning scores, also when depression was controlled for.

With regard to FA, previous studies imply that this symptom is more primary in nature, as studies report that FA is not significantly influenced by positive and depressive symptoms (Malla et al., 2002) or medication (Kelley et al., 1999, 2008).

5.2.3 The diagnostic heterogeneity of the sample

Assessing individual symptoms and diagnosis often proves challenging when patients initially become ill, both because information about symptoms may be withheld by the patient, or because some symptoms only develop later in the disease process. Like many FEP studies, the TIPS study included a broad range of psychotic disorders. A broad diagnostic inclusion criterium was used as many patients with a non-schizophrenia spectrum diagnosis at baseline later convert to a schizophrenia spectrum disorder (Haahr et al., 2008). A further reason to include a broad spectrum of psychotic disorders is that these disorders share symptomatology, and that even enduring negative symptoms have been documented in non-schizophrenia spectrum psychotic disorders (Gerbaldo et al., 1995a, b, Herbener and Harrow, 2001, 2004, Malla et al., 2004). In the recent debate on how to best describe psychotic disorders the shared biological and genetic correlates of these disorders have made many question the dichotomous separation of affective and

non-affective psychosis. Some studies of patients with psychotic disorders have found that a dimensional approach may be superior to a categorical approach in terms of predictive validity (Allardyce et al., 2007, Peralta and Cuesta, 2008), providing a further reason to include patients with a broad spectrum of diagnoses in studies of longitudinal symptom development. In the three papers included in this thesis the issues of diagnostic differences is explored. The papers mainly compare the patient groups with regard to having a schizophrenia spectrum diagnosis or not. The first paper compared a hallucination only group to a delusion only group, and found no significant difference between the two groups with regard to the percentage of patients with a baseline schizophrenia spectrum diagnosis. In paper II the relationship between diagnosis at baseline and apathy at ten years was non-significant. In paper III there were no differences between the five FA groups at baseline, but at ten years the differences between the groups were significant. To assess if the inclusion of non-schizophrenia spectrum patients had influenced the results, we repeated the analyses on the schizophrenia spectrum patients only (N=139). We found little change in group distribution, and only very minor differences with regard to baseline variables and outcome measures at ten years, compared to analyses of the full sample.

5.3 Implications and further research

5.3.1 Clinical implications

5.3.1.1 Specific symptoms, specific needs

The findings in paper I alert us to a patient group with a heightened risk of suicidality. Consequently, identifying patients with hallucination only, and paying special attention to risk factors of suicidality, like insight, is important.

Papers II and III supports previous literature describing apathy and FA as separate factors within the negative symptom construct, the clinical implication being that the symptoms need to be described and assessed separately. The AES may be a useful tool in clinical practice. The instrument is quick and easy to use, and appears to tap into motivational difficulties experienced by patients that have implications for functioning. Similarly the assessment of flat affect is important, and a better, more specific, instrument for assessment could aid clinicians in this task.

This thesis shows that negative symptoms appear to be more fluid than anticipated. This may imply a greater potential for treatment responsiveness. As the focus of psychosis research has turned from positive symptoms to negative and cognitive symptoms, treatment forms and rehabilitation programs have been modified or created anew to target these symptom components. Our finding that patients appear to have some degree of insight into their motivational difficulties and that these difficulties are related to poorer quality of life makes apathy more accessible as a therapeutic target. In a cognitive behavioural treatment setting this implies addressing motivational difficulties directly and working to reduce apathy and amotivation through activity scheduling, mastery and pleasure recording, as well as breaking goals into sub-goals that are more easily

achievable. This strategy may also be useful in cognitive remediation based rehabilitation programs and other rehabilitation programs where motivational difficulties are a major obstacle for progression.

Paper III alerts us to an apparent association between social function and flat affect. Identifying patients with enduring FA and recruiting these patients to treatment programs with a particular focus on enhancing social cognition and functioning may prove fruitful. FA might even prove a possible treatment target, and exercises to modulate and enhance affect display could enhance social proficiency. Furthermore, clinicians should be observant of the patients that develop FA over the course of illness, as our findings imply that these patients have a poorer prognosis.

5.3.1.2 What does a diagnosis tell us?

A diagnosis of schizophrenia tells us that a patient has been ill for a period longer than six months, and that the illness has been affecting their lives and daily functioning. It does not, however, give much information with regard to what symptoms the patient is experiencing. As clinicians we want to describe our patients and relay information about them in a way that can be best and most efficiently used by the treatment team. By describing to what extent different symptom groups are present in each patient we can give a fuller picture of patients' illness and the implications of the illness in their daily life. However, by only referring to symptom groups, such as positive, negative, cognitive and affective symptom constructs, we may be missing vital information. Describing someone as experiencing positive symptoms does not tell us if the patient is experiencing hallucinations or delusions, if these symptoms are co-occuring, or to what degree patients express insight into the pathological nature of either symptom. Specifying a symptom

profile is even more important for negative symptoms, as these symptoms are less clearly defined and more difficult to measure.

The human mind appears to have a preference of categories to dimensions, as categorical classification systems allow us to more easily describe and recognize similar phenomena and relay information. Classifying disorders into diagnostic entities thus has a high utility value. The philosopher Carl Hempel, however, observed that although most sciences start by categorically classifying their subject matter, categories are often replaced by dimensions as more accurate measurements become possible (Hempel, 1961). Uniting the categorical and the dimensional approaches may allow us to preserve the utility of the diagnostic system while refining the information about the symptoms that any individual patients suffer from. The fifth edition of the Diagnostic Statistical Manual, the DSM-V, is in the pipeline and efforts are being made to integrate a dimensional approach in this version. There are hopes that a combined categorical and dimensional diagnostic system could enrich how we describe patients with psychotic disorders, and contribute to both efficient relaying of information that describes patients' individual needs, and give an estimate of prognosis.

5.3.2 Future research

The focus of this thesis has been to learn more about specific symptoms experienced in psychotic disorders through the exploration of longitudinal symptom profiles. More can be learned about these symptoms by studying their potential biological correlates. As categorically based diagnosis have proven insufficient in the search for genetic and endophenotypic correlates, more can possibly be gained through studies of well

described patients with similar longitudinal symptom trajectory. Such studies could inform us of possible differences in neurocognitive impairment in patients with hallucinations only and delusions only, and how these impairments possibly give rise to failure of source monitoring and biased processing. Similarly, this strategy could also inform us about the possibly different genetic correlates and structural and functional cortical and subcortical changes in patients with enduring, or developing, flat affect and apathy.

To conduct such studies we need better tools to describe and measure the symptoms our patients experiences. This is particularly important for negative symptoms. An improved instrument for the assessment of negative symptoms would include: 1) clear definitions of the included symptoms, 2) improved delineation between symptoms, 3) the ability to separate primary from secondary negative symptoms, and 4) being user friendly and intuitive both for researchers and clinicians. Two new tools have recently been developed for the assessment of negative symptoms, both reporting promising psychometric properties (Horan et al., 2011, Kirkpatrick et al., 2011). These tools could help pave way for a better understanding of the symptoms within the negative symptom construct. They would also allow an examination of how these symptoms are related to each other, to symptoms within other domains, and to functioning.

6. Conclusions

This thesis aims to explore the symptom development of two positive symptoms, hallucinations and delusions, and two negative symptoms, apathy and flat affect, in a longitudinal perspective. By examining individual symptoms, rather than symptom components, we have gained knowledge about patients with symptom profiles that previously have received limited attention. This approach has also allowed us to learn more about the development of the individual symptoms over time, the longitudinal association between symptoms, and between symptoms and outcome measures. The main conclusions of this thesis are as follows:

- Subgroups of patients with hallucinations only and with delusions only can be identified in a five year follow-up study, and the groups differ on multiple variables. Most importantly, the hallucination only group scored higher on measures of suicidality, and insight might be a possible mediator of suicidality in this group.

- Both apathy and flat affect are common symptoms ten years after the first psychotic episode, affecting 30 % and 41 % respectively. While the overall level of apathy (proxy-rated) in our sample decreased over the follow-up period, the level of FA appeared to be largely stable or somewhat increased, with less patients showing improvement of FA levels, than patients developing the symptom. Also, in the majority of patients FA showed a fluctuant course, and

only a very small part of the sample had enduring FA. This implies that FA, and negative symptoms in general, are less stable and enduring than anticipated.

- Clinical apathy is strongly related to poorer functioning and subjective quality of life in patients ten years after the first psychotic episode. FA is also strongly related to poorer functional outcome measures, and in particular to objective social functioning. The association between FA and poor social functioning was evident both premorbidly and throughout the ten year follow-up period.

- The combined findings show hallucination, delusions, apathy and flat affect as separate from each other. The symptoms differed in prevalence and symptom development. Each of these symptoms also had a different relationship to outcome measures including suicidality, subjective quality of life and social functioning.

- The exploration of mono-symptomatic patients has alerted us to a patient group with hallucinations only that appears vulnerable to suicidality. Clinicians should be conscious of this symptom profile, which has received little attention in the earlier literature. The assessment of both apathy and FA can aid clinicians in caring for patients with psychotic illness and can be a useful starting point for rehabilitative efforts. Patients with clinical apathy might benefit from rehabilitation programs focusing on experienced motivational difficulties, while patients with flat affect might benefit from rehabilitation programs that focus on improving social cognition.

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Papers I-III

I

II

III