

Apathy in First Episode Psychosis Patients

One Year Follow-up and Clinical Characteristics

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List of papers

The present thesis is based on the papers listed below:

1: Assessing apathy: the use of the Apathy Evaluation Scale in first episode psychosis

Faerden A, Nesvåg R, Barrett EA, Agartz I, Finset A, Friis S, Rossberg JI, Melle I. *Eur Psychiatry*. 2008 Jan;23(1):33-9. Epub 2007 Oct 29. PubMed PMID: 18029152.

2: Apathy and functioning in first episode psychosis

Faerden A, Friis S, Agartz I, Barrett AE, Nesvåg R, Finset A, Melle I Psychiatric Services. (APPI-PS-00468-2008) Accepted for publication June 2009.

3: Apathy is associated with executive functioning in first episode psychosis

Faerden A, Vaskinn A, Finset A, Agartz I, Ann Barrett E, Friis S, Simonsen C, Andreassen OA, Melle I. *BMC Psychiatry*. 2009 Jan 8;9:1. PubMed PMID: 19133132; PubMed Central PMCID: PMC2640391.

4: Apathy in first episode psychosis patients: One year follow up

Faerden A, Finset A, Friis S, Agartz I, Barrett AE, Nesvåg R, Andreassen OA, Marder SR, Melle I. Submitted *Schizophrenia Research* 31st of July 2009. Under review.

Summary of study

Background: Negative symptoms are present already during the first episode of psychosis, are often treatment resistant and contribute significantly to functional decline in psychotic disorders. Negative symptoms can be enduring or fluctuate and are associated with poor cognitive function. The limited progress in the development of effective treatments for negative symptoms has recently prompted studies of the different symptoms making up the negative symptom complex (apathy, flat affect, anhedonia, alogia) as one way forward. Kraepelin believed that apathy played an important role in poor functioning, a belief still held today. Despite the importance given to apathy, there are only four studies investigating apathy in schizophrenia, and none are of first episode patients. Apathy is a symptom that has been studied in other brain disorders and has there been found to be associated with poor executive function and poor functioning. Validated scales such as the Apathy Evaluation Scale (AES) are used for its assessment, but it has not been tested for use in first episode patients. The aim of this thesis is to gain more knowledge about apathy in first episode patients by testing the psychometric properties of the AES, followed by an analysis of the frequency, predication, stability, clinical-, and neuropsychological correlates of apathy and its association to functioning at baseline and one year follow up.

Methods: One hundred and four first episode patients consented to participate in the study and were assessed with an extensive clinical and neuropsychological battery. Factor analysis, correlation, Students' t-test, ANOVA, paired sample t-test and multiple linear regression were the statistical methods used.

Results: The AES was found to have sound psychometric properties in the first episode patients and the abbreviated 12-item AES-C-Apathy was used in the subsequent studies. At baseline 50% and at follow up 40% of all patients were considered clinically apathetic. The schizophrenia spectrum patients had the highest mean apathy score both at baseline and at follow-up. Thirty percent had

enduring high levels of apathy over the first year. This group consisted of greater number of males, a longer duration of untreated psychosis (DUP), and a greater likelihood of a schizophrenia spectrum diagnosis. There were fewer in remission and they had poorer functioning. Apathy correlated significantly only with tests of executive function and working memory, and the association was independent of depression and level of medication. Apathy was significantly associated with poor functioning both at baseline and follow-up.

Conclusions: Apathy can be reliably assessed with the AES-C-Apathy in first episode patients. Apathy is a frequent symptom and has a strong association with poor functioning both at baseline and at follow-up in first episode patients. Those in danger of high apathy levels at follow-up, and hence poor functioning, can be identified with the baseline variables of being of male gender, a long DUP, a schizophrenia spectrum diagnosis and a high baseline AES-C-Apathy score, results that may have implications for early detection strategies. As in other brain disorders apathy was associated with poor executive function, implying a possible common underlying mechanism across disorders.

Concepts, synonyms and abbreviations

Definitions of concepts

Apathy: Lack of motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress

Disorder: A functional abnormality in mental or physical health that interferes with a person's life.

Functioning: Daily life functioning in the areas of independent living, social and family life, work or studies and recreational activities

Neuropsychiatric symptom: Mental symptoms attributable to diseases of the nervous system

Psychosis: Lack of insight into the occurrence of hallucinations and delusions

Symptom: Something that indicates a physical disorder

Synonyms

Apathy/avolition/amotivation/lack of motivation

Cognitive function/neurocognitive function

First episode psychosis/first episode

Negative symptoms/negative syndrome/negative symptom complex

Abbreviations

AES: Apathy Evaluation Scale

AES-C: Clinical version of the AES

AES-S: Self rated version of the AES

AES-C-Apathy: The abridged 12 item clinical version of the AES

CI: Confidence Interval

DSM- IV: Diagnostic and Statistical Manual of Mental Disorders, version 4

DUP: Duration of untreated psychosis

GAF: Global Assessment of Functioning Scale

GAF-F: Functioning score of the split version of GAF

GAF-S: Symptom score of the split version of GAF

ICD-10: International Classification of Disease, version 10

NIMH -MATRICS: The National Institute of Mental Health project on Measurement and Treatment Research to Improve Cognition in Schizophrenia

PANSS: Positive and Negative Syndrome Scale

PAS: The Premorbid Assessment Scale

SANS: The Scale for Assessment of Negative Symptoms

SCID-I/P: Structured Clinical Interview for DSM- IV-TR AXIS I disorders, Patient edition

SD: Standard Deviation

TOP study: Thematically Organized Psychosis Research study

1. Introduction

The onset of psychotic disorders usually occurs between the ages of 15 and 30 at a time when people are about to start a life of their own. After the acute episode is over, from 50 to 75% experience problems with daily functioning, impeding a return to normal life with possible lifelong disabilities (1-4). Why this occurs is not fully understood and is of great concern (5-8).

Psychotic disorders are characterized by the presence of delusions and hallucinations, but can present with a wide range of symptoms related to different areas of mental functioning: thought, affect, cognition and behavior (4). This heterogeneity has challenged the understanding of which symptoms are central to psychotic disorders and to the development of functional difficulties. Thirty years ago the most common symptoms were clustered into two main categories; positive and negative symptoms (9-11). Positive symptoms included symptoms of “excess” mental functioning: delusions, hallucinations and thought disturbance (12). Negative symptoms are those of “reduced” – or diminished mental functioning: apathy (lack of goal-directed behavior), anhedonia (reduced experience of pleasure), blunted affect (reduced emotion expression) and alogia (diminished speech output)(12). Negative symptoms are found to have a stronger association to poor functioning than positive symptoms (4;6;13), although cognitive dysfunction also plays a major role (14-16).

There was great optimism for better understanding, along with better treatment and outcome, when the positive-negative distinction was first introduced (12). Treatment for positive symptoms are effective; with up to a 70% remission rate (4;17). Unfortunately, the same is not found for negative symptoms (8;18;19), and the conclusions are that effective treatment for negative symptoms is still lacking (6;7;20). One way forward, suggested by the consensus statement from the National Institute of Mental Health project on Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH –MATRICS) (6) and others (7;21-23), has been to gain more knowledge of the different negative symptoms that underlie the negative symptom construct. Negative symptoms are

already found at the onset of psychosis (18;24-30) and the functional disabilities seem to be established during the first years of illness (31-33). Hence, studies of the different negative symptoms should start with the first episode of psychosis.

Apathy is one of the negative symptoms where more knowledge has been specifically asked for (22;23;34-36). The importance of apathy was first pointed out by Kraepelin who considered apathy to play a major role in the deteriorating course of schizophrenia (37). However, despite the importance denoted to apathy, only four studies are identified addressing this negative symptom (38-41).

Apathy is well studied in other brain disorders, and has here been found associated with poor functioning (42-45). Only one study has explored the relationship between apathy and functioning in psychosis (39). This study, conducted in patients with an already long duration of illness, found that apathy was more strongly associated with poor functioning than other symptom areas. Samples with chronic disease can bias the conclusions, since several secondary phenomena related to treatment and long-term institutionalization can affect the results. Therefore, the results from early phase samples are often of more value. There is no study on apathy in first episode psychosis, and this is the aim of the present study.

2. Background

2.1 Psychotic disorders

Psychotic disorders have a lifetime prevalence of 1-3% (46) and are characterized by a prominence of delusions or hallucinations (psychotic symptoms). In the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) schizophrenia and other psychotic disorders consist of 9 different diagnostic categories (47). Of these, schizophrenia, schizophreniform -, schizoaffective-, delusional-, brief psychotic disorder, and psychosis not otherwise specified (NOS) are the disorders most studied.

Table 1 in the appendix shows the different diagnostic groups and diagnostic criteria as given in the DSM IV (47).

2.1.1 Schizophrenia

Schizophrenia is the most prevalent of the psychotic disorders with a prevalence among adults ranging between 0.5 to 1.5 % (47). It has been described throughout history, is recognized in almost all cultures and under study worldwide in all countries with a mental health service. Kraepelin was the first to describe it as a separate diagnostic entity among the psychotic disorders (37).

Schizophrenia often gives rise to great suffering both for the patient and for the family involved (48;49). It is one of the most serious illnesses a psychiatrist can treat, and with its early onset and long lasting functioning disabilities it is one of the most costly disorders for society, estimated to be 1% of the Gross National Budget in Norway (26 billion Norwegian kroner in 2009) (50).

Schizophrenia is currently considered a brain disorder of complex genetic and environmental interaction, the cause of which is still unknown (51). Changes in brain volume, brain signaling and brain functioning are found on the group level for patients with schizophrenia and underlines schizophrenia as a brain disorder (4), with the most consistent findings found within the prefrontal and temporal cortices and subcortical structures (4). The correlation between underlying neural mechanisms to symptoms in schizophrenia is complex and the relationship between underlying pathophysiology and clinical symptoms is weak. Cognitive dysfunctions are thought to be more directly linked to the underlying pathology than clinical symptoms and are considered a core feature of the disorder (52;53).

The development of schizophrenia is divided into a premorbid -, a prodromal -, and a period with full-blown psychotic symptoms (54). Psychotic symptoms can be present for a short or long period before treatment of the first episode is initiated (54). Recommended treatments for schizophrenia are both psychopharmacological and psychosocial (4;46;55;56). Different results exist regarding the long term prognosis for schizophrenia depending on follow-up time and criteria used (57). A

systematic review of the literature found that 42% have a good outcome, 35% intermediate and 27% a poor outcome (4) with 5-15% being fully recovered both for symptoms and functioning (57).

2.1.2 First episode psychosis

There is currently a worldwide focus on the first episode of psychosis and on getting people as early as possible into treatment (58). The development of symptoms propelling people to seek treatment can be of short duration and start acutely or insidiously over a long time period (59). The presenting symptoms can vary between either openly delusional beliefs and disturbed behavior in need of acute hospitalization, or with a more insidious onset characterized by retracting from friends or falling out of studies or work, making it harder to intervene (60;61). This period, the duration of untreated psychosis, is shortened to DUP in the international literature. DUP can be of days, weeks, months and, for some, even years, (54) defined as the period from when clear, psychotic (=positive) symptoms appear until the initiation of adequate treatment (54;62). This great variability in presenting symptoms and course challenges the diagnostics in the early phases of illness. This is one of the reasons for including the whole range of psychotic disorders, and also major affective disorders, in studies involving first episode psychosis (63;64). Depending upon the population under study, the frequency of the different diagnostic groups in a first episode sample will vary; with around 50-60% being diagnosed with schizophrenia or schizophrenia spectrum psychosis at first contact (64;65).

A long DUP is found associated to poor functioning in numerous studies (66-68) and this is the background for the world-wide implementation of early intervention (69) and detection clinics (70). The effort directed at shortening of DUP is mostly concentrated around awareness of positive symptoms, despite the finding that a long DUP is also associated with negative symptoms (67;71). The effect of early intervention is currently reviewed (72). The current results imply a need for a more differentiated focus, and that negative symptoms may also need to be targeted in order to improve outcome (61).

2.2 Positive and negative symptoms of psychotic disorders

Hippocrates may have been the first to describe what we today call positive and negative symptoms when he described madness to be of two kinds; one quiet, and one noisy (73). The concept of positive and negative symptoms is not new, and was first used in the late eighteenth century by different physicians trying to describe, and understand, what they observed as two different states, or stages, of psychotic symptoms (74). At that time, they believed that some symptoms represented a relatively pure loss of functioning (negative symptoms), while other symptoms such as delusions and hallucinations, represented an exaggeration of normal functioning and were understood as release phenomena when the primary function was lost (positive symptoms). The term “negative and positive symptoms” was introduced to psychiatry by the French psychiatrist Cleramboult around 1942, but did not come into use in the English speaking world before the 1970s (75). In modern psychiatry, it was Nancy Andreasen who coined the term “negative and positive symptoms” and who developed and validated scales for their assessment (12;76). She based her work on the hypothesis published by Crow in 1980 on schizophrenia being of two types. Type I was equivalent to “acute schizophrenia” and characterized by a good prognosis and with positive symptoms, and Type II was equivalent to the “defect state “ and characterized by negative symptoms with a graver prognosis (77).

Different scales are used for assessment of positive and negative symptoms, such as the Brief Psychiatric Rating Scale (BPRS) (78) , Scale for the Assessment of Positive Symptoms (SAPS) (12), Scale for the Assessment of Negative Symptoms (SANS) (12) and the Positive and Negative Syndrome Scale (PANSS) (79). The positive-negative dichotomy for symptoms in psychotic disorders has survived despite different factor analyses suggesting that a three-dimensional model consisting of positive, disorganized and negative, better represent the heterogeneity of symptoms (80;81). Also, other factorial solutions of up to five (82;83) and eight dimensions (84) have been found, but no

consensus exists, and no new scales have been developed. Instead, different factorial solutions that represent symptom dimensions are used from one study to the other.

2.2.1 Positive symptoms

Positive symptoms are made up of the symptoms of delusions, hallucinations and thought disorders, and are used synonymously with psychotic symptoms. The clinical picture of one who is having delusions, hallucinations or thought disorders is of one having lost contact with reality; often describing their reality as disturbing and scary. Positive symptoms are the hallmark for psychotic disorders in the two most used diagnostic systems, the DSM-IV (47) and the International Classification of Disease, Tenth revision (ICD-10) (85). Their prominence above other symptoms is used to differentiate psychotic disorders from other mental disorders. Further differentiation within psychotic disorders is based on their duration; other co-occurring symptoms and functional decline (see Table 1 in the Appendix for differentiation). Psychotic symptoms can also be present in other mental disorders such as affective disorders, but their presence is brief compared to the key symptoms of the disorder. Positive symptoms are used for identification of psychosis in both prodromal and early intervention studies, and a cut-off score is used as the crossing line from prodromal - to fully present symptoms (86). The length of DUP is based on any one of the positive symptoms being present.

2.2.2 Negative symptoms

There is no consensus about which symptoms make up the negative symptom complex (6). Blunted affect and alogia were the negative symptoms described by Crow (10) and in the DSM-III only flat and grossly inappropriate affect are included (87). Nancy Andreasen expanded this by including avolition-apathy (reduced will), anhedonia, asociality (reduced interest in social relationships), and inattention (76). Also, some authors include stereotyped thinking and motor retardation in the concept (88).

The clinical picture of negative symptoms is harder to define than positive symptoms because they are a continuum of normal behavior and assess complex human functioning that is reduced. The description of what symptoms encompass the negative symptom complex throughout the history of psychiatry is difficult to follow from one author to another. Like the term “negative symptoms”, the names assigned to describe these complex behaviors have often been reduced to one word, such as “process symptoms” (89) or “psychomotor poverty syndrome” (90) or the “deficit syndrome” (91). These words are not in common use and do not describe well what symptoms or behavior they represent. Krapelin may have had the best description when he stated the following: “Dementia praecox consist of a series of states, the common characteristics of which is the peculiar destruction of the internal connections of the psychic personality. The effects of this injury predominate in the emotional and volitional spheres” (37). He followed up on this, and both emotions and volition are among the psychic symptoms he listed as characteristics of dementia praecox (37).

Negative symptoms are most comprehensively assessed by the SANS (76) and the PANSS negative subscale (79), but the two scales differ in their number and content of items (92). The SANS consists of 24 items divided among five subscales representing the different negative symptoms of alolia, affective flattening, apathy-avolition, anhedonia and inattention. The PANSS negative subscale consists of seven items and the items are not defined in such a way that they clearly represent the different negative symptoms as is found in the SANS. Another challenge is that the PANSS scoring is based mostly on observation, while the SANS is a mixture of interview, observation and patients’ reports. New scales for assessment of negative symptoms have, therefore, been asked for (6).

How negative symptoms develop during the prodromal phase and over the first years of falling ill have not been much studied. But negative symptoms are found to be present in the premorbid period (93) in patients fulfilling criteria for the prodromal risk syndrome, (94) and to be present at the first episode (24;30). One study aimed at reducing DUP with the intervention of a public information campaign, found reduced negative symptoms both at baseline (86) and after two years

follow-up (95) in the intervention group compared with the non-intervention group, which may indicate that negative symptoms undergo development in the pretreatment phase. Level of negative symptoms is found to be reduced over the first years of treatment (12;96;97), but relatively less than positive symptoms (12;96-98). While a subgroup of patients has stable, enduring, negative symptoms during the first year of treatment, for others they may fluctuate and go into remission (21;24;98).

The association between negative symptoms and poor functioning is found in both first episode – and in patients with long-term illness and cross-sectional and longitudinally (4;6). The presence of negative symptoms in first episode are found to predict poor functioning both at one(21), two (24), four (99), five (24), seven (100) and ten years follow-up (101), which underlines the importance of studying negative symptoms in first episode patients.

Negative symptoms are thought to be of two kinds: those that are primary and associated with underlying pathophysiology and considered treatment resistant, and those that are secondary to co-occurring states of depression, delusions, side effects of antipsychotics, illness chronicity and hence treatment responsive (12). It is hard to differentiate the distinction between primary and secondary origin in clinical practice (91;102). When considered as secondary, apathy and anhedonia can be part of depressive symptoms, and apathy can be a reaction to treatment failure and the effect of living in an institution with little stimulation. Asociality may be a symptom of persecutory delusions, and lack of affective expression may be due to Parkinsonian side effects of antipsychotics. The deficit syndrome was introduced to help with the distinction between primary and secondary negative symptoms (91;103). The criteria for the deficit syndrome are stability of at least two negative symptoms over a one-year period, excluding those with co-occurring depression and side effects of medication (103). Reliable diagnosis of the deficit syndrome requires training as well as longitudinal clinical observation (102). It is, therefore, of limited use, especially for persons coming into treatment with their first psychotic episode. Recently, a more pragmatic method has been suggested by dividing negative symptoms into those that are enduring and those that are non enduring, or

fluctuating (104). Patients with enduring negative symptoms, or the deficit syndrome, are found to be related to a worse pre-morbid functioning, to be more frequent among males, -have a longer DUP, - poorer functioning, correlating with biological substrates, and to be treatment refractive (91;105).

Negative symptoms are not exclusive for schizophrenia or psychotic disorders and are also found, with less frequency, to be present in severe affective disorders (106;107) and other brain disorders such as Alzheimer`s dementia (107;108), traumatic brain disorder (109;110), and epilepsy (111).

2.3 Cognitive function and psychotic disorders

Cognitive function refers to how the brain handles information, its ability to select and store information, and how this information is retrieved and then communicated or acted upon (112).

Cognitive dysfunction is usually not detected by traditional clinical observation and is, instead, assessed by different neuropsychological tests. Cognitive function is often divided into different domains, but studies differ in the description of domains and the tests that represent them (112).

The domains most often tested in psychotic disorders are motor function, psychomotor speed, attention, working memory, verbal learning, visual learning, and executive function.

Among psychotic disorders, cognitive dysfunction is extensively studied in patients with schizophrenia and considered a core feature of the illness, independent of symptoms and medication status (52;113). Processing speed, attention, working memory, and executive functioning, are the cognitive domains that have been the most studied and found to be dysfunctional (53). Cognitive difficulties in psychotic disorders seem to be established years before the onset of symptoms and are detectable at the first episode (4), are stable and enduring over time, persist after remission of symptoms, and do not deteriorate in the chronically ill (4;56).

The association between cognitive dysfunction and symptoms is mixed, in that most studies find a moderately significant association to negative symptoms and no association to positive symptoms

(16;88;114). The association between negative symptoms and cognitive dysfunction is found both at the start, and after years of psychosis (115). However, the direction of the association is not established, and different theories and models are proposed (16;115).

There is a clear and significant association between cognitive dysfunction and poor daily life functioning (14;15). This association is found to be stronger than that for negative symptoms in some studies (14), but not in others (100). Cognitive impairments are largely treatment refractory to current interventions, but new promising initiatives are underway. Cognitive remediation and pharmacological interventions are the two areas of most interest (116).

3. Apathy

Apathy is derived from the Greek word “apatheia”, meaning without feeling (117). In medical dictionaries, apathy is synonymous with indifference, insensibility, and lack of emotion (118). In psychiatry, apathy is mostly associated with the negative symptoms of schizophrenia, but also with depression. Apathy is considered a neuropsychiatric symptom within the field of neurology defined as reduced motivation and goal-directed behavior, reflecting lesions of the prefrontal cortex, or of its sub-cortical connections (108;119-123). In the field of psychology, extra and intro version are personality traits concerned with degree of motivation (124). Apathy is also considered a psychological reaction to grave personal bereavement or to witnessing extreme conditions, long standing lack of political influence, and living in institutions with little stimulation. Apathy is a word in common use, referring to some of the above conditions without further specification, and used interchangeably with “avolition” and “amotivation” in the literature. With so many different meanings, apathy can be hard to study without a clear definition.

Within the medical field, Marin was one of the first to define apathy (125). He defined apathy as lack of motivation not attributed to diminished level of consciousness, cognitive impairment, or emotional distress (42;125;126). From this definition he developed the Apathy Evaluation scale (AES)

(126). Other scales have since been developed from this definition such as the Apathy Scale (AS) (127), the Apathy Inventory (AI), the Dementia Apathy Interview Rating Scale (DAIRS) (128) and the Lille Apathy Rating Scale (LARS)(129). Apathy is also assessed among other neuropsychiatric symptoms in the Frontal System Behavior Scale (FrSbe) (130) and the Neuropsychiatric Inventory (NPI) (131). Table 4.1 to 4.7 in the Appendix shows how apathy is assessed by different scales. Apathy was not much studied before these assessment scales were introduced early in the 1990's (42). The AES has been useful across disorders and languages, was translated to Norwegian in 1998, and used in several studies of patients with traumatic brain damage (132-134).

3.1 Apathy and psychotic disorders

Apathy has been infrequently studied in psychiatry. Only four studies were found in the preparation for the current study, all of patients with schizophrenia (38-41). Kraepelin used volition, avolition or apathy interchangeably when he described what he considered to be the key features of schizophrenia, and especially when he described what he thought lay behind those with a deteriorating and chronic course (37). Bleuler emphasized the lack of affects for the chronic course of schizophrenia. His description of this fundamental symptom have a lot in common with Kraepelin's description of volition (135). Kraepelin listed volition as a separate psychic symptom of Dementia Praecox and it is also found as such in textbooks following Kraepelin (136). However, in the current major text books of psychiatry, volition is no longer listed as a separate symptom of psychotic disorders (4;56).

Apathy was also not part of the negative symptoms as they were first described (137), but incorporated by Nancy Andreasen into the SANS as a separate subscale named avolition-apathy (76). Apathy is not clearly defined in the PANSS negative subscale, but included into the definition of three items in the PANSS negative subscale, the N2 (Emotional withdrawal), N4 (Passive/apathetic social withdrawal) and N6 (Lack of spontaneity and flow of conversation). See Table 4.2 in the Appendix for further definition of the items.

In the four studies of apathy mentioned above, one found apathy associated with poor functioning. (39). Another found apathy related to prefrontal reduced volume and executive functioning (40), while a third studied the effect of motivated behavior, without finding any difference between those with and without apathy (41). One study, more than 40 years old, found increased activation in patients with apathy who were motivated by the staff (38). All studies have been cross sectional of patients with long-term illness, and of a small sample size, New studies have been asked for, and currently there are no follow-up studies of apathy.

3.2 Apathy and other brain disorders

Apathy is classified as a neuropsychiatric symptom in other brain disorders and has been studied in disorders such as Frontotemporal dementia (138), Alzheimer's - (139), Parkinson's - (140), Huntington's disease (141), stroke (142), traumatic brain damage (133;143), multiple sclerosis (144), and epilepsy (145). Apathy is a primary diagnostic criterion for Frontotemporal dementia (125). In the other brain disorders, apathy is one of several co-occurring neuropsychiatric symptoms, but without diagnostic consequences (146).

Neuropsychiatric symptoms are found to reflect the behavioral effect of lesions and not the psychological reaction to being ill (146). There is an increasing focus on neuropsychiatric symptoms in different brain disorders because, when present, they often influence the course more than the primary symptoms of the disorder (146). The presence and degree of apathy varies both between and within disorders, depending on lesion localization, severity of illness and illness duration (147). Apathy is mostly studied in Alzheimer's disease where it is the most common and persistent neuropsychiatric symptom ranging from 30% in a community sample to 80% in nursing home residents (43). In Parkinson's disease the prevalence of apathy ranges from 17% (148) to 45% (149;150), in Huntington's disease between 34% to 76% (151), and in traumatic brain damage it ranges between 27% (142) to 79% (132;152).

The relationship between apathy and depression is of special interest, since they clinically overlap (42;153;154). The relationship has been studied in many of the above disorders. The two have been found to be highly correlated but, despite this, found to be independent of each other in Alzheimer's (155;156), Parkinson's (129;149;157), Huntington's disorder (141), stroke (142) and traumatic brain damage (152), in that apathy, and not depression, are found associated with functional decline and reduced executive function (158;159). Two follow up studies on apathy have been identified. In both, the presence of apathy was related to a worse course (160) and outcome (161). Apathy may also be a reaction to chronic disease. This has been investigated in two studies comparing the level of apathy in patients with Parkinson's disease to those with dystonia (162) and osteoarthritis (44), finding that the dystonia and osteoarthritic patients had a level of apathy comparable to healthy controls.

3.2.1 Apathy and functioning in other brain disorders

Apathy is found significantly related to functional impairment when present in all the above disorders (43;163-165). In one study of patients with Alzheimer's disease, the presence of apathy was associated with a more rapid progression of dementia and decline of functioning which is not found for other neuropsychiatric symptoms (164). Apathy is also found to predict a more rapid conversion from mild cognitive decline to dementia in Alzheimer's disease (166-171), and suggested it be used diagnostically for early identification of Alzheimer's (166;171).

3.2.2 Apathy and cognitive function in other brain disorders

The relationship between apathy and cognitive function has also been extensively studied in the brain disorders described above. Common to studies, is the finding of a consistent relationship between high levels of apathy and poorer performance on tests representing executive function (44;134;141;150;158;172;173). In addition, significant associations are found to other cognitive domains, but the pattern of association is less systematic. This same relationship has been found in

one study of patients with schizophrenia. However, the study sample was small, of chronic patients, and warranted replication (40).

3.3 Apathy in healthy volunteers

In some of the studies above, the level of apathy has been compared with that of healthy control persons. For the different control groups the frequency of apathy ranges from 0% (127;174) to 5.4% (142;169;175).

4. Aims and research questions of the thesis

Negative symptoms are found to be one of the major predictors of poor functioning in psychosis, both in chronic and first episode psychosis patients. There has been limited progress in the development of effective treatment of negative symptoms, and poor functioning is still the major concern and cost for persons affected with psychosis. Negative symptoms are not a unitary construct, but made up of different symptoms. We have limited knowledge of the different symptoms and more knowledge is needed.

Negative symptoms have been found to be present already at the first episode of psychosis. In order to avoid the possible confounding influence of treatment failure and institutional life, it is of particular interest to study the relationship between apathy and functioning in patients with a first episode psychosis.

Apathy is one of the negative symptoms where more knowledge has been especially asked for since it is suggested to play a major role in the development of poor functioning. It has been little studied; one reason being the lack of both a clear definition and valid assessment tools. Apathy is a neuropsychiatric symptom studied in other brain disorders and several rating scales have been found reliable and valid for its assessment. In these disorders, apathy is found related to poor functioning and associated with poor executive function. There are few studies of apathy in psychosis, and they are only of patients with long-term illness.

Clinical assessments of negative symptoms are challenging because they are based on observation of a broad range of reduced behaviors rather than defined symptoms. The different negative symptoms are also differently represented in the two most-used rating scales for negative symptoms. Better and more valid assessment instruments for the different negative symptoms have been asked for. The AES has been used to assess apathy in different brain disorders and in one study of patients with chronic schizophrenia. Before the AES can be used to assess apathy in first episode psychosis patients, its use needs to be validated.

With this background, the aim of the following thesis is to improve our understanding of apathy in first episode psychosis patients by answering the following research questions:

1: Does the Apathy Evaluation Scale have sound psychometric properties when used in a first episode psychosis sample? Does the AES show good discriminative and convergent properties to the five factors of PANSS and the PANSS items by correlating highly only with the PANSS negative factor and the three PANSS negative items thought to measure apathy (N2, N4 and N6)? This will be answered in Paper 1.

2: To what degree are first episode psychosis patients apathetic compared to a healthy control group? What clinical variables are associated with apathy at start of treatment in first episode? How does apathy, together with other symptom groups as assessed by the PANSS, influence functioning at start of treatment? This will be answered in Paper 2.

3: Does apathy have the same relationship to neurocognitive function as found in other brain disorders? How do the co-occurring states of depression, positive symptoms or degree of medication, influence the relationship? This will be answered in Paper 3.

4: How does apathy develop over the first year in first episode psychosis patients? What predicts high levels of apathy at one year follow up? Is there a group with enduring high levels of apathy over

the first year and, if so, what characterizes this group? How is apathy, together with other symptoms, related to poor functioning at the one-year follow up? This will be answered in paper 4.

5 Material and Methods

5.1 The Thematically Organized Psychosis Research (TOP) Study

TOP is a large translational multicenter research study investigating clinical and biological characteristics of psychosis in order to gain more knowledge of the underlying pathophysiological mechanisms. The study is carried out by the University of Oslo in joint collaboration with two major hospitals in Oslo and 9 hospitals outside Oslo. All participating hospitals are catchment area based and publicly funded with no private specialized service for this group of patients. Patients are referred from primary care. All patients with a possible, or already diagnosed, severe mental disorder registered in the specialist health service are asked to participate, and inclusion is still ongoing. The TOP study also includes a healthy control group which is randomly selected from the population registries of Oslo and from one neighboring community. The controls are contacted by a letter giving information about the study inviting them to participate and make contact either by phone or by a letter.

The TOP study was approved by the Regional Committee for Medical Research Ethics (RCMRE) and the Norwegian Data Inspectorate in 2004, and the data file has received an Audit Certificate from the Center for Clinical Research at Oslo University Hospital, Ullevål in 2007. This study was approved by the RCMRE on the 22nd of April 2004 as a separate study within the TOP study.

5.2 Ethical and clinical considerations

In a study with mostly young patients being treated for their first episode of psychosis, consideration of ethics and good clinical skills are of utmost importance to avoid harm and additional burden. Therefore, the participants were introduced to the study by different routes. Brochures and posters with general information about the study were placed in the waiting rooms and on the wards. The

appropriate time for asking for participation was discussed in a weekly clinical meeting between the clinical staff and researcher. All were informed that declining participation would have no consequences for further treatment.

The TOP protocol includes clinical assessments, neuropsychological tests, fasting blood tests, urine sample, and structural and functional magnetic imaging. The participants have to meet for the different assessments over several days. The clinical assessment, in itself, takes many hours, and for many participants it had to be broken up over several days. The clinical assessments were done at the site the participant preferred, either in the clinic or at the research office, and transportation by taxi was used when necessary. The patients were not compensated for their participation, with the exception of their traveling expenses. Both the clinical assessment and neuropsychological tests were summarized in a written report for use in the clinic. All patients were asked at baseline about the follow up interview. None declined beforehand, but 18 did not show up.

5.3 Research Design

The study is a naturalistic one year follow up study. Three out of the four studies are cross sectional and one is a follow-up over one year.

5.4 Material

5.4.1 The patients

This study includes the 104 consenting patients coming into treatment for their first episode of psychosis at the Oslo University Hospital or Diakonhjemmet Hospital between July 1st 2004 and 31st of June, 2006. The study inclusion criteria were: a) admitted for treatment of psychotic symptoms for the first time either as an out, or an in patient to any of the participating hospitals and with a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis not otherwise specified (NOS), delusional disorder, brief psychosis or major affective disorder with mood incongruent psychotic symptoms, b) age between 18 and 65 years, c) understanding and speaking a

Scandinavian language, d) having no history of severe head trauma or neurological disease, and e) having an intelligent Coefficient (IQ) score over 70. Being psychotic was defined as having a rating of 4 or more on the PANSS items P1, P2, P3, P5, P6 or G9. Patients were eligible for inclusion up to 52 weeks following the start of adequate treatment. Adequate treatment was defined as having started treatment in clinically recommended dosage with any antipsychotic medication. Exclusion criteria meant having one or more previous psychotic episodes treated with antipsychotic medication for more than twelve weeks or if treatment led to symptomatic remission before twelve weeks.

One patient withdrew his participation in August 2006, also wanting his data withdrawn, which came into consequence from Paper 2 and onwards, where participating patients were reduced to 103. In Paper 3, only those with primary school and higher education in Norway were included, reducing the group to 71. Eighteen subjects did not attend the one year evaluation and one met for follow-up, but did not complete a full evaluation, totaling 84 patients (81% of the original cohort) for the analysis in Paper 4. Of the 18 subjects who did not meet for the one year assessment, 11 refrained from further attendance, five had moved and their current address was not available, two consented to attend, but never showed up. There were no statistically significant differences at baseline between those who participated and those who did not participate in the one year follow up regarding sex, age, premorbid function, years of education, DUP, diagnostic distribution, degree of drug or alcohol use, clinical symptoms or use of antipsychotic medication.

5.4.2 The healthy control sample

The healthy control group in this study consisted of 62 individuals who filled out the AES. Inclusion criteria included being born in Norway, holding a Norwegian citizenship, and within an age range of 18 to 55. The controls were screened with the Primary Care Evaluation of Mental Disorders (176). Criteria for exclusion were if they, or any of their close relatives, had a lifetime history of a severe psychiatric disorder (schizophrenia, bipolar disorder and major depression), if they had a history of

medical problems thought to interfere with brain function (hypothyroidism, uncontrolled hypertension and diabetes), or had recent cannabis use (during the last three months). The healthy controls received financial compensation for participation of 500 Norwegian kroner.

Background demographics are presented at the bottom of Table 2 in the Appendix. There were no significant differences in gender distribution between patients and the healthy control group, but the control group was significantly older than the patients (mean difference 4.7 years, Confidence Interval (CI)=1.6 - 0.9, $p=.002$) and had slightly more years of education (mean difference .9 years; CI=0.2 - 1.7, $p=.03$).

5.5 Methods

Background demographics and the results of the clinical assessments for patients at baseline and follow up for each of the four studies are given in Table 2 in the Appendix. An overview of measures and statistical procedures used in the four different papers is given in Table 3 in the Appendix.

5.5.1 Diagnostic assessment

Diagnosis was assessed with Structured Clinical Interview for DSM-IV –TR Axis I Disorders Patient Edition (SCID-I/P) (177) both at baseline and after one year. For the statistical analysis, schizophrenia, schizophreniform, and schizoaffective were combined to “Schizophrenia spectrum” group; major affective disorder with mood incongruent psychotic symptoms and bipolar I disorder with mood incongruent psychotic symptoms were combined to the “Affective psychosis” group, and psychosis NOS, brief psychosis and delusional disorder, were combined to “Other psychosis” group. At one year follow-up there was a change of diagnostic group for 18 patients (21 %). See Table 2 in the Appendix for change within each diagnostic group.

5.5.2 Assessment of positive, negative and other symptoms

Symptoms were assessed by the Structural Clinical Interview of the Positive And Negative Syndrome Scale (SCI-PANSS) (79). The scale is a 30-item Likert scale ranging between 1-7; where each item is

defined and scored according to it being absent or present in the following way: 1=absent, 2=minimal, 3=mild, 4=moderate, 5= moderate severe, 6=severe, 7=extreme. The PANSS items are divided into three subscales, the Positive consisting of 7 P- items, Negative consisting of 7 N-items and General psychopathology scale with 16 G-items. Several factor analyses have since indicated that the PANSS measures five symptom dimensions (82;83) . We chose to use Emsley et al's five factor solutions in studies 1, 2 and 4 to represent the symptom dimensions of positive (PANSS-POS) consisting of the items P1,P3,P5, P6, G9,G12; disorganized (PANSS-DIS) consisting of the items P2, N5, N7, G5, G10, G11, G15; negative (PANSS-NEG) consisting of the items N1, N2, N3, N4,N6, G7,G13, G16; depressive (PANSS-DEPR) consisting of the items G1,G2,G3, G4,G6; and excited (PANSS-EXC) symptoms consisting of the items P4,P7,G8,G14 (82). Emsley et al's solution was used since it is based on first episode psychosis patients (82). In study 3 we only used the PANSS negative and positive subscores, and depression was assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (178).

5.5.3 Assessment of apathy

Apathy was assessed using the Apathy Evaluation scale (AES). The AES is an 18-item Likert scale with a scoring ranging from 0–4 (0 = not at all and 4 = very much). The AES has three versions with identical questions; clinician (AES-C), self (AES-S), and informant rated (AES-I) (126). The clinical interview lasts from 15 to 30 minutes; the self-report from 5 to 10 minutes. Study 1 showed that the 12-item clinical AES (AES-C-Apathy) gave a better assessment of apathy than the full 18-item version in a population with first episode patients (179) and both the abridged clinical (AES-C-Apathy) and the self-rated (AES-S-Apathy) were used in the subsequent studies. In Table 4.1 in the Appendix the 12 items making up the abridged version are kept in white. For the control group, we only used the self-report form. We used a score of 27 on both the AES-S-Apathy and AES-C-Apathy as the cut-off value for being clinically apathetic. This score is based on the distribution of the healthy control

group(180), and is the sum of the mean AES-S-Apathy score and two standard deviations ($18+8.6=26.6\sim 27$).

Training was supervised by two experienced clinicians that had previously used the scale in other patient groups (132), and reliability testing of AES-C was done by scoring of live interviews of random study patients. The inter rater reliability using the Intra Class Coefficient (ICC1-1) of Shrout and Fleiss and was 0.98 (95% CI 0.92–0.99) for the AES-C.

5.5.4 Assessment of alcohol and drug use

We used the Clinician's Alcohol and Drug use Scale which separately measures drug and alcohol use for the last six months (181). The scoring goes from 1-5, where 1 = no use, 2 = use without impairment, 3 = abuse, 4 = dependence and 5 = dependence with institutionalization.

5.5.5 Assessment of daily dose of antipsychotic medication

The Daily Dose of Antipsychotic medication (DDD-AP) was measured using the World Health Organization Collaborating Center for Drug Statistics Methodology (182). Two patients at baseline and four at the one-year follow up used first- generation antipsychotics. All others used second generation antipsychotics.

5.5.6 Assessment of side effects of medication

We used The Committee on Clinical Investigations under the Scandinavian Society of Psychopharmacology (Utvalg for Kliniske Studier) side effect scale for psychotropic drugs (UKU) (183). Only the subscale for the presence of neurological (UKU-neuro) or autonomic (UKU-autonom) side effects was used in the present study. The UKU-neuro consists of 8 items and the UKU-autonom consists of 11 items. Each item is rated from 0 - 3 (0= not or doubtfully present; 1= present to a mild degree; 2= present to a moderate degree; 3= present to a severe degree).

5.5.7 Premorbid functioning assessment

Premorbid functioning was assessed with the Premorbid Adjustment Scale (PAS) (184). The premorbid phase was defined as the time from birth until 6 months before the onset of psychosis. The premorbid phase is divided into four life periods: childhood (up to 11 years), early adolescence (12–15 years), adolescence (16–18 years) and adulthood (19 years and beyond). The scoring ranges from 0–6, with 0 indicating the best level of functioning, and 6 the worst. Several studies have confirmed two basic dimensions in the PAS: social (PAS-Social cluster) and academic (PAS-Academic cluster) (185;186). We used the method described by Larsen et al when calculating separate sum scores for PAS-Social cluster and PAS-Academic cluster functioning (185) and the method by Simonsen et al to calculate change scores for social (PAS-Social-change) and academic functioning (PAS-Academic-change) (187).

5.5.8 Assessment of functioning

We used the function score from the split version of the Global Assessment of Functioning scale (GAF-F) to measure change in global functioning (188). The split version has been found to discriminate well between symptoms and function (189) and has been used in other studies of first episode psychosis (95). The GAF-F is a continuous scale ranging from 1–100, where 1 is the lowest functioning, and 100 is the best, with each 10 point being defined; i.e. 31-40: poor functioning in two life areas, 41-50: poor functioning in one life areas; 51-60 moderate functional difficulties.

5.5.9 Neuropsychological assessments

A comprehensive neuropsychological battery of tests was administered to all participants by psychologists or psychology students trained in clinical neuropsychology. The tests cover domains shown to be sensitive to the cognitive dysfunction of psychosis (113;190): motor function (Grooved Pegboard) (191), psychomotor speed (Digit Symbol from WAIS-III) (192), attention (Digit Span forwards from WAIS-III) (192), working memory (Letter Number Span from WAIS-III) (192), verbal learning (California Verbal Learning Test; CVLT-II) (193), visual memory (Rey-Oesterrrieth Complex Figure Test) (194) and executive function. For the executive function domain, several tests from the

Delis-Kaplan Executive Function System (D-KEFS) (195) were included in order to enable the investigation of the association of apathy with three different aspects of executive function; initiation, set shifting and inhibition. Initiation was assessed with Semantic fluency and Phonetic fluency (from the Verbal Fluency test) (195). Set shifting was assessed with Category Switching (also from the Verbal Fluency test) (195), whereas inhibition was measured with the third trial on the Color-Word Interference test (the “Stroop” condition) (195).

Premorbid IQ was assessed with a Norwegian Research version of the National Adult Reading Test (NART) (196); and current IQ with Wechsler Abbreviated Scale of Intelligence (WASI;) (197). All participants showed adequate neuropsychological test effort indicated by two errors or less on the forced recognition trial of the CVLT-II.

5.5.10 Procedures

All participants gave written informed consent to participate. The investigators in the study completed the common training and reliability program in the TOP study. SCID-I/P training was based on the training program by University of California in Los Angeles (UCLA)(198). For DSM-IV diagnostics, mean overall kappa for the standard diagnosis of training videos was $K=0.77$, and mean overall kappa for a randomly drawn subset of actual study patients was also $K=0.77$ (95% CI 0.60–0.94). Inter-rater reliability with Intra Class Coefficient [(ICC) 1.1] for the different PANSS subscales was : PANSS positive subscale 0.82 (95% CI 0.66–0.94) PANSS negative subscale 0.76 (95% CI 0.58–0.93), PANSS general subscale 0.73 (95% CI 0.54–0.90) and for GAF-F 0.85 (95% CI 0.76–0.92).

5.6 Data and statistical analyses

Preliminary analyses were performed to examine distribution of each variable and all data was inspected for skewness and linearity. Logarithmic transformation (ln) was used for data that was not normally distributed. Only the variable representing the duration of untreated psychosis was transformed. All analyses were checked for the influence of outliers. One extreme outlier being 4

Standard Deviations (SD) outside the group mean on the verbal fluency test was taken out of the analysis in paper 3. All tests were two tailed. The statistical significance level was pre set to $p \leq .05$, except in paper 1 where it was preset to $p < .01$ due to multiple testing and in paper 3 to $<.02$ for some analyses for the same reason.

Descriptive statistics were presented as mean and standard deviation (\pm SD) or median and range for non-normally distributed data. Observed values are presented with actual number (n) and percent (%) and adjusted values in means and with a 95% confidence interval (CI). Independent t- tests were used to test the difference in continuous variables between two groups. One-way analysis of variance (ANOVA) with post-hoc Scheffe's test was used to test for differences with more than two groups. Paired sample t-test was used to analyze the difference between measures at baseline and one year follow up. Mann-Whitney U test (U) was used to test for differences between groups for non parametric data. Differences between categorical data were analyzed with Chi-squared test (χ^2). The strength of the linear relationships between variables was calculated using Pearson product moment correlation (r) and Chi square test for categorical variables. The relationship between one continuous dependent variable and multiple independent variables was analyzed by linear regression methods and only independent dependent variables with a significant ($p \leq .05$) correlation with the dependent variable under study were included. The final models were checked for violations of assumptions and for the effects of outliers and influential observations. Psychometric properties of the AES were analyzed using principal factor analysis with Varimax rotation. All data was analyzed using the Statistical Package for Social Sciences (SPSS) for Windows, first version 12, later version 15, SPSS Inc., Chicago, IL, USA. For an overview of the statistical methods used in each paper see table 2.

6. Results and summary of the four studies

Paper 1: Assessing apathy: The use of the Apathy Evaluation Scale in first episode psychosis

Background and aims: Recently there has been a renewed interest in the different symptoms that constitute the negative symptoms in schizophrenia and new scales for their assessment have been asked for. Apathy is one of the negative symptoms in focus. The Apathy Evaluation Scale (AES) with its clinical version (AES-C) is one of the most used scales for assessment of apathy in an interdisciplinary context, but it has never been used in a population with a first episode of psychosis. The main aims of this study were to examine the psychometric properties of the AES-C.

Material and method: A total of 104 patients with a first episode psychosis from the ongoing Thematic Organized Psychosis Research (TOP) study were included in this study. The psychometric properties of the AES-C were tested by correlation and factor analysis. The Positive and negative Syndrome Scale (PANSS) was used to test the convergent and discriminative properties of the AES-C. A five-factor model of PANSS was used to represent the positive, disorganized, negative, depressive and excitatory symptoms of psychosis.

Results: Factor analysis of the AES-C identified a three-factor model that gave the most clinically meaningful model, accounting for 53% of the variance in the AES-C. The major subscale was made up of 12 of the original 18 items, all items concerned with motivation, initiative and interests. It was named AES-C-Apathy. The six items left for the two minor subscales were concerned with insight and social contacts. The three subscales had from modest ($r = .37$) to no intercorrelation ($r = .04$), indicating that the three scales measure different dimensions. The AES-C-Apathy subscale showed satisfactory internal consistency with a Cronbach's alpha of .90 and a high inter-rater reliability (ICC) of .98 (CI .92 - .99), which was also found for the AES-C. The AES-C-Apathy had good discriminative and convergent properties towards the five factors of PANSS, by correlating strongly ($r = .6$) only with the PANSS-negative, modest ($r = .3$) with the PANSS-disorganized and weakly with the three other PANSS factors of -positive ($r = .2$), - depressive ($r = .2$) and -excitement ($r = .03$). The AES-C-Apathy also had good convergent and discriminative properties with the 30 different PANSS items, by correlating strongly ($r = .6$, $r = .5$) with only the three apathy-related items of the PANSS negative subscale, N2

($r=.6$), N4 ($r=.5$) and N6 ($r=.5$), and with modest ($r=.3$) to no correlation ($r=-.06$) with all the other 27 PANSS items. The two minor subscales had weak correlations with the PANSS negative items, as well as most other PANSS items, and were not used in the subsequent work.

Conclusion: The conclusion drawn from this study is that the abridged AES-C, the AES-C-Apathy, had sound psychometric properties and can be used to assess apathy in the ongoing work of refining the negative symptoms in first episode psychosis.

Paper 2: Apathy and functioning in first episode psychosis

Background and aims: Negative symptoms, more than other clinical symptom areas of psychosis, have been found to be one of the major predictors of poor functioning both in chronic and first episode patients. It is currently of great concern that there are no established treatments for negative symptoms. Negative symptoms are not a unitary construct but made up of different symptoms, mainly apathy (reduced goal directed behavior), anhedonia (reduced experience of pleasure), flat affect (reduced affective expression), asociality (reduced interest in social contacts), and inattention. The recent NIMH-MATRICES statement on negative symptoms, and others, has suggested that one way forward in developing more effective treatments, is to get a better understanding of the different negative symptoms. Apathy is one of the symptoms where more knowledge has been requested. The aim of this paper is, thus, to study apathy closer in first episode patients to determine to which degree first episode psychosis patients, at the start of treatment, are apathetic compared to healthy controls, if schizophrenia spectrum patients have higher levels of apathy than other diagnostic groups, and which patient characteristics relate to higher levels of apathy, and to what degree apathy contributes to functional loss.

Material and Method: The study includes 103 first episode psychosis patients and 62 healthy control persons participating in the TOP study. Apathy was assessed with the abridged Apathy Evaluation Scale (AES-C-Apathy). Other clinical symptoms were assessed with the Positive and

Negative Syndrome Scale (PANSS). The PANSS five-factor model was used in the subsequent analyses. Functioning was assessed with the split version of Global Assessment of Functioning scale (GAF-F). Correlation and multiple linear regression analysis were used as the statistical methods to answer the research questions.

Results: There was a significant difference in mean AES-C-Apathy score between controls and first episode patients (18.0 ± 4.3 vs. 27.7 ± 7.2 ; $p < .001$). The cut off score for being clinically apathetic was set to 27, defined as 2 SD above the mean score of AES-S-Apathy for the healthy control group. With this cut off score, slightly more than 50% of FEP patients were found to be clinically apathetic compared to 3% of healthy controls. There was a significant diagnostic group difference in AES-C-Apathy score, with the highest mean score in the Schizophrenia spectrum group. Only the difference between the Schizophrenia spectrum – and Other psychosis group was statistically significant. Of the clinical variables only premorbid childhood social functioning, change in premorbid social functioning and PANSS -disorganized symptoms had a significant association to the AES-C-Apathy score; explaining 18% of the variance. Multiple regression analysis revealed that of the entire five PANSS symptoms, only PANSS-positive together with AES-C-Apathy had a significant independent association to global functioning as assessed with GAF-F. Together they explained 37% of the variance in the GAF-F score.

Conclusion: The conclusion drawn from this study is that apathy is a prevalent symptom in first episode patients already from the start of illness, and significantly different from what was found in the healthy control group. We also found that apathy was significantly associated with poor functioning. The significant association between apathy and functioning at this early stage of illness points to the need of evaluation and attention of apathy for tailoring the right treatment- and rehabilitative goals.

Paper 3: Apathy is associated with executive functioning in first episode psychosis

Background and aim: The underlying nature of negative symptoms in psychosis is poorly understood. Negative symptoms have repeatedly shown to have a significant association to cognitive deficits. Cognitive deficits are found to be more closely associated to underlying brain pathology than symptoms. Therefore, an exploration of the association between the different negative symptoms and cognitive function may aid the search for the mechanisms behind negative symptoms. Apathy, one of the negative symptoms, is also a common symptom in other brain disorders and its association to cognitive dysfunction, in particular executive dysfunction, is well documented. A significant association was found in the relationship between apathy and cognitive function explored in one former study of chronic patients with schizophrenia. But the study was of small sample size and of patients being ill for many years. This study investigates the association between apathy and cognitive function in first episode patients, with the hypothesis that apathy, also in first episode patients, is more strongly associated with tests representing executive function than tests representing other cognitive domains, and that the relationship is unrelated to depression, positive symptoms or degree of medication.

Material and methods: Seventy-one first episode patients with a fluent understanding of Norwegian were assessed with an extensive neuropsychological test battery. Level of apathy was assessed with the abridged Apathy Evaluation Scale (AES-C-Apathy) and other symptoms with the Positive and Negative Syndrome Scale (PANSS). Correlation and multiple linear regression analyses were the statistical methods used to answer the research questions.

Results: We found that the AES-C-Apathy was significantly associated with tests from the executive domain representing initiation [Semantic fluency ($r = .37, p < .01$), Phonetic fluency ($r = .25, p < .05$)] and working memory [Letter Number Span ($r = .26; p < .05$)]; but not other neurocognitive domains or tests. Co-occurring depression, positive symptoms or use of antipsychotic medication did not significantly influence these results.

Conclusion: The conclusion drawn from this study is that apathy in first episode psychosis has a specific significant association to executive function which replicates the findings in chronic patients with schizophrenia and is the same as what is also found in other brain disorders.

Paper 4: Apathy in first episode psychosis patients: one year follow up

Background and aims: Negative symptoms are often more treatment resistant and, thus, among the most severe symptoms of psychotic disorders. Enduring high levels of negative symptoms has a stronger association to poor functioning than those that are transient and are found to be enduring already from the first episode of psychosis. We do not know how this applies to the different negative symptoms. At baseline, more than half of the 103 first episode patients were considered apathetic and apathy was found strongly associated with poor functioning. The aim of this study is, therefore, to study how apathy develops from baseline to the one year follow up; to study what predicts high levels of apathy at one year; if there is a subgroup of patients with enduring high levels of apathy; and the association between apathy, other symptoms, and functioning.

Material and methods: Eighty-four first episode patients were assessed both at baseline and after one year with the abridged clinical version of the Apathy Evaluation Scale (AES-C-Apathy). A cut off score of 27 was used for being clinical apathetic. The Positive and Negative syndrome scale (PANSS) was used to assess other symptoms. Functioning was assessed with the split version of the Global Assessment of Functioning Scale (GAF-F). Correlation, t-tests, ANOVA, paired sample t-tests and multiple linear regression analyses were used as the statistical methods to answer the research questions.

Results: We found that 40% of the first episode patients were apathetic at the one-year follow up compared to 50% at baseline. The mean level of apathy decreased significantly for the whole group from baseline to follow up. At the diagnostic group level the decrease was only statistically significant for the Other psychosis, not for the Affective or the Schizophrenia spectrum group. At

both time points, the Schizophrenia spectrum group had the highest mean level of apathy and the Other psychosis group the lowest. There was a statistically significant difference in mean level of apathy between the diagnostic groups in such a way that at baseline this difference was only significant between the Schizophrenia spectrum and Other psychosis group, but at follow up the difference was statistically significant between all three groups (Schizophrenia >Affective psychosis>Other psychosis). High levels of apathy at the one year follow up were best predicted by high levels of apathy at baseline, a long DUP and a Schizophrenia spectrum diagnosis. Twenty five (30%) of the 84 FEP patients had enduring high levels of AES-C-Apathy. The enduring apathy group, compared to the non-enduring group, consisted of statistically significantly more males (80% vs. 51%), more had a DSM-IV Schizophrenia spectrum diagnosis (88% vs. 53%), they had a longer DUP (52 vs. 24 weeks), were less likely to have remission of positive symptoms at baseline (16 % vs. 49%) and at one year (36% vs. 73%), had a lower mean GAF-F score both at baseline (37 vs. 49) and at one year (42 vs. 59) and fewer were working or studying both at baseline and follow up. We also found that at the one year follow up AES-C-Apathy had a strong association to poor functioning, as measured by GAF-F, and showed the strongest relationship when analyzed together with other PANSS symptom areas.

Conclusion: The conclusion drawn from this paper is that apathy is most prevalent and enduring in the Schizophrenia spectrum group and that the clinical variables characterizing the group with enduring apathy are the same as found for enduring negative symptoms. Also, at the one-year follow up, apathy was strongly associated to poor functioning. This underlines the significance of assessing apathy in first episode patients and supports the recent initiatives to include negative symptoms in early intervention studies. The study also supports the value of assessing the individual negative symptoms as suggested by the NIMH-MATRICES consensus.

7. Discussion of methodological issues

7.1 Reliability

Clinical assessments were done by three experienced clinicians; two medical doctors and one psychologist. All took part in the TOP training program to secure reliability for DSM IV, GAF and PANSS. In addition, the three of us met regularly to discuss inclusion issues and performed assessments together to increase reliability beyond the formal training. We were especially trained by the research group who had long experience in the use of the AES at the Oslo University hospital, Rikshospitalet in Oslo. All took part in the reliability testing of AES, which was done from taped interviews with participating patients. The inter rater reliability, ICC, ranges from 0.73 to 0.82 for the PANSS subscales, and was 0.85 for GAF-F and 0.98 for the AES-C. The above are the accepted standards required for research (180), which provide our assessments and data with good quality support.

7.2 Biased assessments

We had no opportunity to do a blind assessment of apathy from other assessments where apathy may play a role, such as the PANSS and GAF. All clinical assessments were done by the same clinician and scoring bias may be present. However, the sum score of the AES was blinded and was not calculated before all assessments were in the database. At the one-year assessment none of the baseline assessments were available. The PAS, which is used to assess premorbid functioning, is based on retrospective information from both the patient and parents. The PAS scoring may, therefore, be due to recall bias and reduced information since we were not able to interview the parents and results must be interpreted with this in mind.

7.3 Validity of the difference between apathy and functioning

Since the influence of apathy on functioning was one of the main aims of the study, it was important to ensure that the assessment covered by the AES-C-Apathy and GAF-F did not overlap. The AES is a

semi-structured interview aimed at assessing the patient's personal experience of initiative, motivation and interests. Each of the 12 items is scored independently of each other, on a Likert scale ranging from 1 to 4, and the sum score is based on the individual scores for each item. There is no additional global apathy score. The GAF-F assesses work, studies and daily life performance. The scoring is based on the clinicians' observations and facts about being unable to work, strained relationships and dependence on others for daily living. The GAF-F score is a global score and can be any score between 1 and 100, where each ten points are defined with examples of functional difficulties. The GAF-F does not take into account what causes the functional difficulties, and reduced initiative and motivation is not used to describe the reduced functioning.

7.4 Timing of baseline assessments

Most of the assessments were not part of the clinical routine for any of the participating hospitals and, therefore, the study assessments could not be done before the patient was clinically stable and found capable of giving written informed consent.

Assessments at baseline were, therefore, not done before symptoms had stabilized, and could be up to 52 weeks after start of adequate treatment. The reason for this was to ensure the appropriate time for consent and to include as many participants as possible, especially those predominantly ill with lack of insight and long lasting florid psychotic symptoms. Baseline is calculated, therefore, not when treatment starts, but at first assessment. This is a problem common to many of the first episode studies. The consequence of this may be that the difference between the two assessment points regarding symptom level will be less, since many patients are already stabilized at the baseline assessment. This has an advantage of eliminating some of the acute phase variation, which is often noise in the statistical analyses.

7.5 Challenges in statistical methods

Correlation, differences between groups, and linear regression are the statistical methods mostly used to analyze the data in this thesis. In addition, a factor analytic method was used in Paper 1.

Both inequality in group sizes and the relative small sample size (ranging between 71 in Paper 3 and 104 in Paper 1) make the data vulnerable to outliers and skewed data, which can give rise to both Type I and Type II errors. This needs to be considered when interpreting results, and is commented on separately in the result section. Many of the results presented in the thesis are based on cross sectional analyses, and, hence, cannot speak to the direction of significant associations. In Study 4, follow up data was used in order to be able to answer the direction of the association between apathy and other variables.

7.6 Representativity and generalizability

The study consisted of 104 patients included over a 2-year period, consecutively recruited as they were coming in to treatment for their first episode of psychosis. In the first year, recruitment of patients was from two hospitals in Oslo covering one catchment area each (Ullevål : population = 190.000, Diakonhjemmet : population = 115.000) and the second year, a third hospital joined covering a third catchment area (Aker: population = 160.000). The three clinicians worked closely with the clinical staff at each hospital, assuring that all potential patients were asked. The study is based on written informed consent and no records were kept of those declining to participate. Thirty-seven patients were included the first year (total population 305.000) and 67 the second year (total population 480.000), which gives a yearly incidence of 12/100000 and 14/100000. The former Treatment and Intervention in Psychosis study (TIPS) recruited from one of the catchment areas (Ullevål) from 1997 to 2000, and their incidence range between 12-17 pr 100000 over a four year period (86), which is reduced to 11 pr 100000 when only those consenting are included (personal communication from professor Svein Friis). Our incidence rate is thus similar to that of the TIPS study. A recent review of annual incidence rates for schizophrenia found a median of 11.1 / 100000, with a range of 4.8 to 22.6 (199). Compared to this, our results are in the lower range, since only about a half of the sample had a diagnosis of schizophrenia at baseline. Of the original cohort of 104, 84 came for the one year follow up assessment giving a response rate of 81 %, which is about

the same as the TIPS study and others (200;201). This also adds to the representativity of our data. Despite the above limitations, with no record of those declining, and an incidence rate in the lower range, we regard our sample as representative for first episode psychosis patients from a large catchment area, and that the results can be generalized for the whole population of first episode patients.

8. Discussion of main results

There are seven important findings in the thesis. The first finding is that the negative symptom of apathy can be reliably and validly assessed with the abridged AES, the AES-C-Apathy in first episode patients. The second finding of importance is that high levels of apathy are prominent in first episode both at baseline assessment and after one year, and with the highest mean AES-C-Apathy score in the Schizophrenia spectrum group. Thirdly, high levels of apathy are strongly associated with poor functioning both at baseline and follow up. The fourth is that AES-C-Apathy correlates significantly only with tests of executive function and working memory, and not other neurocognitive tests. The fifth finding is that, despite significant associations between apathy and co-occurring states, these associations seem to have only minor to no influence on the significant associations between apathy and executive function and GAF-F. The sixth is that the group with enduring apathy consists of significantly more males, more have a diagnosis within the schizophrenia spectrum patients, have a longer DUP, fewer are in remission, and they have worse functioning both at baseline and at follow up. Lastly, that high levels of apathy at the one year follow up are best predicted by baseline level of apathy, a long DUP and a Schizophrenia spectrum diagnosis.

8.1 The negative sub symptom of apathy can be reliably and validly assessed with an abridged AES, the AES-C-Apathy in first episode psychosis patients

This is the first study testing the psychometric properties of the clinical version of the AES-C in first episode psychosis patients. We found good psychometric properties with good internal consistency and convergent and discriminative ability, much the same as was found in the study by Kiang et al in

patients with chronic schizophrenia (39), in the original study by Marin and others (126;164;202) and as concluded in a recent review of the AES-C (203). Factor analysis gave one main factor, also the same as found in other studies (126;132;164;204), and with considerable overlap between the studies in the retained items in the main factor (126;202). There is also overlap between the studies in that items of social contact and insight belong to the minor factors (126). As can be seen in Table 4.1 and 4.4-4.7 in the Appendix, the content of the items in the AES-C-Apathy corresponds well with other apathy scales in use, which supports the use of the abridged version rather than the full length scale.

There are some methodological limitations in our psychometric testing of the AES that need to be mentioned. As discussed under 7.1.2, one limitation is that the clinical interviews and scoring of the AES and the PANSS were done by the same person. Ideally, they should have been assessed by different persons blind to the others' ratings in order to secure unbiased scoring of apathy. This weakness is partly compensated by the fact that there are clear differences between the PANSS and the AES in how they assess apathy. As can be seen in Table 4.2 in the Appendix, PANSS has not assigned a specific item to apathy; rather apathy is a one of several words used to describe a behavior in three of the seven items making up the PANSS negative subscale. Also, assessment of PANSS negative items is based mainly on observation, while the AES actively asks the patient about his/her experience. The second limitation is that we have not tested the specificity and sensitivity of our cut off score against a clinical judgment of apathy. Our cut off score is based on standard deviation from a mean value with a cut off score of 27 for the abridged AES-C-Apathy, corresponding to 39 for the full AES-C. Different methods can be applied when determining a cut off score for a scale (180). Different cut off scores for the AES-C exist, ranging from 34 (132;134;152) to 41 (202) and one study has found difficulties with finding a clinically meaningful cut off score for the AES when validated against a clinical judgment (204). Our cut off score is, thus, in the upper end, securing that we have not over reported the frequency of apathy. But with so many different cut off

scores for the AES, there is a clear need for a clinical validation. Despite the above shortcomings, the AES was found to have sound psychometric properties and we recommend the use of the abridged AES-C-Apathy for assessment of apathy in first episode patients.

8.2 High levels of apathy are prominent in first episode psychosis patients and with the highest level in the Schizophrenia spectrum group

Fifty percent of the first episode psychosis patients at baseline, and 40% at one year follow up, were considered clinically apathetic. Fennig et al is the only other study found to report on the frequency of apathy in first episode psychosis patients at baseline (27), finding that 61% of patients diagnosed with schizophrenia had a score of 3 or more on the SANS avolition/apathy subscale. For the other diagnostic groups the frequency ranged between 53% in the schizoaffective to 13% in the bipolar group. Our frequency is slightly lower than in this study, but we report for the whole group of patients, and not on the diagnostic level, which can partly explain this difference.

The Schizophrenia spectrum patients had the highest mean AES-C-Apathy score both at baseline and follow up of the three diagnostic groups. The score was statistically significantly higher compared to the Other psychosis group both at baseline and follow up, and to the Affective group at follow up. These results must be interpreted with some caution due to small group size for the Affective and Other psychosis groups. However, the differences are in line with Fennig et al, who also found the highest rating of apathy in patients with schizophrenia compared to other diagnostic groups (27). Apathy can also be a psychological reaction to extreme life events and is often thought of as a reaction to being seriously ill. Schizophrenia is a serious illness, and the high level of apathy in this group could reflect such a reaction. But there are also good reasons to think that some of the difference in mean apathy score reflects differences in underlying psychopathology. Apathy is considered to reflect lesions of the prefrontal cortex and there is much evidence for schizophrenia being a disorder involving the prefrontal cortex, more so than for affective disorders and other psychosis. Also, other brain disorders have found significant differences in apathy score between site

of lesion and diagnostic groups and with higher scores when the prefrontal cortex is involved. (126;132). However, these differences need to be further explored before a firm conclusion can be drawn.

8.3 Apathy is strongly associated with poor functioning both at baseline and at one year follow up

This study replicates the significant association between high levels of apathy and poor functioning, as was found in the study by Kiang et al of chronic patients with schizophrenia (39). The significant association between negative symptoms and poor functioning in first episode patients is well documented (21;24;101). In our study, PANSS negative symptoms had a significant association to GAF-F in the univariate analysis, but in the multivariate analysis, with AES-C-Apathy as one of the other independent variables, the association became non significant. Apathy thus shows a stronger association to functioning than the broader measure of PANSS negative factor, which points to the advantage of assessing the different negative sub symptoms and not the concept as a whole. We were not able to assess the other negative symptoms at the same level of accuracy, and hence study their interaction and how they differently may contribute to poor functioning. This is a problem with most of the current literature in the area, and needs to be explored further, before we fully can understand the interaction between negative symptoms and poor functioning.

Different studies of apathy in other brain disorders, regardless of assessment instruments used, have found significant associations to functioning (205). These results, together with our study, point to the importance of apathy and a possible common influence from apathy on functioning across disorders.

This study did not explore the influence of other variables, together with apathy, on poor functioning. Poor premorbid functioning (187;206), long DUP(71;207) and cognitive dysfunction (100;208) have all been found to be significantly associated with poor functioning. The combined influence also needs to be explored further to give a more complete picture of the mechanisms

behind poor functioning. Despite these shortcomings, the repeated results, both at baseline and follow up, underline the importance of apathy for functioning in psychotic disorders, a relationship that many have proposed to be important, but that has not been studied in first episode psychosis patients before.

8.4 High levels of apathy correlate significantly with tests of executive function and working memory, and not other neurocognitive tests

This study replicated the findings of Roth et al of a significant association between apathy and executive dysfunction in patients with psychotic disorders (40), this despite the two studies using different measures, and the Roth et al study including chronic patients. In both studies, the association was independent of degree of depression. This same association between apathy and executive functioning has also been found in numerous studies in other brain disorders (43;44;134). Several of these studies used the verbal fluency tests (43;44;141;150), and in two of these studies apathy was assessed with the AES(44;150), eliminating the challenge of comparing results between different scales. This supports the idea of a common underlying psychopathology for apathy across disorders involving the prefrontal cortex, since executive function tests are found to reflect lesions from this area. It needs to be explored if other negative symptoms have the same associations.

8.5 Apathy and co occurring depression, positive symptoms and medication

In clinical work, apathy is difficult to differentiate from depression, reaction to psychotic symptoms, degree and side effects of medication and the presence of apathy has often been considered secondary to these states (125;154). This thesis did not aim at fully studying the interaction between apathy and co-occurring states but, rather, their influence upon significant associations between apathy and general functioning, apathy and cognitive function, and in prediction of apathy at one year. The bivariate relationship between AES-C-Apathy and the variables representing these co-occurring states [PANSS-depressive, PANSS-positive, DDD (daily dose of antipsychotic medication), UKU-neuro (neurological side effects) and UKU-Autonom (autonomic side effects)] was mostly found

to be significant, and the strength of the association increased from baseline to follow up. Despite the correlation, their influence on the significant association between apathy and executive function and GAF-F, was found to be minor or mostly negligible. This results adds to the importance of treating apathy as an independent symptom in need of its own treatment interventions (209).

Of special interest has been the relationship between apathy and depression (153;154). Studies have shown that one can be both apathetic and depressed at the same time, and that many who are apathetic are not depressed and vice versa (132;155;210-212). The affective component of psychosis was highlighted by E. Bleuler, who addressed anhedonia and flat affect as a fundamental symptom of psychosis (135). Only recently have the interaction between affect and motivation been explored (22;36), relationships that are of special interest for a better understanding of the underlying mechanisms of negative symptoms.

8.6 Patient characteristics of the group with enduring apathy

We found that 30% of the first episode patients had enduring high levels of apathy over the first year. Enduring high levels of negative symptoms over the first year for first episode patients has been investigated in three previous studies (21;28;98). Of these, Malla et al's study required the stability of one of the SANS sub scores and found a rate of 23% (98). The Gerbaldo et al study found a rate of 31% (28), applying the Scale for the Deficit Syndrome (SDS) (103), which requires stability of two sub symptoms. Depending on method used, Edwards et al have found the rate of enduring negative symptoms to vary between 3.8% to 41.2% (21). Our results are, thus, within the range of what is found in other studies. Our study is best compared with Malla et al's, since they studied only one of the negative symptoms. However, none of these studies specified which of the different negative symptoms were enduring and direct comparison, therefore, is difficult.

The group with enduring apathy is characterized by having significantly more males, a longer DUP, a greater likelihood of Schizophrenia spectrum diagnosis, fewer subjects in remission of positive

symptoms, and poorer functioning; the same patient characteristics as found for enduring negative symptoms and the deficit syndrome.

This study was not designed to specifically answer the question of a primary versus a secondary origin for apathy, but many of the results in our study give argument for considering apathy to be a primary symptom reflecting underlying psychopathology and not a symptom of co-occurring states. The findings supporting this are that a) premorbid social functioning were significantly associated with high apathy levels at baseline b) a high proportion of patients already at start of treatment are considered apathetic, c) the differences between the diagnostic groups and that the highest mean level of apathy were found among patients with Schizophrenia spectrum diagnosis, d) the group with enduring high levels of apathy has the same characteristics as found for enduring negative symptoms e) the significant association to executive functioning as also found in other brain disorders independent of co-occurring states; and, lastly, f) its strong and independent association to poor functioning both at baseline and follow up. Enduring negative symptoms have, for a long time, been synonymous with “permanent ” and being resistant to treatment, while secondary have led to focus on the co-occurring states and more or less ignoring the presence of negative symptoms (61). This dichotic division of the negative symptoms needs to be challenged. In our study, the level of apathy was reduced at follow up for half of those with high levels at baseline, indicating that apathy is a symptom that changes. What makes it change is important to study further. Many factors can contribute to the durability. One suggested mechanism is the experience over time that gives rise to negative expectancy appraisals (213-215). To seek further support for this may be a fruitful path in the search for effective treatments of apathy and also other negative symptoms (216), since development of new medications may be years away.

8.7 High levels of apathy at the one year follow up is best predicted by baseline level of apathy, a long DUP and a Schizophrenia spectrum diagnosis

Signs or symptoms that can predict the outcome are of importance for medical practice and allocation of resources. This study found that high apathy levels are strongly associated with poor functioning and that those with enduring high levels of apathy had a poorer outcome than the other patients. High apathy levels at one year were best predicted by a high baseline level of apathy, long duration of untreated psychosis and a schizophrenia spectrum diagnosis. Being male had significant predictive influence before controlling for baseline levels of apathy. The same variables that predict high levels of apathy at follow up are similar to variables that characterize those with enduring levels of apathy. Identifying those at risk of enduring apathy, and hence poor functioning, should therefore be possible at the start of treatment. This may be important in allocating resources to those most in need and explaining why motivation is low and goals take a longer time to achieve.

9 Strengths and weaknesses of the study

The study has its strength in being catchment-area based in a health system where no private hospitals operate; thus securing representativity for the population seeking help. We have both cross sectional - and follow up data, and a high response rate. Assessments were done by a few, all with long clinical experience and with extensive training through the whole inclusion period and with good to excellent inter rater reliability for tested assessment instruments. The AES was found to have the same good psychometric properties as found in other patient populations making it a reliable scale for assessment of apathy. The main weakness is that inclusion was possible up to a year after start of adequate treatment, and that we were not able to study other negative symptoms and how they interact with the results found for apathy. Also, the lack of recording those that declined to participate is a weakness. Apathy and functioning should have ideally been assessed by independent raters, and the cut off score of the AES-C-Apathy for being apathetic needed a clinical validation.

10 Implications

10.1 Clinical implications

This study has important clinical implications in that it shows that apathy can be reliably assessed, is present already at an early phase of treatment in first episode psychosis patients, has serious influence on functioning, and that the group in danger of enduring apathy and poor functioning can be identified early after coming into treatment. The AES has a larger potential to serve as a starting point for interventions than the PANSS negative subscale. Apathy is a common phenomenon that can be discussed with the patient, whereas the PANSS ratings do not adequately communicate which behavior is diminished. The assessment of apathy can be used in the clinical work with the patient, his family and others, in the understanding of why goals may be hard to achieve, and to find new ways of increasing motivation. The consequences of high levels of apathy are most obviously seen in the group with enduring high levels of apathy, where only 16% were studying or working at start of treatment compared to 54% in the non-enduring group. It is reasonable to think that apathy is present in the premorbid phase and that focusing not only on positive symptoms but also on negative symptoms in early intervention programs is needed. There is currently no evidence-based treatment for apathy (209). Different interventions are currently being tested in other brain disorders that could also work as models for the field of psychiatry, since at least some of the underlying mechanisms seem to be of common origin.

10.2 Implications for future work

The finding of a reliable scale to assess apathy in psychotic disorders has implications for the ongoing work in exploring the boundaries between the individual negative symptoms and their underlying mechanisms. Apathy may also serve as a more proximate target to pathophysiology than the negative symptoms, and has the advantage of being a clinically feasible and easily measured concept. It can thus serve as a test case for new drugs and specific psychosocial interventions. This study also shows that much is still unknown regarding the nature of apathy. Why does the level of apathy

fluctuate for some? Why is it more enduringly high for others? At what stage in development of psychosis does apathy start to influence functioning? And is there a common mechanism for all patients with apathy that can tell us something more about how the brain works? But, probably, the largest challenge for the future is to implement these results into the clinical work.

11. Conclusions

- *Apathy can be reliably assessed in first episode psychosis patients with the AES-C-Apathy, the shortened AES.*
- *Apathy is an important symptom in first episode psychosis patients that needs attention from the start of treatment*
 - *A strikingly high proportion of first episode patients are apathetic at first assessment and after one year.*
 - *High levels of apathy have a strong association to functioning, both at first assessment and after one year.*
- *The group at risk of high levels of apathy after one year can be identified by having a high AES-C-Apathy score at baseline, having a long DUP and a schizophrenia spectrum diagnosis*
- *There are strong indications that apathy is a primary symptom reflecting underlying pathophysiology and not secondary to other co-occurring states*
 - *Clinical variables with significant associations to apathy have also been found to have significant relationships to underlying pathology*
 - *Apathy is related to poor executive function*

- *Positive symptoms, depression, degree of medication and side effects do, only to a minor degree, interfere with the significant associations between apathy and other clinical variables*

Appendix

Table 1: Diagnostic criteria for psychotic disorders (DSM-IV)

Schizophrenia		
Criteria	A	<i>Characteristic symptoms:</i> Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated): 1)delusions 2) hallucinations 3)disorganized speech 4)grossly disorganized or catatonic behavior 5)negative symptoms i.e., affective flattening, avolition and anhedonia
	B	<i>Social occupational dysfunction:</i> for a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self care are markedly below the level of achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement
	C	<i>Duration:</i> Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed under criterion A presented in an attenuated form.
	D	<i>Schizoaffective and Mood disorder exclusion:</i> Schizoaffective Disorder and Mood disorder with psychotic features have been ruled out because either 1) no Major depressive, Manic or Mixed Episodes have occurred concurrently with the active phase symptoms; or 2) if mood episodes have occurred during active phase symptoms, their total duration has been brief relative to the duration of the active and residual periods
	E	<i>Substance/general medical condition exclusion:</i> The disturbance is not due to the direct physiological effects of a substance (e-g drug of abuse, a medication) or a general medical condition
	F	<i>Relationship to a pervasive Developmental disorder:</i> If there is a history of Autistic Disorder or another pervasive Developmental disorder, the additional diagnosis of Schizophrenia is made only if prominent delusional or hallucinations are present for at least a month (or less if successfully treated)
Schizophreniform disorder		
	A	Criteria A,D and E for schizophrenia are met
	B	An episode of the disorder (including prodromal, active, and residual phases) lasts at least 1 month but less than 6 months
Schizoaffective Disorder		
	A	An uninterrupted period of illness during which, at some time, there is either a Major Depressive Episode, a Manic Episode, or a Mixed Episode concurrent with symptoms that meet Criterion A for schizophrenia
	B	During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms
	C	Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and the residual periods of the illness
	D	The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or general medical condition.
Delusional disorder		
	A	No bizarre delusions (i.e. involving situations that occur in real life, such as being followed, poisoned, infected, loved at a distance, or deceived by spouse or lover, or having a disease) of at least 1 month's duration
	B	Criterion A for Schizophrenia has never been met
	C	Apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired and behavior is not obviously odd or bizarre
	D	If mood episodes have occurred concurrently with delusions, their total duration has been brief relative to the duration of the delusional periods
	E	The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition
Brief Psychotic Disorder		
	A	Presence of one of the following 1)delusions 2)hallucinations 3)disorganized speech 4)grossly disorganized or catatonic behavior
	B	Duration of an episode of the disturbance is at least 1 day but less than a month, with eventual return to premorbid level of functioning
	C	The disturbance is not better accounted for by a Mood Disorder with Psychotic features, Schizoaffective Disorder, or Schizophrenia and is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or general medical condition
Shared psychotic Disorder (Folie a Deux)		
	A	A delusional develops in an individual in the context of a close relationship with another persons (s), who has an already-established delusion.
	B	The delusion is similar in content to that of the person who already has the established delusions
	C	The disturbance is not better accounted for another Psychotic Disorder (e.g. Schizophrenia) or a Mood

	Disorder With Psychotic Features and is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or general medical condition
Psychotic Disorder Due to a General Medical Condition	
A	Prominent hallucinations or delusions
B	There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition
C	The disturbance is not better accounted for by another mental disorder
D	The disturbance does not occur exclusive during the course of delirium
Substance-Induced Psychotic Disorder	
A	Prominent hallucinations or delusions
B	There is evidence from the history, physical examination, or laboratory findings of either 1) or 2): 1) the symptoms in Criterion A developed during, or within a month of Substance Intoxication or Withdrawal 2) medication use is etiologically related to the disturbance
C	The disturbance is not better accounted for by a Psychotic Disorder that is not substance induced. Evidence that the symptoms are better accounted for by a Psychotic Disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g. about a month) after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration use; or there is other evidence that suggests the existence of an independent non-substance-induced Psychotic Disorder
D	The disorder does not occur exclusively during the course of a delirium
Psychotic Disorders not Otherwise Specified	
	This category include psychotic symptomatology about which there is inadequate information to make a specific diagnosis or about which there is contradictory information, or disorders with psychotic symptoms that do not meet criteria for any specific Psychotic disorder
1	Postpartum psychosis that does not meet criteria for Mood Disorders with Psychotic features, Brief Psychotic Disorder, Psychotic Disorder Due to a General Medical Condition, or Substance-Induced psychotic Disorder
2	Psychotic Symptoms that have lasted for less than 1 month but have not yet remitted, so that criteria for Brief Psychotic Disorders are not met
3	Persistent auditory hallucinations in the absence of any other features
4	Persistent non-bizarre delusions with periods of overlapping mood episodes that have been present for a substantial portion of the delusional disturbance
5	Situations in which the clinical has concluded that the Psychotic Disorder is present, but is unable to determine whether it is primary, due to a general medical condition, or substance induced

Table 2: Demographics for each study

Data given as either N(%) or mean (\pm SD)	Paper 1	Paper 2	Paper 3	Paper 4	
Patients (N)	104	103	71	84	
Male	61 (57 %)	60 (58 %)	37(52 %)	50 (60 %)	
Age	27.3 (\pm 7.7)	27.3 (\pm 7.7)	27.4 (\pm 8.1)	27.4 (\pm 8.2)	
Years of education	13.0 (\pm 2.7)	13.0(\pm 2.7)	12.5 (\pm 2.7)	12.8 (\pm 2.7)	
Living alone			63(89%)		
Premorbid Functioning					
PAS social cluster childhood		1.4(\pm 1.6)		1.5(\pm 1.6)	
PAS social cluster early adolescence		1.3(\pm 1.4)		1.1(\pm 1.3)	
PAS social cluster adolescence		1.7(\pm 1.5)		1.5(\pm 1.3)	
PAS academic cluster childhood		1.6(\pm 1.2)		1.7(\pm 1.2)	
PAS academic cluster early adol		2.0(\pm 1.3)		1.9(\pm 1.4)	
PAS academic cluster adolescence		2.3(\pm 1.4)		2.1(\pm 1.4)	
Duration untreated psychosis weeks (median range)	35 (1-1040)	35(1-1040)	30 (1-1040)	35(1-1040)	
Hospitalized for psychosis	69 (66%)	69(67%)		53 (63%)	
	Baseline	Baseline	Baseline	Baseline / 1 year	
Diagnostic categories					
Schizophrenia Spectrum		57(55%)	36 (51%)	45(54%)	53(63%)
Schizophrenia		45(43.7%)		35(41.6%)	45(53.5%)
Schizoaffective		2(1.9%)		2(2.3%)	7(8.3%)
Schizophreniform		10(9.7%)		8(9.5%)	1(1.2%)
Affective Psychosis		17(17%)	15 (21%)	16(19%)	17(20%)
Major affective		14(13.5%)		13(15.4%)	11(13.1%)
Bipolar I		3(2.9%)		3(3.6%)	6 (7.1%)
Other psychosis		29(28%)	20 (28%)	23(27%)	14(17%)
Psychosis NOS		20(19.4%)		16(19.0%)	8 (9.5%)
Brief Psychosis		7(6.8%)		6(7.1%)	5(6%)
Delusional disorder		2(1.9%)		1(1.2%)	1(1.2%)
AES-C-Apathy	27.1(\pm 7.2)	27.2(\pm 7.1)	27.2(\pm 7.1)	27(\pm 7.4)	24.9(\pm 6.9)
PANSS total score	60.7 (\pm 14.6)	60.9 (\pm 14.5)	60.5(15.1)	61.6(\pm 15.1)	53.5(+14.6)
PANSS-positive		14.7 (\pm 5.2)		15.2(\pm 6.0)	12.7(\pm 6.3)
PANSS-disorganized		11.1 (\pm 3.6)		11.2(\pm 3.7)	10.4(\pm 3.7)
PANSS-negative		16.5 (\pm 6.6)		16.9(\pm 6.8)	15.1(\pm 5.7)
PANSS-depressive		12.4 (\pm 4.1)		12.6(\pm 4.2)	10.6(\pm 4.2)
PANSS-excitement		5.6 (\pm 1.99)		5.5(\pm 1.9)	5.0(\pm 1.9)
Alcohol misuse or depend		12 (11.7%)		12(14.3%)	8(9.5%)
Drug misuse or depend		22 (21.4%)		18(21.4%)	15(17.9%)
Using antipsychotic medication	82(79%)	81(78.6%)	57(80.3)	65(78.8%)	57(67.8%)
DDD-AP		1.0(\pm 0.6)	1.1(0.6)	1.0(\pm 0.6)	0.3(\pm 0.9)
UKU-neuro				1.1(\pm 1.4)	0.5(\pm 0.8)
UKU-autonom				2.2(\pm 2.2)	2.0(\pm 2.4)
GAF-S (mean,SD)	42.1(\pm 12.8)	41.9 (\pm 12.7)	42.8 (14.0)	42.4(13.1)	53.7 (16.5)
GAF-F (mean, SD)	45.7(+14.0)	45.5 (+12.7)	46.1 (46.1)	45.6(14.1)	54.3 (15.8)
Controls (N)		62			
Male N (%)		28(45%)			
Age (mean,SD)		32(\pm 9.3)			
Years of education (mean,SD)		13.9(\pm 1.9)			
AES-S-Apathy (mean,SD)		18.0(\pm 4.3)			

^aPAS Premorbid Assessment of Functioning Scale; ^b Alcohol and Drug use scale: a score >3 indicate misuse or dependence

Table 3: Clinical assessments and statistical methods for each study

	Paper 1	Paper 2	Paper 3	Paper 4
Clinical measures	SCID PANSS AES-C	PAS DUP SCID PANSS AES-C AES-S Alcohol and Drug use scale GAF- S /GAF-F	SCID PANSS CDSS AES-C	PAS DUP SCID PANSS AES-C Alcohol and Drug use scale GAF-S/GAF-F UKU
Design	Cross sectional	Cross sectional	Cross sectional	Follow up
Statistical analysis	Correlation Principal factor analysis with Varimax rotation Cronbach's α	Correlation Differences continuous variables: Independent Students t- tests ANOVA Paired sample t-test Linear regression	Correlation Linear regression	Correlation Differences continuous variables: Independent Students t-test ANOVA Paired sample t-test Group differences: Chi-squared test Mann Whitney U-test Linear regression

Table 4.1

AES	Apathy Evaluation Scale
1	S/he is interested in things
2	S/he gets things done during the day
3	Getting things started on his/her own is important to him/her
4	S/he is interested in having new experiences
5	S/he is interested in learning new things
6	S/he puts little effort into things
7	S/he approaches life with intensity
8	Seeing a job through to the end is important to her/him
9	S/he spends time doing things that interest her/him
10	Someone has to tell her/him what to do each day
11	S/he is less concerned about her/his problem
12	S/he has friends
13	Getting together with friends is important to her/him
14	When something good happens, s/he gets excited
15	S/he has an accurate understanding of her/his problem
16	Getting things done during the day is important to her/him
17	S/he has initiative
18	S/he has motivation

Table 4.2

PANSS	Negative subscale
N1	<i>Blunted affect</i> : Diminished emotional responsiveness as characterized by a reduction in facial expression, modulation of feelings, and communicative gestures
N2	<i>Emotional withdrawal</i> : Lack of interest in, involvement with, and affective commitment to life's events
N3	<i>Poor rapport</i> : Lack of interpersonal empathy, openness in conversation, and sense of closeness, interest or involvement with the interviewer
N4	<i>Passive/apathetic social withdrawal</i> : Diminished interest and initiative in social interactions due to passivity, apathy, anergy or avolition. This leads to reduced interpersonal involvements and neglect of activities of daily living
N5	<i>Difficulty in abstract thinking</i> : Impairment in the use of abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalizations, and proceeding beyond concrete or egocentric thinking in problem-solving tasks
N6	<i>Lack of spontaneity and flow of conversation</i> : Reduction in the normal flow of communication associated with apathy, avolition, defensiveness cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal-interactive process
N7	<i>Stereotyped thinking</i> . Reduction in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive deficit. This is manifested by diminished fluidity and productivity in the verbal interaction

Table 4.3

SANS	Avolition-Apathy Subscale
1	<i>Grooming hygiene:</i> The patient's clothes may be sloppy or soiled, and he or she may have greasy hair, body odor, etc
2	<i>Impersistence at work or school (relative to general population):</i> Based on the patient's age and sex, rate the degree to which the patient has difficulty in seeking or maintaining employment, attending school, keeping house or engage in volunteer work
3	<i>Physical Anergia:</i> The patient tends to be physically inert. He or she may sit for hours and does not initiate spontaneous activity
	<i>Global rating of Avolition-Apathy:</i> Strong weight may be given to one or two prominent symptoms if particularly striking

Table 4.4

AS	The Apathy Scale
1	Are you interested in learning new things?
2	Does anything interest you?
3	Are you concerned about your condition?
4	Do you put much effort into things?
5	Are you always looking for something to do?
6	Do you have plans and goals for the future?
7	Do you have motivation?
8	Do you have the energy for daily activities?
9	Does someone have to tell you what to do each day?
10	Are you indifferent to things?
11	Are you unconcerned with many things?
12	Do you need a push to get started on things?
13	Are you neither happy nor sad, just in between?
14	Would you consider yourself apathetic?

Table 4.5

DAIR	The Dementia Apathy Interview and Rating
1	Does s/he seem indifferent to what is going on around her/him?
2	Does it seem important to her/him to succeed in things s/he tries to do?
3	Does s/he tend to just sit and do nothing?
4	Does s/he seem less active?
5	Is s/he able to keep busy during the day?
6	Will s/he start activities on her/his own?
7	Are there things s/he is enthusiastic about?
8	Does s/he show a full range of emotions?
9	Does she no longer seem to react to things as much as s/he used to prior to illness?
10	Does she start conversations?
11	Is she less spontaneous?
12	Does she show interest in news about friends and relatives?
13	Does she suggest things to do for the day?
14	Does she enjoy things she can do as much as she used to before the illness began?
15	Is she concerned about how people feel?
16	Does she seem to care less about finishing things that she has started?

Table 4.6

NPI	Apathy / Indifference subscale
Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or does he/she lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent? If yes, proceed	
1	Does the patient seem less spontaneous and less active than usual?
2	Is the patient less likely to initiate a conversation?
3	Is the patient less affectionate or lacking emotions when compared to his/her normal self?
4	Does the patient contribute less to household chores?
5	Does the patient seem less interested in the activities and plans of others?
6	Has the patient lost interest in friends and family members?
7	Is the patient less enthusiastic about his/her usual interests?
8	Does the patient show any sign other signs that he/she doesn't care about things?

Table 4.7

Diagnostic criteria for Apathy
<p>A: Loss of, or diminished, motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.</p>
<p>B: Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time</p>
<p>Domain B1: <i>Loss of, or diminished, goal-directed behavior as evidenced by at least one of the following:</i> - Loss of self-initiated behavior (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices) - Loss of environment-stimulated behavior (for example: responding to conversation, participating in social activities)</p>
<p>Domain B2: <i>Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:</i> - Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs). - Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the persons residence, neighborhood or community).</p>
<p>Domain B3: <i>Loss of, or diminished, emotion as evidenced by at least one of the following:</i> - Loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect) - Loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)</p>
<p>C: These symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.</p>
<p>D: The symptoms (A - B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication).</p>

Errata

The printed version of this thesis is a reprint of the originally submitted thesis to the University of Oslo. The following changes (seen in bold) have been made:

1) Thesis

p 8, line 21: Confidence

p19, line 24: Table 4.2 in the Appendix

p20, line 2: functioning (**40**), while

p 23, line 12: PANSS

p28, line 8: N4, **N6**,G7

p51, line 15: AES-C-Apathy score **at baseline**,

p51, line 21: functioning

2) Papers

Paper 2

p 8, line 7: G7, **G13** and G16

p13, line 19: Type **II** error

Table 1

“Other psychosis” should be **29**, not 27.

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Apathy and functioning in first episode psychosis

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Abstract

Objective: To determine which patient characteristics relates to higher levels of apathy, to which degree first episode psychosis patients are apathetic compared to healthy controls and to which degree apathy together with other symptoms including negative subsymptoms influences functioning in first episode psychosis.

Method: The study includes 103 first episode psychosis patients and 62 healthy control persons participating in the Norwegian Thematically Organized Psychosis research study. Apathy was assessed with the abridged Apathy Evaluation Scale (AES-C-Apathy). Other clinical symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS). The PANSS five-factor model was used in the subsequent analyses. Functioning was assessed with the split version of Global Assessment of Functioning scale (GAF-F).

Results: More than 50% of first episode psychosis patients were found to be clinically apathetic compared with healthy controls. Of all clinical variables, only premorbid childhood social functioning, change in social functioning and disorganized symptoms (PANSS disorganized component) had a significant influence on AES-C-Apathy, explaining 18% of the variance. Multiple regression analysis revealed that of the entire five different PANSS symptoms, only PANSS positive component together with AES-C-Apathy made significant independent contribution to GAF-F, explaining 37% of the variance. Using the same model, only N1 (flat affect) of the different items comprised by the PANSS negative component made an independent significant contribution to functioning. **Conclusion:** Apathy is a prevalent symptom in first episode psychosis

with a significant association to real life functioning, and its presence and consequences should thus be evaluated at the start of treatment.

Keywords: First episode psychosis, apathy, negative symptoms, premorbid function, global function, self-assessed function

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Introduction

The high risk of prominent functional decline makes schizophrenia one of the most disabling disorders affecting young people [1,2]. Negative symptoms are found to be one of the major predictors of poor functioning across studies both in chronic patients [3-5] and in patients with first episode psychosis [6,7]. The importance of this area is illustrated by the recent NIMH-MATRICES consensus statement on negative symptoms, which concluded that there has been limited progress in the development of effective treatments [8]. Both the consensus statement and other clinical researchers [9-11] argue that we need to shift focus from regarding negative symptoms as a unitary construct and instead study the different components or subsymptoms that underlie the symptom area. The concept of negative symptoms is old [12], but was re-introduced as a meaningful concept at the end of the 1970's [13] to explain the heterogeneity of symptoms and outcome in schizophrenia [14]. We know that negative symptoms is not a unitary construct but a syndrome made up of different subsymptoms, mainly apathy/avolition, anhedonia, alogia, asociality, flat affect and inattention [14]. Our knowledge of the underlying mechanisms behind these subsymptoms are limited [8].

Apathy is a neuropsychiatric symptom associated with dysfunction of the prefrontal cortex or its subcortical connections [15-17]. Apathy is found to be a common symptom in a broad range of neuropsychiatric- or brain disorders such as Alzheimer's dementia [18], Parkinson's disease [19], Huntington's diseases [20], and in traumatic brain damage [21]. Already Kraepelin considered apathy to be the core symptom of the chronic stages of schizophrenia [22], a view that is also held and emphasized today [23-25].

One challenge for the study of negative symptoms and subsymptoms has been the lack of valid and reliable rating scales for use in clinical settings [11,26]. The Apathy Evaluation Scale (AES) was developed to assess apathy in neuropsychiatric disorders [27] and has been widely used in studies of apathy [19,21,28]. In the AES, apathy is defined as “lack of motivation or goal directed behavior not attributable to diminished level of consciousness, cognitive impairment or emotional distress”. The scale has been validated for use across different medical disciplines, and recently also for patients with first episode of psychosis [29] and chronic schizophrenia [30]. The availability of a well-validated assessment method for apathy makes it a good candidate for exploration of the mechanisms behind the development of negative symptoms.

The clinical importance of negative symptoms more broadly defined is based on their clear association to functional decline. An increase in knowledge about their underlying mechanism will thus aid our understanding of what lies behind the functional decline itself. To evaluate whether apathy is a good model system for understanding functional decline, it is of importance to know whether also apathy as a symptom is associated with decreased functioning. Apathy has been found to be clearly related to poor functioning in several neuropsychiatric disorders [18,31]. The only existing study addressing the relationship between apathy and functioning in schizophrenia, reported that apathy more than other symptoms predicted poor functioning in a group of chronic patients, indicating an association at least in this patient group [30].

However, to avoid the possible confounding influences of treatment failures and social defeat in chronic schizophrenia, it is of particular interest to study the relationship between apathy and functioning in a first episode psychosis patient group. The aim of the

present study is thus to answer the four following questions: Do first episode psychosis patients experience higher levels of apathy than persons without psychiatric disorders do? Do first episode psychosis patients with schizophrenia spectrum disorders have higher levels of apathy than patients with other first episode psychosis disorders? What other clinical characteristics (outside of diagnosis) are related to apathy in the early treatment phase? And finally to what degree does apathy contribute to functional loss in first episode psychosis patients?

Material and methods

Participants

Patient group: One hundred and three consecutively recruited first episode psychosis patients that had given written informed consent to participate in the ongoing Thematically Organized Psychosis research (TOP) study were included in the study. The patients were treated for a first episode psychosis between July 2004 and July 2006 in the catchment area based out- or inpatient psychiatric units of the three major hospitals in Oslo, Norway covering more than two-thirds of the city. Patients were eligible for the study if they were between 18 and 65 years, having a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis NOS, delusional disorder, brief psychosis or major depressive- or bipolar I disorder with mood incongruent psychotic symptoms. All the clinical assessments, including assessment of premorbid function and the duration of untreated psychosis were made after the start of adequate treatment and in a stable phase; hence, patients could be included into the study up to 52 weeks after start of adequate treatment. Patients were not included if they had on any occasion prior to inclusion in the study, been psychotic and treated with adequate

doses of antipsychotic medication for more than 12 weeks or until symptomatic remission if that was achieved before 12 weeks (in those cases they would be considered as patients treated for their second episode). The duration of untreated psychosis was measured from the first week with psychotic symptoms (i.e. having a rating of 4 or more on the PANSS items P1, P3, P5, P6 or G9) until the first week of adequate antipsychotic treatment, defined as either admission to hospital or starting adequate antipsychotic medication. The demographic, diagnostics and symptomatic distribution of the patient group is presented in Table 1.

Healthy control group: The 62 persons forming the healthy control group consisted of persons randomly selected from statistical records in the same catchment areas as the study patients. They were invited to participate by letter. The participants were screened with the Primary Care Evaluation of Mental Disorders [32], and were excluded if they, or any of their close relatives, had a lifetime history of a severe psychiatric disorder (schizophrenia, bipolar disorder and major depression), if they had a history of medical problems thought to interfere with brain function (hypothyroidism, uncontrolled hypertension or diabetes), or had recent cannabis use (used the last three months).

There was no significant difference in gender distribution between the patient group and the control group, but the control group was significantly older than the patients (mean difference 4.7 years, CI=1.6 - .9, $p=.002$) and had slightly more years of education (mean difference .9 years; CI=.2 -1.7, $p=.03$) (Table1).

General clinical assessment

Symptoms were assessed by the Structural Clinical Interview of the Positive And Negative Syndrome Scale (SCI-PANSS) [33]. Repeated factor analyses have

consistently indicated that the PANSS measures five symptom dimensions, but with some variations in the composition of the different dimensions in the different studies [34]. We chose to use the components based on Emsley et al's factor analysis of PANSS since this analysis was based on a first episode psychosis sample [35]. The components represent positive (PANSS-POS), negative (PANSS-NEG), disorganized (PANSS-DIS) depressive (PANSS-DEPR) and excited (PANSS-EXC) symptoms. In the follow-up analysis, the different items included in the PANSS-NEG (N1, N2, N3, N4, N6, G7, G13 and G16) were used to represent aspects of the different subsyptoms of negative symptoms.

Assessment of apathy

Apathy was assessed by the Apathy Evaluation scale (AES). The AES has several versions with identical questions but with different respondents; clinical- (AES-C), self- (AES-S), and informant rated (AES-I) [27]. All three versions have 18 identical questions to be answered on a likert scale ranging from 0 – 4 (0=not at all and 4=very much). Example of the questions are: “Are you interested in things?”, “Is it important for you to get things done during the day?”, “Do you spend time doing things that interest you?” and “Do you feel motivated?” In the self-report form, the respondents make their own direct assessments. In the clinician-based form, the respondents are interviewed to facilitate probing and evaluate the validity of the respondent's report (since apathy often coincides with disorders of insight and compromised self-evaluation). The clinician's rating is not based on observation of functioning, only on information about the respondent's feelings and experiences. For the control group we had no reasons to expect invalid information and only the self-report form was used. Both the self-report and

clinician rated form were used for the patient group to avoid the risk of underreports of amotivation. The two scales were highly intercorrelated ($r=.6$, $p<.01$).

We have previously shown that a shortened 12-item form of the clinical AES gave a better assessment of apathy than the full 18-item version in a first episode psychosis population [29]. The abridged version for both the clinical (AES-C-Apathy) and the self-rated (AES-S-Apathy) was therefore used in the present study. A score of 27 on both the AES-S-Apathy and AES-C-Apathy was used as the cut off value for being clinically apathetic based on this score being two standard deviations ($2\text{ SD}=8.6$) above the mean sum scores (mean= 18.0 ± 4.3) of AES-S-Apathy for controls.

Diagnostic assessment

Diagnosis was assessed with Structural Clinical Interview for DSM-IV (SCID-I interview) [36]. For the statistical analysis schizophrenia (N=45) schizophreniform (N=10) and schizoaffective disorder (N=2) were combined to “Schizophrenia spectrum” group; major affective disorder with mood incongruent psychotic symptoms (N=14) and bipolar I disorder with mood incongruent psychotic symptoms (N=3) to the “Affective psychosis” group; and psychosis NOS (N=20), brief psychosis (N=7) and delusional disorder (N=2) were to the “Other psychosis” group.

Assessment of drug use

The Alcohol and Drug use Scale, which separately measures drug and alcohol use the last six months [37], was used. The scores range from 1-5, with 1=no use, 2=use without impairment, 3=abuse, 4=dependence and 5=dependence with institutionalization.

Assessment of premorbid functioning

Premorbid functioning was assessed with the Premorbid Adjustment Scale (PAS) [38]. The premorbid phase was defined as the time from birth until 6 months before the onset of psychosis. The premorbid phase is divided into four life periods: childhood (up to 11 years), early adolescence (12–15 years), adolescence (16–18 years) and adulthood (19 years and beyond). The scores range from 0–6, with 0 indicating the best level of functioning and 6 the worst. Several studies have confirmed two basic dimensions in the PAS: social (PAS-Social cluster) and academic (PAS-Academic cluster) [39,40]. We used the method described by Larsen et al. when calculating separate sum scores for PAS-Social cluster and PAS-Academic cluster functioning [39], and the method of Haahr et al [41] to calculate change scores for social (PAS-Social-change) and academic functioning (PAS-Academic-change).

Assessment of global functioning

The function score from the split version of the Global Assessment of Functioning scale (GAF-F) was used to measure change in global functioning [42]. The split version has been found to discriminate adequately between symptoms and function [43] and has been used in other studies of first episode psychosis [44]. The GAF-F is a continuous scale ranging from 1–100, where 1 indicate the poorest- and 100 the highest functioning. The ratings are based on the assessor's evaluation of the patient's actual and functioning in concrete areas such as work, social contacts and independent living.

Procedures

All participants gave written informed consent to participate, and the Regional Committee approved the study for Medical Research Ethics and the Norwegian Data

Inspectorate. The data file has received an Audit Certificate from the Center for Clinical research at Ullevål University Hospital.

The three investigators that carried out the assessments completed the common training and reliability program in the TOP study group. Training in the use of AES was done by scoring videos, supervised by two experienced clinicians that had previously used the scale with other patient groups [21]. The reliability testing of the AES was completed by blind rating seven live interviews with randomly chosen patients from the study sample. The SCID training was based on the UCLA training program [45], and supervised by UCLA. For DSM-IV diagnostics, mean overall kappa for the standard diagnosis of training videos was $\kappa=.77$, and mean overall kappa for a randomly drawn subset of actual study patients was also $\kappa=.77$ (95% CI=.60 - .94). Inter-rater reliability was acceptable with Intra Class Coefficient ((ICC)1.1) for the different subscales: PANSS positive subscale =.82 (95% CI=.66 - .94), PANSS negative subscale=.76 (95% CI=.58 - .93), PANSS general subscale=.73 (95% CI=.54 - .90), GAF-S=.86 (95% CI=.77 - .92) GAF-F=.85 (95% CI=.76 - .92) and AES-C=.98 (95% CI=.92 - .99).

Statistical analyses

All analyses were done with SPSS version 16.0. Preliminary analyses were performed to examine the distribution of each variable. Logarithmic transformation was conducted when appropriate. Only duration of untreated psychosis required transformation to its natural logarithm, due to skewed data distribution. All tests were two tailed, with a preset level of significance of $p=.05$. Descriptive data are presented by either means and standard deviation (SD), or median and range when appropriate. Bivariate correlations were calculated as Pearson product moment coefficients (r). Independent sample t-tests,

paired sample t-tests and one-way ANOVAs with post-hoc Scheffe's test were used to analyze differences between groups.

Because several of the characteristics associated with measures of apathy and functioning (or both) were interdependent, the question of which patient characteristics that were independently related to apathy in the early treatment phase and to what degree apathy gave a specific contribution to the variation in functioning in first episode psychosis patients was explored through two separate multiple linear regression analyses. The independent variables were chosen for the regression analyses if they had a statistically significant correlation ($p < .05$) with the dependent variable in question (AES-C-Apathy and GAF-F, respectively) (Table 2). For the purpose of a uniform and easy to read table the relationship between all dependent variables and independent variables are in this table presented through their correlation coefficients (also for dichotomous variables). For research question three (which patient characteristics influence level of apathy), the independent variables were entered hierarchically in order of their life time appearance, with the first step representing background and premorbid variables (gender, age and premorbid adjustment), step two diagnosis and on the third step information about current status (drug or alcohol use, antipsychotic medication and symptoms). For research question four (to what degree apathy gave an independent contribution to level of functioning), symptoms were entered in order of their strength of their correlation with functioning in the bivariate analyses, with AES-C-Apathy on the last step after controlling for the influence of all other current symptoms. The final models were checked for violation of assumptions and for the effects of outliers and influential

observations. Analyses were done using the statistical package SPSS, version 15.0 for Windows.

Results

Level of apathy in the patient- and healthy control group.

There was a statistically significant difference between the healthy control group and first episode psychosis patients in the mean AES-S-Apathy score ($t=-9.7$, $df=162$, $p<.001$) (Table 1). Based on the pre-defined cut off for being clinically apathetic, 55 (53%) of the first episode psychosis patients were rated apathetic by the clinician (AES-C-Apathy) and 56 (54%) rated them selves (AES-S-Apathy) as being apathetic, compared to only two (3%) of the healthy control group.

Level of apathy in different diagnostic groups

There was a significant group difference in AES-C-Apathy score ($F=4.16$, $df=2,100$, $p=.02$) between the diagnostic groups. Post hoc comparison (Scheffe) showed that this difference reached the level of statistical significance ($p=.03$) for the “Schizophrenia spectrum” (mean 28.3 ± 6.4) and the “Other psychosis” group (mean 24.1 ± 8.2). While the numerical score for the patients with “Affective psychosis” (mean 28.8 ± 6.3) was nearly identical to that of patients with “Schizophrenia spectrum” it did not appear as statistically significantly different from the patients with “Other Psychosis”, probably due to a small N (i.e. a type II error cannot be ruled out).

Patient characteristics and relationship to apathy

Neither gender, current age, age at start of psychosis, duration of untreated psychosis, use of antipsychotic medication, use of alcohol or drugs or the level of PANSS-POS had

independent significant relationship with AES-C-Apathy (Table 2). In addition, PAS academic childhood cluster and PAS academic change did not have significant association with AES-C-Apathy, and were thus not entered into the subsequent hierarchical regression analysis. Of the three diagnostic categories, only “Other psychosis” was statistically significantly correlated with AES-C-Apathy (negatively). Of the different symptoms, only PANSS-DIS and PANSS-DEP were statistically significantly correlated (positively) (Table 2). These independent variables together with PAS social cluster childhood and PAS social change were thus entered into a hierarchical regression analysis in three steps (Table 3). This model explained 18% of the variance in the AES-C-Apathy score (Table 3), with all steps having significant contributions. When the combined contribution of the different independent variables were studied together, PAS social cluster childhood had the strongest significant contribution, together with PANSS-DIS and PAS social change, while the influence of “Other psychosis” diagnosis and PANSS-DEPR became non significant (Table 3).

Apathy and functioning

GAF-F scores were statistically significantly negatively associated not only with AES-C-Apathy, but also with PANSS-NEG, PANSS-POS and PANSS-DIS (Table 2). These variables were entered into the hierarchical regression analysis with GAF-F as the dependent (Table 4). Even when all other symptoms were controlled for, AES-C-Apathy had a significant contribution when entered at the last step (Table 4). This model explained 37% of the variance of the GAF-F scores (Table 4).

When the combined contribution of the different independent variables were studied together, only PANSS-POS and AES-C-Apathy had significant independent

contributions while the contribution of PANSS-NEG and PANSS-DIS, became non-significant (Table 4).

To study whether the aspects of different negative subsymptoms represented by the seven items comprised by the PANSS-NEG component had independent contributions, we repeated the above analysis entering these items at the first step of the hierarchical regression analysis (Table 5). The total explanatory power of this model was not changed compared to the original solution, and only the item PANSS-N 1, (flat affect) had a significant contribution together with PANSS-POS and AES-C-Apathy.

Discussion

The first important finding of this study is that apathy is a prevalent symptom in first episode psychosis patient. We found that more than 50 % of the participating patients were clinically apathetic, with the level of apathy was significantly higher in the patient group compared to the control group. The mean level of apathy in this study also appears to be higher than levels found in left- or right sided acquired brain damage patients [21], similar levels found in hypoxic brain damage patients [21], but lower than levels found in patients with Alzheimer's dementia [27] (all measured by the AES). This underlines that the level of apathy in first episode psychosis patients is of a level associated with clinical consequences in other brain disorders [18,19] and thus warrants clinical attention also in this patient group.

The second main finding is the clear and statistically significant contribution of apathy to functional loss in first episode psychosis patients, in line with a previous study of more chronic patients with schizophrenia who also found apathy as the best predictor of poor functioning [30]. The importance of apathy in relation to functioning must be seen in the

light of its definition as “lack of motivation and goal directed behavior” [27]. Goal directed behavior is one of the most important factors supporting development in a young person’s life [46] and the lack of motivation is thus a core feature of the negative symptoms [23].

The third main finding is the patient characteristics that have a significant influence on apathy. Poor premorbid social functioning and the presence of disorganized symptoms were significantly related to current level of apathy, while diagnosis, use of antipsychotic medication or depression was not. The clear associations with premorbid social functioning support the theory that apathy is a primary symptom linked to the neurodevelopmental origins of the disorders [47], and indicate that motivational loss influencing functioning may have been present even before the onset of psychotic symptoms. The relationship with disorganized symptoms adds further support to this theory as disorganization comprises different aspects of formal thought disorders often regarded as more primary in nature compared to delusions and hallucinations [48]. The additional finding, that the level of AES-C-Apathy was independent of depression and use of antipsychotic medication is of interest, since the clinical evaluation of whether treatable causes such as side-effects or depression lies behind lack of motivation is often difficult in clinical situations [9]. Since this is a cross sectional study, we cannot draw any conclusions with certainty about their relative independence, but our findings are supported by studies of other brain disorders finding the same relative independence between apathy and depression [21,49,50].

The finding that the only other negative subsymptom (as measured by the PANSS) that contributed to poor functioning was flat affect (PANSS-NEG item N1) is of interest for

the further understanding of negative symptoms, since this is in line with the proposed subdivision of negative symptoms into the two domains of affective flattening on the one hand and apathy/avolition and anhedonia on the other [8,51].

Apathy is less diagnostically specific for schizophrenia spectrum disorders than hypothesized, as the level of apathy appears relatively similar in patients with first episode “Schizophrenia-spectrum” disorders and in patients with first episode “Affective psychosis” disorders (while the level in the “Other psychosis” group is significantly lower). Other studies have also pointed to similarities in the presence of negative symptoms in affective psychoses and schizophrenia [52,53]. Our finding thus supports the notion that studying similar symptoms across diagnostic boundaries may help us to better understand the underlying disease mechanisms, including easier linkage to underlying neurobiological substrates [54-56].

Finally, the measurement of apathy as a separate symptom rather than the broader concept of negative symptoms have several important clinical implications. Negative symptoms are often treatment refractive, is one of the main causes for functional disability and seriously impedes rehabilitation efforts. However, the current behavioral description of negative symptoms as “social withdrawal” does not give aid on how we can improve patients’ functioning through focused interventions. The AES is a short and relatively simple rating scale that can help clinicians disentangle primary amotivation from treatable depression and medication side effects. Since rehabilitation is a goal directed process actively involving the patient, amotivation and lack of goal directed behavior is directly interfering with and obstructing this process. The possibility to assess the degree of motivational loss is thus a good starting point for rehabilitative efforts,

since patients with high levels of apathy will need additional support and interventions. Awareness of the problem among staff can increase the proper use of remediation techniques such as prompting and encouragement instead of critique. The use of motivational interviewing or other motivational techniques can be used in the treatment process and help patients with motivational problems focus on their goals and thus improve their engagement in the rehabilitation process. The above are in line with recent suggestions for more specific rehabilitative efforts [57-59] and a recent review on cognitive remediation naming motivation as the critical treatment target in order to optimize outcome [60]. Increased awareness of apathy in neuropsychiatric disorders has increased the search for effective treatments [61]. Specific motivational and behavioral approaches are taken into use such as engaging the patients through discussion groups, interactive education and homework assignments [61]. Studies also indicate that apathy to some extent can be alleviated by the use of dopamine agonists, but this type of treatment is problematic to use in psychotic disorders due to the risk of increasing psychotic symptoms. In the longer run, more knowledge of the biological basis of apathy in schizophrenia may aid the development of more specific pharmacological treatments.

Limitations

This is a cross sectional study and thus cannot conclude about the directions of the relationships. First episode psychoses are rare, and hence number of participants is limited. The functional measure is global, and thus cannot indicate if specific functional areas are more affected by apathy than others are.

Conclusion

Apathy is a common and clinically important symptom that is present at the beginning of treatment in first episode psychosis patients, can be disentangled from depression and medication side effects and already at this point of time is significantly associated with functional loss. These findings have implications for services, as negative symptoms have been difficult to assess in clinical settings through existing evaluation methods. A high level of apathy needs to be addressed in dealings with the patient, to find ways to strengthen motivation and set achievable goals. Staff and other caretakers must be informed, so that this symptom is not misinterpreted as laziness or met with critique, but instead handled in ways that increase motivation.

Acknowledgments

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Table 1

Demographic and clinical data for 103 first episode psychosis patients and 62 from the healthy control group

	Patients (N = 103)		Healthy Control group (N = 62)	
	N or mean	%	N or mean	%
Age (mean \pm SD years)	27.3 \pm 7.7		32.0 \pm 9.3	
Male gender	60	58	28	45
Education (mean \pm SD years)	13.0 \pm 2.7		13.9 \pm 1.9	
Age at onset of illness (mean \pm SD years)	24.3 \pm 7.6			
Duration of untreated psychosis in weeks (median, range)	35 (1-1040)			
Antipsychotic medication	81	79		
Hospitalized for psychosis	69	67		
Alcohol misuse or dependence ^a	11	12		
Drug misuse or dependence ^a	22	21		
Premorbid Function ^b				
PAS - Social cluster level childhood	1.4 \pm 1.6			
PAS - Social-change	.1 \pm 1.9			
PAS - Academic cluster level childhood	1.6 \pm 1.2			
PAS - Academic-change	0.7 \pm 1.4			
Diagnosis				
"Schizophrenia spectrum"	57	55		
"Affective psychosis"	17	17		
"Other Psychosis"	29	28		
Symptoms and function				
AES-C-Apathy ^c	27.2 \pm 7.1			
AES-S-Apathy ^c	27.7 \pm 7.2		18.0 \pm 4.3	
PANSS - Total score ^d	60.9 \pm 14.5			
PANSS - POS (P1,P3,P5,P6,G9,G12) ^d	14.7 \pm 5.2			
PANSS - DIS (P2,N5,N7,G5,G10,G11,G15) ^d	11.1 \pm 3.6			
PANSS - NEG (N1,N2,N3,N4,N6,G7,G13,G16) ^d	16.8 \pm 6.0			
PANSS - DEP (G1,G2,G3,G4,G6) ^d	12.4 \pm 4.1			
PANSS - EXC (P4,P7,G8,G14) ^d	5.6 \pm 1.9			
GAF- Symptoms ^f	41.9 \pm 12.7			
GAF- Functioning ^f	45.5 \pm 12.7			
Abbreviations:				
^a Alcohol and drug use scale. Scores range from 1-5 with higher scores indicating more severe dependence. A score \geq 3 indicate misuse or dependence				
^b PAS Premorbid Adjustment Scale. Possible scores range from 0, best functioning, to 6, worst functioning				
^c AES-C-Apathy Apathy Evaluation Scale clinician rated abridged version; Possible scores range from 12 to 48, with higher scores indicating more apathy				
^d AES-S-Apathy Apathy Evaluation Scale self assessed bridged version; Possible scores range from 12 to 48, with higher scores indicating more apathy				
^e PANSS Positive and Negative Syndrome Scale. Possible scores range from 30-210 for the PANSS-total, for PANSS-POS from 6- 42, PANSS-DIS from 7- 49; PANSS-NEG from 7- 49, PANSS-DEPR from 5 - 35, PANSS-EXC 4 to 20. For all higher score indicating more symptoms				
^f GAF Global Assessment of Functioning Scale, split version Possible scores range from 1-100, with higher scores indicating less symptoms or better functioning				

Table 2		
Pearson correlations between clinical variables and AES-C-Apathy and GAF-F		
	AES-C-Apathy	GAF-F
Gender	-.07	
Age	-.03	
Age at start psychosis	-.05	
Duration of untreated psychosis	.16	
Use of antipsychotic medicine	.01	
Alcohol use scale	.04	
Drug use scale	.16	
"Schizophrenia spectrum"	.17	
"Affective psychosis"	.10	
"Other psychosis "	-.28**	
AES-C-Apathy		-.44**
PANSS Five Subscores		
PANSS - POS	.19	-.47**
PANSS - DIS	.28**	-.47**
PANSS - NEG	.58**	-.50**
PANSS - DEP	.23*	-.17
PANSS - EXC	.02	-.10
Abbreviations AES-C-Apathy Apathy Evaluation Scale, clinician-rated and abridged version GAF-F Global Assessment of Functioning Scale, split version functioning DUP Duration of untreated psychosis AES-S-Apathy Apathy Evaluation Scale, self assessed abridged version PANSS Positive and Negative Syndrome Scale * $p \leq 0.05$ ** $p \leq 0.01$		

Table 3
Hierarchical multivariate regression analysis with AES-C-Apathy as the dependent

	Model summary of each step			Contribution of different variables at last step						95% CI Interval B	
	R ² change	F change	p	B	Std.Error	β	t	p	Lower	Upper	
Constant				18.34	3.07		5.97	<.001			
Step 1	.13	7.36	.001								
PAS - Social cluster level childhood				1.50	.54	.34	2.77	<.01	.42	2.58	
PAS – Social-cluster-change				1.03	.46	.27	2.24	.03	.12	1.94	
Step2	.04	4.22	.04								
“Other Psychosis group”				-2.16	1.54	-.14	-1.40	.16	-5.22	-.90	
Step 3	.05	3.18	.05								
PANSS - DIS				.43	.19	.21	2.29	.02	.06	.80	
PANSS - DEPR				.16	.17	.09	.93	.35	-.18	.49	

Explained variance for the total model : R = .46, R² adjusted =.18; F=5.33, df =5, 97, p> .01

Abbreviations:

AES-C-Apathy Apathy Evaluation Scale clinician rated abridged version

PAS Premorbid Adjustment Scale

PANSS Positive and Negative Syndrome Scale

Table 4

Hierarchical multivariate regression analyzing the effect of symptoms on the variation in GAF-F

	Model summary of each step			Contribution of separate variables for the last step					95% CI interval B	
	R ² change	F change	p	B	Std. Error	β	t	p	Lower	Upper
constant				81.2	5.08		16.0	<.001	71.13	-91.30
Step1										
PANSS-NEG	.24	31.8	<.001	-.35	.23	-.17	-1.50	.13	-.81	-.11
Step2										
PANSS-DIS	.06	8.50	.004	-.64	.41	-.17	-1.58	.12	-1.46	-.16
Step3										
PANSS-POS	.06	8.39	.005	-.65	.22	-.27	-2.92	.004	-1.09	-.21
Step4										
AES-C-Apathy	.04	6.45	.01	-.48	.19	-.25	-2.53	.01	-.85	-.10
Explained variance total model: R = .63, R²adj = .37; F=15.9, df= 4,98, p <.001										
Abbreviations:										
GAF-F Global Assessment of Functioning Scale, functioning score										
PANSS Positive and Negative Syndrome Scale										
AES-C-Apathy Apathy Evaluation Scale clinician rated abridged version										

Table 5
Hierarchical multivariate regression analysis with GAF-F as the dependent and PANSS-NEG items, PANSS-DIS, PANSS-POS and AES-C-Apathy as independent variables

		Contribution of separate variables to last step					95% CI Interval for B	
		B	Std Error	β	t	p	Lower-Upper	
Constant		83.07	5.59		14.85	<.001	72.00 - 94.18	
Step1								
PANSS-N 1 (Flat Affect)		-3.34	1.36	-.31	-2.45	.02	-6.05 - -.64	
PANSS-N 2 (Emotional withdrawal)		2.02	1.61	.18	1.26	.21	-1.17 - 5.22	
PANSS-N 3 (Poor Rapport)		1.13	1.56	.09	.72	.47	-1.97 - 4.22	
PANSS-N 4 (Passive/Apathetic withdrawal)		-1.13	1.14	-.12	-.99	.32	-3.44 - 1.14	
PANSS-N 6 (Lack of spontaneity of conversation)		-.02	1.58	-.01	-.01	.99	-3.14 - 3.12	
PANSS-G 7 (Motor retardation)		1.24	1.64	.08	.76	.45	-2.01 - 4.50	
PANSS-G 13 (Disturbance of volition)		-1.35	1.29	-.10	-1.05	.30	-3.91 - 1.21	
PANSS-G 16 (Active social avoidance)		-.75	1.09	-.07	-.68	.50	-2.92 - 1.42	
Step 2								
PANSS-DIS		-.57	.44	-.15	-1.28	.20	-1.45 - .31	
Step 3								
PANSS-POS		-.70	.24	-.30	-2.89	.005	-1.19 - -.22	
Step 4								
AES-C-Apathy		-.57	.21	-.30	-2.76	.007	-.99 - -.16	
Total model explaining R = .66; R² adjusted .37; F=6.44, df=1, 91, p<.001)								
Abbreviations								
PANSS Positive and Negative Syndrome Scale; N Negative symptom items; G General symptom items								
AES-C-Apathy Apathy Evaluation Scale clinician rated abridged version								

Apathy is associated with executive functioning in first episode psychosis

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Abstract

Background: The underlying nature of negative symptoms in psychosis is poorly understood. Investigation of the relationship between the different negative subsymptoms and neurocognition is one approach to understand more of the underlying nature. Apathy, one of the subsymptoms, is also a common symptom in other brain disorders. Its association with neurocognition, in particular executive functioning, is well documented in other brain disorders, but only studied in one former study of chronic patients with schizophrenia. This study investigates the association between apathy and neurocognitive functioning in patients with first episode psychosis (FEP), with the hypothesis that apathy is more associated with tests representing executive function than tests representing other neurocognitive domains.

Methods: Seventy-one FEP patients were assessed with an extensive neuropsychological test battery. Level of apathy was assessed with the abridged Apathy Evaluation Scale (AES-C-Apathy).

Results: AES-C-Apathy was only significantly associated with tests from the executive domain [Semantic fluency ($r = .37, p < .01$), Phonetic fluency ($r = .25, p < .05$)] and working memory [Letter Number Span ($r = .26; p < .05$)]; the first two representing the initiation part of executive function. Confounding variables such as co-occurring depression, positive symptoms or use of antipsychotic medication did not significantly influence the results.

Conclusion: We replicated in FEP patients the relationship between apathy and executive functioning reported in another study for chronic patients with schizophrenia. We also found apathy in FEP to have the same relationship to executive functioning, as assessed with the Verbal fluency tests, as that reported in patients with other brain disorders, pointing to a common underlying nature of this symptom across disorders.

Background

Negative symptoms are common in patients with psychosis, but the underlying mechanisms are still poorly understood [1]. Neurocognitive deficits are also common in schizophrenia spectrum disorders, and are thought to be more closely linked to the biological underpinnings of the disorder than clinical symptoms [2]. As negative symptoms is repeatedly shown to have a consistent relationship with neurocognitive deficits [3-6], a further exploration of their relationship may aid the search for the mechanisms behind negative symptoms. A recent review by Harvey et al suggested four models as potential explanations for their association [7]: 1) the two categories of symptoms represent the same identical features or alternate manifestations of the same basic underlying process, or 2) the two features of the illness are separable but share similar underlying etiological factors, or 3) the two are of separate, but related etiologies, or 4) the two dimensions are distinct from each other and with separate etiology. The review concluded by inviting innovations in the assessment of negative symptoms to come closer to an understanding of negative symptoms and other aspects of psychosis [7].

One problem in studies of negative symptoms is the heterogeneity of patient samples examined, with an admixture of chronic samples marked by treatment failures, institutionalization, hopelessness and subsequent social consequences that are difficult to distinguish from primary negative symptoms based solely on behavioral observations. Another problem is the diverse nature of the negative symptoms per se, as it includes several subsymptoms (apathy or avolition, anhedonia, alolia, asociality, flat affect and inattention) that might have different etiologies. Based on the recognition of this diversity, the "NIMH-MATRICES consensus statement on negative symptoms" has suggested that studies specific to the nature of these negative subsymptoms is one way to move forward [1]. So far, very few studies on the association between negative symptoms and neurocognitive function have included analysis on the subsymptom level. We have thus found only four studies addressing the specific relationship between any of the negative subsymptoms and neurocognitive function [8-11]; the subsymptoms studied being alolia [8,10] flat affect [8,11] and apathy [9].

Apathy, defined as lack of motivation or goal directed behavior [12], has lately been targeted as an important negative subsymptom that need further study [13-15]. However, the only study concerned with the association between apathy and neurocognition in psychosis is based on a small sample of chronic patients with schizophrenia and a narrow test battery [9]. Here, a high level of apathy was associated with lower performance IQ scores and poor performance on tests assessing executive function

and visual- and verbal memory. The authors called for new studies in order to generalize their findings, due to the small sample size and lack of a comprehensive neuropsychological test battery. Studying patients with their first episode of psychosis (FEP) is of particular interest, since the negative symptoms in such a sample cannot be secondary to chronic effects, treatment failures or social deprivation.

Apathy is considered a symptom arising from the prefrontal cortex [16] or from dysfunction in the frontal-subcortical circuits [17]. Its relationship to neurocognitive function has been extensively studied in other brain disorders, such as Alzheimer - (AD) [18], Parkinson - (PD) [19] and Huntington disease (HD) [20] in addition to traumatic brain injury (TBI) [21]. Common to studies of all the above disorders is the finding of a consistent relationship between high levels of apathy and poorer performance on tests representing executive function [19-24]. In addition, significant associations are found to other neurocognitive domains, especially working memory [19,24], psychomotor speed [21], attention [20] and episodic memory [20,21], but for these domains the pattern of association is less systematic.

The aim of the present study is to improve our understanding of apathy in FEP patients. Consequently, we wish to investigate the association between apathy and neurocognitive function. First, we hypothesize that also in FEP patients the degree of apathy will be significantly related to tests representing executive function, and less with tests representing other neurocognitive domains. Secondly, we hypothesize that this relationship is not influenced by confounding variables, such as depression, use of antipsychotic medication or positive symptoms, supporting the notion of a linked etiology between the two areas.

Methods

2.1 Participants

The present study includes 71 FEP patients with a fluent understanding of Norwegian, recruited between July 2004 and end of June 2006. They all took part in both the clinical and the neuropsychological assessment in the ongoing Thematically Organized Psychosis (TOP) research study in Oslo, Norway. All patients were assessed in a stable phase. The neurocognitive testing was done in as close connection to the clinical assessment as possible, within one to eight weeks. Inclusion criteria were: Age between 18 and 65 years, with a first episode of psychosis and a DSM-IV diagnosis of either schizophrenia, schizophreniform disorder, schizoaffective disorder (constituting schizophrenia spectrum disorders); psychosis NOS, delusional disorder, brief psychosis (constituting other psychotic disorders), or affective disorder with mood

incongruent psychotic symptoms and bipolar disorder (constituting affective psychotic disorders). Patients were eligible for inclusion up to 52 weeks following the start of the first adequate treatment. Being psychotic was defined as having a rating of 4 or more on anyone of the PANSS items P1, P3, P5, P6 or G9. Fifty seven (80.3%) of all used antipsychotic medication (AP); 51 on monotherapy and six on two AP's. Of these 57, three were using first generation AP [Zuclopentixol (N = 2); Perphenazine (N = 1)] and the rest second generation AP [Olanzapine (N = 28); Risperidone (N = 9); Ziprazidone (N = 9); Quetiapine (N = 7), Aripiprazole (N = 5) and Amisulpride (N 01)]. The average Defined Daily Dosage of Antipsychotics (DDD-AP) assignment according to the World Health Organization was 1.08 (SD .61) [25]. Table 1 shows the demographics, diagnostic groups and symptoms of the 71 participants.

2.2 Assessment

2.2.1 Measures

Assessment of apathy

Apathy was assessed by the clinical version of the Apathy Evaluation scale (AES-C), an 18-item Likert scale ranging from 0–4 (0 = not at all and 4 = very much) [26]. The scale is based on Marin's definition of apathy as "diminished motivation and goal directed behavior, not attributed to diminished level of consciousness, general cognitive impairment or emotional distress" [26]. Examples of the questions are: "Are you interested in things?", "Is it important for you to get things done during the day?" and "Do you feel motivated?" The scale has been used across different medical disciplines. We have previously shown that a shortened 12-item AES-C scale (AES-C-Apathy) was a better assessor of apathy than the full version in a population with a FEP [27]. This abridged version was used in all the analyses in the present study.

Assessment of other symptoms and diagnosis

Symptoms were assessed by the Structural Clinical Interview of the PANSS (SCI-PANSS) [28]. Depression was assessed with the Calgary Depression Scale for schizophrenia (CDSS) [29]. Diagnostic assessment was carried out with the Structural Clinical Interview for DSM-IV (SCID-I interview) [30].

2.3 Neuropsychological assessments

A comprehensive neuropsychological test battery was administered to all participants by psychologists or psychology students trained in clinical neuropsychology. The tests cover domains shown to be sensitive to the neurocognitive dysfunction of psychosis [31,32]: motor function (Grooved Pegboard) [33], psychomotor speed (Digit Symbol from WAIS-III) [34], attention (Digit Span forwards from WAIS-III) [34], working memory (Letter Number Span from WAIS-III) [34], verbal learning (Cali-

Table 1: Sociodemographic and clinical variables for 71 FEP patients

	Mean	SD
Age (years)	27.4	8.1
Education (years)	12.5	2.7
DUP (weeks) median/range	30	1–1040
GAF symptoms	42.8	14.0
GAF function	46.1	14.4
AES-C-Apathy	27.2	7.1
PANSS total score	60.5	15.1
PANSS positive	14.4	5.1
PANSS negative	14.7	5.8
PANSS general	31.3	7.4
CDSS	6.4	4.5
	N	%
Male gender	37	52%
Living alone	63	89%
Diagnosis		
Schizophrenia spectrum group	36	51%
Affective psychosis group	15	21%
Other psychosis group	20	28%

Abbreviations: DUP, duration of untreated psychosis; GAF, Global Assessment of Functioning Scale; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; Schizophrenia spectrum group [schizophrenia (N = 30), schizophreniform (N = 6)]; Affective psychosis group [major depressive psychosis with mood incongruent psychosis (N = 12), Bipolar (N = 3)]; Other psychosis group [psychosis NOS (N = 13), brief psychosis (N = 6), delusional disorder (N = 1)]

fornia Verbal Learning Test; CVLT-II) [35], visual learning (Rey-Oesterrieth Complex Figure Test) [36] and executive function. For the executive function domain several tests from the Delis-Kaplan Executive Function System (D-KEFS) [37] were included in order to enable the investigation of the association of apathy with three different aspects of executive function; initiation, set shifting and inhibition. Initiation was assessed with Semantic fluency and Phonetic fluency (from the Verbal Fluency test) [37].

Set shifting was assessed with Category Switching (also from the Verbal Fluency test) [37], whereas inhibition was measured with the third trial on the Color-Word Interference test (the "Stroop" condition) [37]. Premorbid IQ was assessed with a Norwegian Research version of the National Adult Reading Test (NART) [38]; and current IQ with Wechsler Abbreviated Scale of Intelligence (WASI;) [39]. All participants showed adequate neuropsychological test effort indicated by two errors or less on the forced recognition trial of the CVLT-II. Table 2 gives the test results of the 71 patients.

2.4 Procedures

All participants gave written informed consent to participate, and the study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. The data file has received an Audit Certificate from the Center for Clinical research at Ullevål University Hospital.

The three investigators who did all the clinical assessments in the current study completed the common training and reliability program of the TOP study. Training in the AES-C was done by scoring videos, supervised by two experienced clinicians who had previously used the scale with other patient groups [40], and reliability testing of the AES-C was completed by seven live interviews with random study patients. The SCID training was based on the UCLA training program [41], and supervised by UCLA. For DSM-IV diagnostics, mean overall kappa for the standard diagnosis of training videos was 0.77, and mean overall kappa for a randomly drawn subset of actual study patients was also 0.77 (95% CI 0.60–0.94). Interrater reliability (Intra Class Coefficient (ICC) 1.1) for the different psychometric scales were: PANSS positive subscale 0.82 (95% CI 0.66–0.94) PANSS negative subscale 0.76 (95% CI 0.58–0.93), PANSS general subscale 0.73 (95% CI 0.54–0.90), GAF-S 0.86 (95% CI 0.77–0.92), GAF-F 0.85 (95% CI 0.76–0.92) and AES-C 0.98 (95% CI 0.92–0.99).

2.5 Analyses

2.5.1 Data and statistical analyses

Analyses were performed with the statistical package SPSS, version 15.0 for Windows. A preliminary analysis was performed to examine the distribution of each variable. One patient was excluded because of being an extreme outlier on the Semantic fluency tests with 4 SD above the group mean (outlier score = 75; group mean = 40.1, SD = 8.6) influencing the results to such a degree that assumptions of homogeneity were violated. All tests were two-tailed, with a preset significance level of 0.05. Bonferroni corrections were applied in analyses where more than one test represented a neurocognitive domain, as noted in Table 3. Descriptive data are presented by either means or stand-

Table 2: Neuropsychological test results for 71 FEP patients

Test	Mean	SD
<i>IQ</i>		
NART (N = 66)	14.4	7.3
WASI (N = 71)	105.2	13.7
<i>Motor function</i>		
Grooved Pegboard (N = 70)	110.2	26.5
<i>Psychomotor speed</i>		
Digit Symbol (N = 71)	63.5	14.4
<i>Attention</i>		
Digit Span forward (N = 71)	5.8	1.1
<i>Verbal memory</i>		
CVLT-II (N = 71)	53.0	10.5
<i>Visual memory</i>		
ROCF long term memory (N = 65)	19.5	6.7
<i>Working memory</i>		
Letter Number Span (N = 65)	9.7	2.5
<i>Executive function</i>		
<i>Initiation</i>		
Phonetic fluency (N = 71)	38.4	11.9
Semantic fluency (N = 71)	39.6	7.6
<i>Set shifting</i>		
Category switching (N = 71)	12.4	2.7
<i>Inhibition</i>		
Color-Word Interference (N = 71)	60.0	21.0

Abbreviations: NART, National Adult Reading test; WASI, Wechsler Abbreviated Scale of Intelligence; CVLT-II, California Verbal Learning Test II; ROCF, Rey-Osterrieth Complex Figure Test.

ard deviation (SD), or by median and range. Independent Student *t*-tests were used to analyze differences between groups. Associations between AES-C-Apathy and neuropsychological tests were investigated with Pearson

Table 3: Correlation between neuropsychological tests, AES-C-Apathy and possible confounding variables

Test (N)	AES-C-Apathy	CDSS	PANSS Positive	DDD-AP
	r	r	r	r
<i>IQ</i>				
Premorbid: NART	.11	<.01	.25*	.11
Current: WASI	-.15	-.02	-.11	-.23
<i>Motor function</i>				
Grooved Pegboard	.09	-.02	.14	.18
<i>Psychomotor speed</i>				
Digit symbol	-.17	-.04	-.11	-.15
<i>Attention</i>				
Digit span forwards	-.13	.02	.04	-.14
<i>Verbal memory</i>				
CVLT-II	-.15	.05	-.15	-.13
<i>Visual memory</i>				
ROCF long term memory	-.16	-.05	-.10	-.21
<i>Working memory</i>				
Letter Number Span	-.26*	-.07	-.13	-.13
<i>Executive function</i>				
<i>Initiation</i>				
Phonetic fluency ^a	-.25*	-.08	<-.01	-.17
Semantic fluency ^a	-.37**	-.05	-.04	-.11
<i>Set shifting</i>				
Category switching	-.18	.06	.02	-.24*
<i>Inhibition</i>				
Color-Word Interference	.23	.10	.25*	.10

r = Pearson product moment correlation; *p <.05; ^a Bonferroni corrected (0.05/2 = .03) * = p ≤ .03; ** = p ≤ .01

Abbreviations: NART, National Adult Reading Test; WASI, Wechsler Abbreviated Scale of Intelligence; CVLT-II, California Verbal Learning Test II; ROCF, Rey-Osterrieth Complex Figure Test; AES-C-Apathy, abridged Apathy Evaluation Scale; CDSS, Calgary Depression Scale for Schizophrenia; PANSS, Positive and Negative Syndrome Scale; DDD-AP, indicates defined daily dose according to the World Health Organization of Antipsychotic medication

product moment correlation analysis (r) and degree of influence by univariate regression analysis.

Since apathy, negative symptoms and neurocognitive function have been found to be under influence from secondary sources, we took steps to control for this. Depression has been tested as a possible confounding variable for apathy in different studies in other medical disciplines [18,21], in addition positive symptoms and current use of antipsychotic medication has in some studies been found to influence either negative symptoms or neurocognitive function [42]. The association between these three variables and neurocognition were firstly examined in a correlation analysis followed by a hierarchical multiple regression analysis with the neurocognitive test results as the dependent. The possible confounders and AES-C-Apathy were the independent variables, with AES-C-Apathy entered in the last step.

Results

3.1 The relationship between apathy, neuropsychological test performance and confounding variables

Three of the neuropsychological tests in the comprehensive TOP battery showed a statistically significant inverse association to AES-C-Apathy (Table 3). Out of these two (Semantic- and Phonetic fluency part of the Verbal Fluency tests) represented the initiation part of executive function, and the third (Letter Number Span) represented working memory. AES-C-Apathy was most strongly correlated with the Semantic fluency test (r = .37, p = .002), explaining 12% of its variance. For the two other tests

(Phonetic fluency and Letter Number Span) the relationship to AES-C-Apathy was statistically significant, but of a smaller magnitude (r = .25, r = .26). AES-C-Apathy was neither significantly associated with any other tests, nor premorbid or current IQ.

There were no statistically significant differences in test performance for any neuropsychological tests (p value between .18 - .99) or in level of apathy (F = .16; p = .69) between the unmedicated patients (N = 14) and patients using antipsychotic medication (N = 57). None of the possible confounding variables (DDD-AP, PANSS positive symptoms or CDSS) had any significant correlations with the three neuropsychological tests that were statistically significantly associated with AES-C-Apathy (Table 3). This lack of influence was confirmed in a hierarchical regression analysis with Semantic-, Phonetic fluency and Letter Number Span as dependent variables. Here only AES-C-Apathy had a statistically significant contribution, even when entered in the last step (Table 4). The entry of the possible confounding variables did not change the influence AES-C-Apathy had on the neuropsychological tests in the univariate regression analysis (Table 4).

Discussion

The main result of the present study is the replicated finding of a significant relationship between apathy and executive function in psychotic disorders, as found previously in one study of patients with chronic schizophrenia [9]. The two findings are corresponding even if the two studies applied different measures both for apathy and executive

Table 4: Univariate and hierarchial multivariate regression analysis with neuropsychological tests as dependent and AES-C-Apathy and possible counfounders as independent variables

	Dependent				Dependent				Dependent			
	Letter Number Span				Phonetic fluency				Semantic fluency			
Independent variables	R ² adj	β	t	p	R ² adj	β	t	p	R ² adj	β	t	p
Univariate												
AES-C-Apathy	.05	-.26	-2.2	.04	.05	-.25	-2.2	.03	.12	-.37	-3.3	<.01
Hierarchical												
DDD-AP	.01	-.13	-1.1	.30	.02	-.19	-1.6	.12	.00	-.12	-1.0	.31
PANSS positive	.01	-.06	-.5	.62	.01	.07	.6	.56	-.01	.04	.3	.75
CDSS	-.09	.05	.3	.72	-.02	.05	.4	.72	-.03	.15	1.2	.25
AES-C-Apathy	.04	-.27	-2.0	.05	.05	-.29	-2.2	.03	.12	-.44	-3.5	<.01

adj = adjusted; DDD-AP, indicates defined daily dose according to the World Health Organization of antipsychotic medication PANSS, Positive and Negative syndrome Scale; CDSS, Calcary Depression Scale for Schizophrenia; AES-C-Apathy, abridged Apathy Evaluation Scale

function, indicating a robust relationship. In addition, in both studies the relationship was not influenced by current level of depression. This supports the view that the presence of apathy and deficits in executive functioning are related in psychotic disorders, and that the relationship is not due to definitional issues since different scales and tests were used.

Additionally, this finding is in line with findings of an association between apathy and the specific executive functioning test of verbal fluency in several other brain disorders [18-20,22]. Two of these studies used the AES in assessing apathy [19,22], eliminating the challenge of comparing results between different scales.

This finding of a consistent relationship between apathy and tests of executive function across different brain disorders and across different levels of chronicity is supported by several studies that implicate prefrontal areas and frontal-subcortical circuitry involving the anterior cingulate gyrus in both apathy and executive function [43-47].

In our opinion, our findings thus support the idea of a common or linked etiology between these negative symptoms and neurocognitive deficits as put forward in Harvey et al's model 2 and 3 [7]. This is in opposition to Harvey's own conclusions, that suggests that the two have different etiologies based on a lack of published studies showing significant relationships. In addition, our findings might imply that there are specific mechanisms behind the different negative subsymptoms. This is supported by a recent study finding that verbal memory was the only neuropsychological test to differentiate between those with and without flat affect, making the authors' suggest that this could reflect a unique neural substrate for this negative subsymptom [11].

We did not, as Roth et al, find associations between high levels of apathy and reduced IQ and memory, associations with apathy that are also found in other disorders. This could be due to the differences between the studies such as assessment of apathy, FEP patients being less chronically ill and diagnostically more diverse. But in order to understand more of the different negative subsymptoms, these associations should also be further studied.

The strength of our study is the use of a specific and validated assessment for the negative subsymptom of apathy together with a comprehensive neuropsychological test battery with tests for several different aspects of executive function. The main limitations to our study are: 1) that we only had access to instruments measuring one of the specific negative subsymptoms and thus cannot conclude anything about the specificity of our finding in regard to the other subsymptoms. 2) that for some patients the clin-

ical assessment of apathy and the neuropsychological testing took place with a time difference and this could weaken our chances to detect weaker associations.

Conclusion

First we replicated the finding in FEP patients, as was found in chronic patients, of a significant relationship between apathy and executive functioning. Second, we found that apathy in FEP have the same relationship to the Verbal Fluency test, as reported in other brain disorders, pointing to a common underlying nature of this symptom across disorders.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AFa study design, collecting data, analysis, drafting and revising the manuscript. AV study design of neuropsychological tests, data collection (neuropsychological tests), data analysis and drafting and revising the manuscript. AFi study design, data analysis and drafting and revising the manuscript. IA conception of the study and revising the manuscript. EAB collecting data and revising the manuscript. SF study design, data analysis and revising the manuscript. CS data collection (neuropsychological testing) and revising the manuscript. OAA conception of the study and revising the manuscript. IM conception of the study, study design, data analysis and drafting and revising the manuscript.

All authors contributed to and have approved of the final version of the manuscript.

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