A 10-year perspective on apathy development in psychotic disorders

Genetic risk and early predictors, associations with depression, and functional outcome

Doctoral thesis

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THESIS SUMMARY

Apathy is characterized by reduced motivation and goal-directed behavior and is part of the heterogeneous negative symptom dimension in psychotic disorders such as schizophrenia. It has long been known that apathy is commonly present in people with chronic illness. The last two decades of research into first-episode psychosis (FEP) has revealed that apathy is highly prevalent even in the early phase of these disorders. The etiology and mechanisms underlying the development of apathy are uncertain, but theories include cognitive impairment, aberrancies in brain reward circuitry, and negative beliefs in one's problem-solving abilities. Epidemiological studies further suggest that the negative symptom dimension may be partly heritable; the genetic underpinnings of apathy as one part of this broader group of negative symptoms are, however, unknown. Further, for more than a hundred years, researchers and clinicians have observed a close link between high levels of negative symptoms and poor functioning in psychotic disorders. More recently, research has indicated that among negative symptoms, apathy has a pivotal role in this functional impairment. Moreover, the associations with poor functioning are even stronger if high levels of apathy persist over time. This reflects how the current treatments for negative symptoms, including apathy, are not clinically effective. So far, most studies of apathy in psychotic disorders have included individuals with chronic illness or had a cross-sectional or short-term follow-up design. The development of apathy in the longer term in FEP and, thus, the early predictors of long-term apathy trajectory are understudied. An improved understanding of apathy's etiology and underlying mechanisms is urgent to enable the development of new treatment alternatives.

Finally, apathy shares clinical features with depression, which makes the two phenotypes difficult to tell apart in the psychosis population. Depression is prevalent in psychotic disorders and has traditionally been regarded as a positive prognostic factor. However, like apathy, depression may persist over time. Studies exploring the relationship between depression and functioning have mixed findings, but persistent depression is suggested to have a more negative impact on the individual. The respective tendencies of apathy and depression to persist in FEP and whether the similar phenotypes overlap in some individuals is not known. The consequences on functioning of having persistent apathy and/or persistent depression have not previously been compared.

Therefore, the main aims of the present thesis were to explore 1) the genetic underpinnings of apathy in schizophrenia spectrum disorders. 2) the cross-sectional and longitudinal associations

between apathy, depression, and functioning, here with a focus on symptom persistence, and 3) the development of apathy, the early predictors of apathy development, and the associations with functioning in the long term. In Study I, we explored the associations between the levels of apathy and an estimate for the genetic risk for schizophrenia (a schizophrenia polygenic risk score, or SZ PRS) in a sample of people with schizophrenia spectrum disorders and in healthy controls. In Study II, we investigated apathy and depression in cross-sectional and longitudinal analyses in a one-year follow-up of FEP participants. We explored the tendency of apathy and depression to persist and overlap and investigated the associations with functioning. In Study III, we explored the development of apathy in a 10-year follow-up of FEP participants and healthy controls. We further investigated the early predictors of apathy development and the associations to functioning in FEP participants at the 10-year follow-up.

First, we found no significant associations between the SZ PRS and levels of apathy in participants with schizophrenia spectrum disorders or in healthy controls. Follow-up regression analyses in the patient group indicated that the nonsignificant associations were not because of confounding factors. Second, persistent depression or persistent apathy was present in 40% of participants during the first year after a FEP. Eleven percent had both persistent apathy and persistent depression, exceeding an overlap expected by chance. At the one-year follow-up, functioning was severely and equally impaired in the participants with persistent apathy, persistent depression, or both persistent symptoms. The participants without persistent symptoms had significantly higher levels of functioning. Cross-sectional analyses at the baseline and one-year follow-up implied that high levels of apathy were significantly and consistently associated with poorer functioning. High levels of depression showed a significant association with reduced functioning only at the one-year follow-up. Third, in FEP participants, the levels of apathy significantly decreased over the 10-year follow-up, and this decline primarily occurred during the first year. In the healthy controls, however, the levels of apathy were lower and followed a stable trajectory. A long duration of untreated psychosis (DUP) and high levels of depression at baseline predicted higher levels of apathy during the follow-up in FEP. Whereas the effect of DUP persisted, the effect of depression declined. Furthermore, our data suggested that FEP participants with high levels of apathy at baseline were more likely to continue having higher apathy levels during the follow-up. At the 10-year follow-up, high levels of apathy showed significant and independent associations with reduced functioning. However, the associations between levels of depression and functioning were nonsignificant.

In sum, the nonsignificant associations between apathy and SZ PRS in patients and healthy controls suggests that the common genetic variants related to the vulnerability for schizophrenia may not be relevant for the development of apathy in these disorders. This adds weight to the importance of further research into the environmental risk factors for the development of apathy, which may be of a biological and/or psychological nature. For several reasons, we would not argue strongly against the existence of a genetic liability underlying apathy. For instance, we may have lacked the statistical power to detect a genetic signal. PRSs already have a role as a clinical tool in the prediction of certain somatic illnesses. Notwithstanding this, mental illnesses like psychotic disorders are more complex in nature, and the clinical utility of PRS in psychiatry has yet to be demonstrated. The study of the heritability of apathy in psychotic disorders may, however, profit from larger sample sizes and the ongoing, high-paced improvements in genetic methodology.

The consistent findings of significant negative associations between apathy and functioning in the short term (Study II) and long term (Study III) affirms the paramount clinical relevance and importance of this symptom in FEP. The indications of an early reduction and critical period in apathy development may represent a time window where apathy levels have not yet stabilized and could be susceptible to secondary prevention. However, during this early phase, a considerable fraction of individuals with a FEP already have persistent symptoms of apathy, depression, or both, hence constituting groups with severely impaired functioning. Our results further imply that factors associated with an unfavorable long-term apathy trajectory are already present in the very early phase of the psychotic illness. According to our data, high levels of baseline apathy and a long DUP (i.e., delayed start of treatment for the first psychotic episode) may signify vulnerable individuals who are prone to higher apathy levels for the decade to come. Similarly, the positive association between baseline depressive symptoms and long-term apathy levels suggests that early concurrent depression may contribute to worsening the apathy trajectory in some individuals with a FEP.

Our findings of overlapping persistent apathy and persistent depression in Study II and depression as a predictor of apathy development in Study III may imply that apathy and depression, perhaps corresponding with their phenomenological overlap, could be more profoundly connected. Whether they share parts of their etiology or mechanisms for development is beyond the scope of our studies and remains a topic for future investigation. Nonetheless, from a clinical perspective, awareness toward concurrent depression—especially

persistent depression in FEP—is important. Depressive symptoms may easily be misinterpreted as negative symptoms or overlooked if positive symptoms or agitation dominate behavior early in the course of psychotic illness. One first step in research and in the clinical context is to apply psychometric scales that enable a reliable differentiation between apathy and other negative symptoms and depression in the FEP population.

LIST OF PAPERS

1. Lyngstad S.H., Bettella F., Aminoff S.R., Athanasiu L., Andreassen O.A., Færden A., Melle I. Associations between schizophrenia polygenic risk and apathy in schizophrenia spectrum disorders and healthy controls.
   Acta Psychiatrica Scandinavica, 2020 May; Volume 141: 452-464.

2. Lyngstad S.H., Gardsjord E.S., Simonsen C., Engen M.J., Romm K.L., Melle I., Færden A. Consequences of persistent depression and apathy in first-episode psychosis - A one-year follow-up study.
   Comprehensive Psychiatry, *2018 October;* Volume 86: 60-6.

3. Lyngstad S.H., Gardsjord E.S., Engen, M.J., Haatveit, B., Ihler, H. M., Wedervang-Resell, K., Simonsen, C., Melle, I., Færden, A. Trajectory and early predictors of apathy development in first-episode psychosis and in healthy controls: A 10-year follow-up study.
   European Archives of Psychiatry and Clinical Neuroscience, 2020 September; Volume 270: 709-722.

NORSK SAMMENDRAG

Et tiårsperspektiv på utvikling av apati hos personer med førstegangspsykose

Etiologien ved psykoselidelser som schizofreni er for det meste ukjent, men heritabiliteten er høy, og flere miljøfaktorer er assosiert med økt forekomst. Sammenlignet med positive symptomer som hallusinasjoner og vrangforestillinger, er negative symptomer ved psykoselidelser forbundet med klart dårligere prognose og funksjon. Nyere forskning viser at negative symptomer omfatter fem sub-symptomer som grupperer seg i to domener som kan ha delvis separat underliggende etiologi og mekanismer. Blant sub-symptomene er det apati, som kjennetegnes ved redusert motivasjon og målrettet atferd, som er sterkest assosiert med redusert funksjon. Denne funksjonssvikten er tydeligst ved persisterende apati, dvs. når høye nivåer av apati vedvarer over tid.

Forskning på personer som har sin første episode med psykose (FEP), viser at ca. 50% har klinisk signifikant apati ved studieinklusjon (dvs. baseline), og at 30% har persisterende apati det første året. De fleste apatistudier ved FEP har hatt tverrsnittsdesign eller longitudinelt design med kort oppfølgingstid. Derfor mangler vi kunnskap om apatiutviklingen over lenger tid, og om hvilke tidlige faktorer som kan predikere utviklingen. Selv om epidemiologiske studier tyder på at negative symptomer som gruppe kan være arvelige, er den genetiske arkitekturen til apati som sub-symptom knapt undersøkt.

Et viktig moment er at depresjon kan ha et fenotypisk uttrykk som ligner apati hos personer med psykoselidelser. Fenomenene kan derfor være vanskelige å skille fra hverandre, noe som kan være spesielt aktuelt ved FEP, hvor prevalensen av depresjon er høyere enn senere i sykdomsforløpet. Ved FEP forekommer også persisterende depresjon, og er assosiert med større funksjonssvikt enn fluktuerende depresjon. Få studier har sammenlignet assosiasjoner til funksjonsnivå ved symptomer på apati og depresjon ved FEP. Ingen tidligere studier har sammenlignet funksjonsnivået mellom personer med persisterende apati og persisterende depresjon, eller undersøkt om noen personer med FEP har begge persisterende symptomer.

Målene med denne avhandlingen var å 1) undersøke assosiasjoner mellom apati og genetisk sårbarhet for schizofreni (representert ved en schizofreni polygen risikoskåre, SZ PRS) hos personer med schizofrenilidelser og friske kontroller, 2) undersøke assosiasjoner mellom apati, depresjon og funksjon i tverrsnittsdesign; beskrive prevalens av og sammenligne funksjon mellom grupper med persisterende symptomer (apati, depresjon eller begge symptomer) i en ett-års oppfølgingsstudie ved FEP, og 3) undersøke tiårsforløpet av apati etter en FEP

sammenlignet med friske kontroller, utforske tidlige prediktorer av apatiforløpet, samt prevalens av klinisk signifikant apati og assosiasjoner til funksjon ti år etter en FEP.

Vi fant non-signifikante assosiasjoner mellom apati og SZ PRS hos personer med schizofrenilidelser og friske kontroller. SZ PRS bidro ikke til å forklare variansen i apatinivåer hos pasientene, mens flere kliniske variabler hadde signifikante bidrag. Videre fant vi at 40% hadde persisterende apati eller persisterende depresjon det første året etter en FEP. En signifikant andel (11%) hadde begge persisterende symptomer. Apati viste signifikante, negative og selvstendige assosiasjoner til funksjon både ved baseline og etter ett år, mens depresjon viste en signifikant, negativ og selvstendig assosiasjon til funksjon kun ved ét år. Tre uavhengige grupper med persisterende symptomer (apati, depresjon eller begge) hadde alvorlig redusert funksjon, signifikant lavere enn gruppen uten persisterende symptomer. Personer med begge persisterende symptomer hadde ikke entydig lavere funksjon enn personer med enten persisterende apati eller persisterende depresjon. I tiårsforløpet etter en FEP, sank gjennomsnittlig apatinivå det første året, men var deretter stabilt de neste ni årene. En lang varighet av ubehandlet psykose (VUP) og høye apatinivåer ved baseline predikerte vedvarende høyere apati i forløpet. Baseline depresjonssymptomer predikerte også høyere apati, men denne effekten avtok over flere år. Ved tiårs-oppfølgingstidspunktet hadde 37% klinisk signifikant apati. Apati hadde igjen en selvstendig, signifikant og negativ assosiasjon til funksjon, mens depresjon ikke hadde et selvstendig, signifikant bidrag. Hos de friske kontrollene var derimot gjennomsnittlig apatinivå lavt og stabilt i tiårsforløpet.

Resultatene kan tyde på at den genetiske sårbarheten for schizofreni ikke er vesentlig for utviklingen av apati ved disse lidelsene, men av flere grunner kan et genetisk bidrag ikke utelukkes. Videre er et synkende apatinivå det første året etter en FEP forenlig med en kritisk fase i apatiutviklingen, hvor apatien ikke er stabilisert og kan være mer tilgjengelig for behandling. Imidlertid har en vesentlig andel allerede persisterende symptomer (apati, depresjon eller begge) dette første året, og flere faktorer som predikerer et uheldig apatiforløp er til stede i en meget tidlig sykdomsfase. Gruppene med persisterende symptomer synes å ha liknende, alvorlig svekket funksjon, og kan representere sårbare undergrupper. Mens tverrsnitts-assosiasjonene mellom depresjon og funksjon var inkonsistente i forløpet etter en FEP, var assosiasjonene mellom apati og funksjon gjennomgående signifikante og negative. Dette støtter en voksende forskningslitteratur som identifiserer apati som sentralt for funksjonssvikten ved psykoselidelser. Funnene av overlappende persisterende apati og depresjon, og av depresjon som prediktor av langtids-apatiforløp, kan kanskje indikere at apati

og depresjon er mer grunnleggende forbundet med hverandre hos en sub-gruppe med FEP, men dette er usikkert, og gjenstår for videre forskning.

Grunnet begrensninger i statistisk kraft, bør funnene fra studie I (genetikk) og studie II (persisterende symptomer) replikeres i større samples. Fremtidig forskning bør videre fokusere på ulike miljøfaktorers betydning for utvikling av apati ved FEP. I den kliniske hverdagen er det meget viktig å undersøke om personer med FEP har apati og/ eller depresjon, og benytte psykometri som reliabelt skiller fenotypene fra hverandre. Om reduksjon av VUP eller tidlig behandling av depresjon kunne føre til et mer fordelaktig apatiforløp for enkelte med FEP, er også spørsmål som gjenstår å besvare.

ABBREVIATIONS

AES-C = Apathy Evaluation Scale, clinician report version

AES-S = Apathy Evaluation Scale, self-report version

AP = Antipsychotic medication

BD = Bipolar disorder

CDSS = Calgary Depression Scale for Schizophrenia

CNV = Copy number variant

DDD = Defined daily dose

DPB = Defeatist performance beliefs

DNA = Deoxyribonucleic acid

DSM = Diagnostic and Statistical Manual for Mental Disorders

DUP = Duration of untreated psychosis

FEP = First-episode psychosis

GAF-F = Global Assessment of Function Scale - Split version, functioning subscale

GWAS = Genome-wide Association Study

HC = Healthy controls

ICD-10 = International Classification of Diseases, 10th version

LD = Linkage disequilibrium

LMM = Linear mixed models

MAF = Minor allele frequency

MEP = Multiple episode psychosis

NIMH = National Institute of Mental Health

NOS = Not otherwise specified

PANSS = Positive and Negative Syndrome Scale

PAS = Premorbid Adjustment Scale

PGC = Psychiatric Genomics Consortium

PRS = Polygenic risk score

SCID-I = Structured Clinical Interview for DSM Axis-I Disorders

SNP = Single nucleotide polymorphism

SPSS = Statistical Package for the Social Sciences

TIPS study = Early Treatment and Intervention in Psychosis study

TOP study = Thematically Organized Psychosis study

1 INTRODUCTION

The term psychosis was introduced in the psychiatric literature in the mid-nineteenth century (1) and stems from Greek, *psykhé* (meaning soul or mind) and *–osis* (meaning abnormal condition). According to the current understanding, a psychosis describes a state of mind in which the ability to distinguish one's inner experiences, thoughts, and perceptions from what is real in the surrounding environment is disturbed (2). Psychotic symptoms comprise delusions, hallucinations, and disorganized speech (i.e., positive symptoms), as well as widespread diminutions in motivation and goal-directed behavior, speech, feelings of pleasure, expression of emotions, and social interest (i.e., negative symptoms) (3-5). The weakening of motivation and reduced goal-directed behavior, which is called apathy, is the negative symptom central to the present thesis.

Psychotic symptoms occur across several mental illnesses or may be precipitated by substance use, medical conditions, or medical treatment. A psychotic *disorder*, however, is a severe mental disorder where psychotic symptoms are the clinical hallmarks and central to the diagnostic criteria (2). At the beginning of the twentieth century, the German psychiatrist Emil Kraepelin (1856–1926) was the first to describe severe mental illness in a systematic manner. He divided metal illnesses into "Dementia praecox" and "Manic-depressive illness" (6), which largely concurs with current diagnoses of schizophrenia and bipolar disorder, respectively. Thus, the work of Kraepelin has had a profound impact on diagnostic categorization in psychiatry.

Currently, psychotic disorders include schizophrenia, schizophreniform disorder, schizoaffective disorder (i.e., schizophrenia spectrum disorders), delusional disorder, brief psychotic disorder, and psychosis not otherwise specified, according to the Diagnostic and Statistical Manual for Mental Disorders 5th version (DSM-V) (7). Together, they are often referred to as nonaffective psychotic disorders (8). In contrast, affective psychotic disorders comprise bipolar and major depressive disorders and are characterized by prominent mood episodes that may have concurrent psychotic symptoms (8). Of note, mood symptoms and episodes—especially depression—are common, even in nonaffective psychotic disorders (9). Because of phenomenological similarity, depressive and negative symptoms may be difficult to tease apart in psychotic disorders (10). Although comorbid depressive symptoms were previously regarded a positive prognostic factor (11), more recent research has had mixed

findings. Some studies report significant negative associations to functioning, whereas other studies do not (9, 12, 13). Still, the research indicates that early persistent depressive symptoms are associated with poorer functioning than fluctuating depressive symptoms (14, 15).

Together, the above diagnoses constitute a broad spectrum of psychotic disorders, of which the underlying etiology remains largely unknown (2, 16). However, the tendency of mental illnesses to aggregate in families has long been known (17). Bipolar disorder and schizophrenia are especially suggested to be highly heritable (18, 19) and are hypothesized to develop as a result of the complex interplay between genetic and environmental factors (3, 20).

Kraepelin emphasized that cognitive impairment and the reduction of affect, speech, interest, and volition were at the core of dementia praecox (21). These phenomena are parallel to what is now called cognitive and negative symptoms. Negative symptoms are still regarded cardinal features and a distinct but heterogeneous symptom domain in schizophrenia (4, 22-24) and they are also present in the broader psychosis spectrum (25, 26). Negative symptoms are prevalent before psychosis onset (27), during the first psychotic episode (28-31), and in the long-term course of a psychotic disorder (32-34). Unlike positive symptoms, current treatments do not have a clinically significant effect in reducing negative symptoms (35, 36). Thus, high levels of negative symptoms are associated with an early functional loss and poor long-term prognosis (5, 37).

Over the past decade, it has become increasingly clear that apathy—one part of the negative symptom dimension—is already prevalent at psychosis onset (30, 38) and that it is a key contributor to functional impairment above and beyond other negative symptoms (4, 39). The associations to reduced functioning are even stronger when apathy persists at high levels over time (29, 38). Thus, apathy is suggested as a pivotal target for the development of new treatments for negative symptoms in psychotic disorders (40). This necessitates an improved understanding of the etiology and mechanisms underpinning apathy development both before psychosis onset and in the early and later course of the illness. Thus, in the three studies comprising this thesis (41-43), we aimed to explore the genetic underpinnings, early clinical predictors, and long-term development of apathy in psychotic disorders. We wanted to investigate the early course prevalence of persistent apathy and persistent depression and any overlap between these phenotypes. We aimed to explore the cross-sectional associations between the symptoms of apathy and depression and functioning and, finally, to compare the

levels of functioning between individuals with one or both persistent symptoms in the early phase of a psychotic disorder.

I now provide a general introduction to psychotic disorders, here with a focus on schizophrenia spectrum disorders because these are the most relevant to the current thesis. Then, I will go on to introduce the specific topics via negative symptoms to apathy, which is the focus.

1.1 Psychotic disorders

1.1.1 Introduction and overview

1.1.1.1 Onset, course, and outcomes

The lifetime risk of developing a psychotic disorder varies depending on the diagnosis, and for schizophrenia, the lifetime risk is approximately 0.7% (16, 44). The onset of the first psychotic episode typically occurs during adolescence or early adulthood, which is a critical period for brain maturation and psychological and social development. The first psychotic episode is frequently preceded by a prodromal phase that may last for months or years (3). In this phase, anxiety and depressive and negative symptoms are common, together with attenuated psychotic symptoms like suspiciousness or perceptual abnormalities that foretell of the upcoming psychotic outbreak (45, 46). Symptoms may be accompanied by behavioral alterations in relation to family or friends and problems with school or work performance. A *diagnosis* of a psychotic disorder relies on the onset of a frank psychotic episode and the resulting functional impediments, at which time the relevant illness processes may have been ongoing for years.

From the onset, schizophrenia spectrum disorders (hereafter: schizophrenia) have a highly heterogeneous clinical presentation. There are no pathognomonic symptoms or clinical signs and no valid biomarkers that can identify the disorder in an objective or reliable manner (3). Therefore, schizophrenia is considered a clinical syndrome, a cluster or collection of symptoms that often occur together. Some symptoms are part of the diagnostic criteria (i.e., positive and negative symptoms), whereas cognitive symptoms (i.e., cognitive impairments) and mood symptoms are not, though they are prevalent and have a significant impact on various outcomes (8, 9, 47).

The typical illness trajectory is fluctuating. Positive symptoms are prone to relapse and remit, while negative and cognitive symptoms are regarded as being more stable over time (3). The long-term prognosis in individuals with schizophrenia is highly diverse (48). Some individuals

regain functioning when psychotic symptoms abate, whereas others have continuous and severe impairments in their ability to attend to work, social relations, or household chores, even between psychotic exacerbations. Systematic reviews and meta-analyses of recovery (defined as symptom remission plus regained functioning lasting for at least two years) suggest pooled recovery rates of 38% in first-episode psychosis (FEP) (49) and 13.5% in mixed samples of FEP and multiple-episode psychosis (MEP) (50). These findings are reflected in the World Health Organization's burden of disease studies, where schizophrenia still resides among the top 20 causes of illness-related disability worldwide (51). Further, there is a considerable comorbidity with other mental illnesses. This is mostly accounted for by substance use disorders, but anxiety and depressive symptoms are also prevalent (9, 52).

Mortality rates are two- to threefold higher in people with schizophrenia than in the general population (44), and on average, life expectancy is reduced by 15–20 years. Evidence indicates that the largest fraction of excess mortality is because of natural causes (53, 54) such as cardiovascular disease (55, 56), but death because of violence, accidents (57), and suicide is also increased, and the risk of suicide is the highest shortly before and after psychosis onset (58-60).

1.1.1.2 Etiology and mechanisms

What causes schizophrenia and related psychotic disorders remains to be answered. However, research suggests that both environmental and genetic factors are at play (2, 3). Here, I focus on the current evidence for a genetic etiology in schizophrenia because of its relevance to Study I as part of the present thesis: genetic epidemiology has long demonstrated a familial aggregation of psychotic disorders (17). First-degree relatives of an individual with schizophrenia have an approximately 10-fold increased risk of developing the disorder (19). The concordance rate in monozygotic twins (i.e., with identical genotypes) was recently reported to be 33% (61), whereas a previous review found a pooled concordance rate of 50% (62). Schizophrenia heritability (which is defined as the proportion of the variability of a phenotype in a population that is attributable to genetic factors) (63) is estimated to be 64–81% (18, 19, 61). Lately, large-scale genome-wide association studies (GWASs) have shed new light on the genetic architecture of psychotic disorders (64, 65). GWASs explore the genotype-phenotype associations in samples of people with schizophrenia (i.e., discovery samples) compared with healthy controls. The genotype frequency of millions of genetic variants, single nucleotide polymorphisms (SNPs) or copy number variants (CNVs), in the DNA are investigated. Although only a subset of SNPs (i.e., tag-SNPs) in the genome is assessed, most

of the genetic variation in the population under study is represented because of linkage disequilibrium (LD) (66). LD signifies that the tag-SNPs are highly correlated with close by SNPs in the genome and are likely inherited together. Thus, when a tag-SNP is present and significantly associated with schizophrenia in a GWAS, it is assumed that the SNPs in LD with it are also represented and that an actual causal SNP resides among them.

GWASs show that heritability in schizophrenia is highly polygenic, involves multiple common SNPs (typically a minor allele frequency > 1%) with small effect sizes (OR < 1.3), and a small number of rare variants (e.g., rare SNPs and CNVs) with larger effect sizes (67-71). Common variants are estimated to contribute to a larger proportion of heritability than rare variants (66). The latest schizophrenia GWAS from the Psychiatric Genomics Consortium (PGC) identified 128 independent SNPs with genome-wide significant (i.e., $p = 5 \times 10^{-8}$) associations to schizophrenia, together representing 108 independent genomic loci (64, 72). The significant SNPs are over-represented in protein-coding and regulatory genomic regions (65, 73). The implied risk genes are expressed in immune system tissue, yet excessively in the central nervous system (CNS), where they converge upon functionally related pathways involving synaptic function and neuronal excitability and are postulated to interfere with neurodevelopment (66). Another 50 novel, genome-wide significant loci were identified in a recent GWAS meta-analysis combining PGC samples with independent samples from the United Kingdom (74).

Moreover, GWASs have shown that schizophrenia heritability is highly pleiotropic. This implies that there is a genetic overlap across mental illnesses, and that the common SNPs and rare variants associated with an increased risk for developing schizophrenia are relevant to susceptibility for other psychiatric (and somatic) disorders and traits (75). The highest degree of SNP-based genetic correlation (r_g) is found between schizophrenia and bipolar (r_g = 0.68–0.70) and major depressive disorders (r_g = 0.34–0.43) (75-77). Similarly, several of the rare variants associated with schizophrenia are associated with an increased likelihood of intellectual disability and developmental disorders, such as ADHD and autism spectrum disorders (78). These findings are in line with the accumulation of some of these disorders in the families of individuals with schizophrenia (19, 79, 80) and may provide one explanation for the high prevalence of mood symptoms and episodes in schizophrenia (9), hence posing a challenge to the biological validity of the diagnostic categories of current diagnostic systems (66, 81).

In 2009, a landmark study capitalized on the combined statistical power of several SZ GWAS samples (70). Purcell et al. first applied a method proposed by Wray et al. (82), computing a schizophrenia polygenic risk score (SZ PRS) based on the added effects of the SNPs with significant associations with schizophrenia in a discovery sample. The authors then used the SZ PRS to successfully discriminate people with schizophrenia from healthy controls in the independent test samples. Since then, the SZ PRS has been applied to detect associations between the genetic vulnerability for schizophrenia and clinical and biological phenotypes within the disorder (83) and across other mental illnesses (75). A SZ PRS is applied to explore the genetic underpinnings of apathy in Study I as part of the present thesis (41).

A range of environmental factors are associated with an increased propensity for developing schizophrenia (84). Some factors present early, such as during pregnancy or birth (e.g., maternal stress, infections, malnutrition, bleeding, preeclampsia, or birth complications). A low birth weight, birth in winter or early spring and advanced age in the father are well-known risk factors (85). Other factors may present later and include childhood adversity (86), immigrant status (87), urbanicity (88), and cannabis use (89). Moreover, a growing body of research indicates that the immune system could be involved, maybe mediating the effect of environmental risk factors on the pathophysiological processes underlying the development of schizophrenia (90).

The hypothesis of an aberrant neurodevelopment was introduced in the late 1980s, spurred by evidence of deviant brain morphology in schizophrenia patients (91, 92), and became a dominant and still widely held paradigm (3). As new evidence has come forth, the hypothesis has developed (92-94). Currently, it incorporates genetic and environmental risk factors and stressors that may affect the neurodevelopmental trajectory, including the formation and connectivity of synapses in fetal life and abnormal synaptic pruning during adolescence (84, 93-95).

However, the underlying pathophysiology in schizophrenia still remains to be understood. Dysregulation of the dopamine pathways in the brain has long been an influential hypothesis. In the most recent revision of the hypothesis, elevated levels of dopamine in striatal synapses and disruptions in a wide range of neural pathways have been suggested (96, 97). It is proposed that a complex interplay between excess striatal dopamine and an imbalance between excitatory and inhibitory stimuli involving glutamatergic and GABA-ergic neurons, respectively, contributes to the development of psychotic symptoms (2, 98, 99). Together, these

neurotransmitter imbalances are primarily implied as affecting the pathways in the striatum, hippocampus, prefrontal cortex, and midbrain (2).

1.1.1.3 Treatment

Because the underlying pathophysiology is mostly unknown, there is no curative pharmacological or psychosocial treatment. The cornerstone of treatment is antipsychotic medication, which blocks or reduces neurotransmission at the dopamine receptors in the brain (100) and aims at alleviating symptoms (2, 3). The efficacy in reducing positive symptoms during acute psychotic exacerbations and in short-term relapse prevention has been well documented (101). Still, approximately 30–50% of individuals with psychotic disorders have partial or no effect (100, 102), and no clinically significant effect is seen on cognitive and negative symptoms (35, 100). It is generally recommended that medication is given in combination with psychological treatment (3, 103) such as social skills training, cognitive remediation therapy, psychoeducation and coping-oriented family interventions, and cognitive behavioral therapy (104).

1.1.2 Symptom domains

Positive symptoms

According to the DSM-IV, positive symptoms include delusions, hallucinations, disorganized speech, and disorganized and catatonic behavior (105). In the three studies in the current thesis, we have further applied Wallwork et al.'s version of the Positive and Negative Syndrome Scale (PANSS) (106), where symptom domains are represented by five factors (positive, disorganized, negative, excitative, and depressive). Here, positive symptoms comprise hallucinations and delusion only, and the disorganized factor appears as distinct.

Delusions are the beliefs or convictions that are strongly held as truth, even though there is ample evidence to the contrary. In schizophrenia, persecutory delusions are common and typically involve ideas of being ridiculed, spied on, or poisoned. Delusions are deemed as bizarre if their content is completely implausible according to the general laws of nature, and "do not derive from ordinary life experiences" (105). Bizarre delusions were previously regarded as characteristic of schizophrenia (107), but evidence no longer supports this notion.

Hallucinations are defined as the occurrence of a sensory experience in the absence of an actual stimulus to the sensory organ and may be visual, auditory, tactile, gustatory, or olfactory. Auditory hallucinations are the most common in schizophrenia and occur in 75% of cases (108).

In the DSM-IV, hearing several voices conversing with each other or commenting on the person's thoughts and behavior in the third person are deemed bizarre hallucinations.

Distortions to one's train of thought, often called "formal thought disorders," leads to *disorganized speech.* Answers to a question may be tangential or irrelevant. Speech may "slip off the track" with loose associations and derailments or become incohesive and, at worst, incomprehensible. *Disorganized behaviors* are severe disturbances that may display as sudden or unpredictable agitation, including swearing or violence, inappropriate behavior, or dressing in a very unusual or inappropriate manner.

Catatonic behavior describes a gross reduction in one's reactivity to the environment. This behavior comprises holding an inappropriate or bizarre posture over time, holding a rigid posture and resisting attempts to be moved, excessive, purposeless, and unstimulated motor activity, and catatonic stupor, where the person is unresponsive to external stimuli (105).

Negative symptoms

In the DSM-IV, negative symptoms comprise affective flattening, alogia, and avolition (105). However, current conceptualizations of negative symptoms include five negative subsymptoms: *avolition-apathy* (reduced initiation and persistence in goal-directed activity because of reduced motivation), *anhedonia* (reduced capacity to experience pleasure), *asociality* (indifference or reduced interest in close relationships and social activities), *blunted affect* (reduced expression of affect in facial expressions, gestures and voice prosody, i.e., intonation, tone and speed), and *alogia* (reduced quantity of speech and diminished tendency to spontaneously elaborate) (5). See also section 1.2.

Cognitive symptoms

Cognitive symptoms are seen as a core feature in schizophrenia (109) and refer to impediments in cognitive domains such as memory, attention, processing speed, executive functioning, learning, and reasoning. Cognitive symptoms are often present years before psychosis onset, may affect all domains, and are strongly associated with reduced functioning in schizophrenia (47, 110).

Excitative symptoms

These symptoms are more often present in psychotic exacerbations with concurrent manic symptoms (111) and include uncooperativeness, reduced impulse control, hostility, agitation, and excitement (106).

Affective symptoms

The most frequent affective symptoms in schizophrenia are depressive symptoms (9). See further descriptions in section 1.1.6. Manic symptoms may also occur, and core symptoms comprise an elevated, expansive, or irritable mood and increased levels of energy or activity (7).

1.1.3 Diagnostic criteria

Currently, the diagnostic manuals in clinical use are DSM-V (7) and the International Classification of Diseases, 10th version (ICD-10) (112). Much like many other research studies, the current study uses the DSM-IV (105), because participant inclusion started before the introduction of the DSM-V in 2013. I will describe the diagnostic criteria for psychotic disorders according to the DSM-IV, as applied in the current thesis.

Schizophrenia

A diagnosis of schizophrenia requires the presence of an active phase: A) At least two (or one, if the symptom is bizarre) out of five symptoms (delusions, hallucinations, disorganized speech, grossly disorganized behavior/catatonia, negative symptoms) should each have been present for a significant proportion of time for one month (or less if successfully treated). B) One or more areas of functioning must have been markedly reduced compared with prior functioning and present a significant proportion of time since onset. C) The disturbance persists for at least six months, including the active phase, and prodromal or residual phases where two or more attenuated symptoms or only negative symptoms are present. D) Schizoaffective disorder and mood disorders with psychosis can be ruled out because 1) no mood episodes have been present concurrent with the active phase or 2) the duration of mood episodes is brief compared with the total duration of the illness. E) The disturbance should not be caused by substance use or a medical condition. F) If the person has a pervasive developmental disorder or autism, a schizophrenia diagnosis is only added if delusions or hallucinations are prominent.

Schizophreniform disorder

The features of this disorder are similar to schizophrenia, except the duration is shorter (at least one month and less than six months). Reduced functioning is not required but may occur. Over time, many people with schizophreniform disorder will go on to fulfill the criteria for schizophrenia (113, 114).

Schizoaffective disorder

The diagnostic criteria are identical to those for schizophrenia, but affective episodes are more prominent. Manic, depressive, or mixed episodes occur concurrently with criterion A symptoms and are present for a substantial proportion of the time since the onset of the psychotic illness. Psychotic symptoms must be present for at least two weeks in the absence of mood symptoms to enable discrimination from a mood disorder with psychotic symptoms.

Delusional disorder

This disorder is characterized by prominent, nonbizarre delusions that persist for at least one month (105). Criterion A for schizophrenia must never have been met. Hallucinations are not prominent, and if they occur, they should be related to delusional content. Mood symptoms or episodes, if present, have a brief duration compared with the duration of delusions. Functioning is not markedly impaired or changed, apart from the impact of the delusions and their consequences.

Brief psychotic disorder

The disorder is characterized by the abrupt onset of a psychotic episode with at least one criterion A symptom for schizophrenia being present. Often, psychosis is accompanied by intense confusion and rapid shifts in affect. The episode lasts at least one day but less than a month and is followed by full recovery to the premorbid level of functioning.

Psychosis not otherwise specified (PNOS)

This category includes psychotic episodes with criterion A symptoms, yet there is inadequate or contradictory information to make a specific diagnosis, or the criteria for a specific diagnosis are not met.

Bipolar or unipolar mood disorder with psychotic symptoms

Mood disorders are characterized by episodes of mania or depression. Some individuals also experience psychotic symptoms. A diagnosis of a mood disorder is given in DSM-IV if the psychotic symptoms are experienced within, but not outside of, a mood episode, irrespective of the characteristics of the psychotic symptoms. Although mood-congruent psychotic symptoms are the most frequent, some individuals experience concurrent psychotic symptoms that are not congruent with the current mood. These may include delusions of thought-broadcasting or thought insertion or delusions of control, which may meet criterion A for schizophrenia. Thus, it may be difficult to differentiate between this type of mood disorder and schizoaffective disorder in FEP.

1.1.4 First-episode psychosis

Until the start of the 1990s, schizophrenia research was typically "watching the endgame". Studies included individuals with chronic illness, whereas the newly ill were comparably neglected. Thus, a better understanding of clinical phenomenology, biological correlates, and treatment effects closer to the first onset of psychosis was crucial (115, 116). FEP studies have allowed for prospective study designs and reduced confounding from chronicity, institutionalization, and medication. Currently, FEP studies may include participants within a broad psychosis spectrum or more narrowly defined, as a first-episode schizophrenia (117). Because there is no general consensus, the definitions of a FEP vary across studies (118). In our studies, a FEP is defined as a psychotic episode that has not previously been adequately treated with antipsychotic medication or by admission to an inpatient clinic (see section 3.2).

Early FEP studies have shown that treatment delay, that is, a long DUP is associated with more severe symptoms and functional impairment (119), which is still supported by evidence (120). Thus, reducing DUP has been a central target for early intervention strategies in psychotic disorders (119, 121). Further, early research indicated that there is an early critical period for illness development during the first two to three years after psychosis onset. During this period, a marked deterioration of functioning takes place and is then followed by a stable plateau (11, 122). The notion of an early critical period may include the early treated and untreated phases of illness and appears to set the stage for the years to come. Early and adequate treatment of the first psychotic episode has shown to be beneficial for the long-term development of symptoms and functioning (123).

1.1.5 The psychosis continuum model

According to Kraepelin, manic-depressive illness and dementia praecox are separate disease entities and could be discriminated by symptoms, illness course, and outcomes (6). The divide between the bipolar and schizophrenia categories has since been criticized for not mapping the underlying biology and for disregarding the co-occurrence of prominent psychotic and affective symptoms in severe mental illness (81, 124, 125). In the alternative psychosis continuum model, symptoms are suggested as having a continuous distribution across current diagnostic borders (126-128). It has been argued that the dimensionality of psychotic phenomena should be reflected in the diagnostic criteria and in the names of the illnesses, for example, "psychosis spectrum disorders" (129). However, there is disagreement with this view (130, 131).

A continuous symptom distribution is first indicated by the presence of psychotic symptoms or experiences in the general population (126, 132) and in mental illnesses other than psychotic disorders (25, 133). Second, the familial coaggregation of bipolar disorder and schizophrenia in relatives of probands with schizophrenia (19) and genetic pleiotropy across schizophrenia, bipolar, and major depressive disorders (and range of other mental illnesses) (76, 77, 134) supports a continuum. Moreover, the frequent presence of affective symptoms in schizophrenia (9) and the longitudinal instability of psychotic disorder diagnoses challenge the notion of separate categories: schizophreniform disorder, brief psychotic disorder, and psychosis not otherwise specified are the most prone to diagnostic shifts, though changes in bipolar and schizophrenia diagnoses may also occur (113, 114, 135, 136). Considering the above, along with the lack of valid biomarkers for any psychotic disorder, it is fair to say that the current diagnostic categories do not likely represent separate disease entities and that neither schizophrenia nor bipolar disorder are unitary constructs. In so far, bipolar disorder and schizophrenia remain separate categories in the current DSM-V, where, however, the autism *spectrum* disorders were introduced (7).

1.1.6 Depression in first-episode psychosis

According to the DSM-IV, a major depressive *episode* is characterized by the presence of a sufficient number of depressive *symptoms* during a period of at least two weeks and causes significant clinical distress or impaired functioning (105). A diagnosis of a major depressive *disorder* requires the presence of one or more major depressive episodes. However, depressive *symptoms* may occur at lower levels and shorter durations and may have fewer negative effects to the individual. Over the course of schizophrenia, different expressions of depressive mood (depressive symptoms or major depressive episodes, here grouped together as "depression")

can occur at any time (137) but are more frequent in the early phase and may antecede psychosis onset by years (138-140).

Depression typically follows a fluctuating trajectory and tends to coincide with psychotic exacerbation (141, 142) but may also be persistent (15, 143, 144) and occur in between psychotic episodes (145). The prevalence of depression after a FEP is reported to be 14–45% (140) but up to 80% when closer to psychosis onset (144). Thus, prevalence rates vary greatly, perhaps because of the differences in study designs, the assessment scales and cut-offs applied, and whether depressive symptoms, episodes, or disorders are reported. The clinical features of depression in the context of a psychotic disorder appears similar to other depressions (146) and a low mood, decreased feelings of pleasure or interest (i.e., anhedonia), and reduced energy are among the central symptoms (147). Persistent depression is understudied in FEP, but current evidence suggests a prevalence between 14% and 26% during follow-up periods of 12–18 months (14, 143, 144). The etiology and mechanisms underlying the development of depression in schizophrenia are still poorly understood. Hypotheses are complex and multiple, involving, for example, depression 1) as a "smoking gun evidence" of previous childhood adversity, 2) as a psychological reaction to the psychotic illness and its implications, or 3) as an intrinsic part of the psychotic illness (9, 137, 145).

Previously, comorbid depression was regarded a positive prognostic factor in schizophrenia (11). More recent evidence tells a different story (12, 13). Concurrent depression in FEP or early course illness is associated with an increased risk of suicide (58, 148) and psychotic relapse, more substance use, and involvement in violence or accidents (142, 149), albeit some studies have reported a reduced likelihood of hospital admissions and substance use (143). Concurrent depression is associated with poorer life satisfaction and quality of life (149-151), and reduced functioning in many (13, 14, 151-153), but not all, studies (141, 143). Moreover, the evidence suggests that persistent depression is associated with more severely impaired functioning in FEP (14, 143) and that early course persistent depression may predict an unfavorable trajectory for years to come (154). However, few studies have explored this phenomenon in FEP, and the interpretation of the findings has been hampered by applying depression assessment scales that do not easily discriminate depression from negative symptoms in this population.

1.2 Negative symptoms

Historically, the understanding of negative symptoms and their significance for diagnosis has varied considerably (22, 155). In 2005, the National Institute of Mental Health (NIMH) reached a consensus conceptualization that is still largely agreed upon today (23): the negative symptom dimension is considered heterogeneous and includes five subsymptoms clustered into two separate but interrelated domains. The *experiential domain* comprises apathy, anhedonia and asociality and is interchangeably called "experiential deficit," "amotivation," or "apathy-avolition." The *expressive domain* (or "diminished expression") includes blunted affect and alogia (24, 156, 157). The two-domain structure is reproduced across different patient populations (24), applying older psychometric scales such as the Scale for the Assessment of Negative Symptoms (SANS) (24) and the PANSS (158) and newer scales such as the Clinical Assessment Interview for Negative Symptoms (CAINS) (159, 160) and the Brief Negative Symptom Scale (BNSS) (161).

The two domains display differential relations to illness antecedents, patient characteristics, and outcomes and are assumed to have partly separate neurobiological substrates (4, 162, 163). Whereas research indicates that the experiential domain is associated with aberrant functioning of brain reward circuitry, specific cognitive impairments, and psychological factors, a reduced perception of emotion and diminished cognitive resources may be more relevant for expressional domain symptoms (162, 164). It is further conceivable that unique or partly discrete mechanisms underpin each subsymptom (157). Recently, it was suggested that the latent structure of negative symptoms was better represented by subsymptoms than by domains, and the authors argued that the mechanisms underlying single subsymptoms should be better explored (165, 166). In sum, progress in etiological research may be impeded by negative symptom heterogeneity, and valuable information is likely overlooked if this dimension is handled as a unifactorial construct (4, 157). Thus, reducing heterogeneity is an explicit strategy in negative symptom research (23, 164).

In a similar line of reasoning, differentiating between *primary* negative symptoms, which are regarded as being inherent to core pathophysiological processes in schizophrenia, and *secondary* negative symptoms, which are caused by other factors such as depression, medication side effects, or positive symptoms, is crucial (10, 167). Primary negative symptoms are suggested as being trait-like, persistent, and treatment resistant, whereas the secondary negative symptoms are more likely transient and responsive to treatments of the underlying

cause (167, 168). Postulating that primary negative symptoms are intrinsic to core illness processes could imply that they only are present in schizophrenia. However, some evidence suggests that putatively primary negative symptoms are present across psychotic disorders, in other mental and neurocognitive illnesses, and at attenuated levels in the general population (25, 26, 37).

Other conceptualizations of inherent negative symptoms are based on their persistent nature (169). Among these, deficit schizophrenia (DS), or deficit syndrome, is characterized by primary negative symptoms that persist for at least 12 months in individuals with a diagnosis of schizophrenia (170, 171) independent of secondary negative symptoms (169). DS is claimed to be a separate disease entity within the broader schizophrenia syndrome (171, 172), but this is not universally accepted (26, 163, 173). A related and broader concept is persistent negative symptoms (PNS). PNS are treatment resistant, persist over time (usually six months), are primary with low levels of co-occurring secondary negative symptoms (23, 169, 174) but may include secondary negative symptoms not responding to treatment (169). Both the DS and PNS are associated with grave functional impairments (169).

The onset of negative symptoms may forerun the first psychotic episode by years (46, 175). Thus, although negative symptom etiology is still poorly understood (25, 164), an early substrate for the development of negative symptoms is plausible. The development of negative symptoms is considered closely related to aberrant neurodevelopment and reflected in impaired premorbid social or school functioning (176-178), more cognitive symptoms, and neurological soft signs in those with severe negative symptoms (169, 179). Furthermore, epidemiological studies suggest that negative symptoms are heritable (180-182), though the results from GWASs are more ambiguous (183, 184). Research has implied that psychological (185, 186) and biological environmental factors (187) may be relevant for negative symptom development and maintenance.

During the course of the disorder, negative symptoms have been previously reported as stable or increasing over time (188, 189), but studies may have been biased by including mainly patients with chronic illnesses (115, 116). In FEP, considerable diversity can be found, with significant fluctuation or even remission along with persistently high or low negative symptom trajectories (33, 190, 191). Some FEP studies have suggested that there is an early critical period for negative symptom development (28, 192), but the evidence on this is unclear (27). The most

consistent predictors of an unfavorable negative symptom course in FEP are male gender, early illness onset, reduced premorbid functioning, a long DUP, and a diagnosis of schizophrenia (28, 32, 33, 190, 193-195). However, the longitudinal development and predictors of the negative symptom domains and subsymptoms in FEP are understudied (29, 34, 196, 197).

Above and beyond positive symptoms in schizophrenia (3), negative symptoms are consistently and strongly associated with a poorer functioning (4, 5, 37). The functional impairments are more pronounced if negative symptoms persist at high levels over time (172). The substandard effectiveness of the current treatments for negative symptoms is evident (169, 198), and negative symptoms are considered an unmet therapeutic need (23). Moreover, the domains display differential relationships to functioning, with consistent associations between functional impairment and the experiential—but not the expressional—domain (4, 37). Among the symptoms of the experiential domain, the role of apathy is suggested as being pivotal to functional loss (39).

1.3 Apathy

1.3.1 Current understanding and conceptualization

Kraepelin noted a "...weakening…of the mainsprings of volition" as a clinical hallmark in dementia praecox cases (6), while Eugene Bleuler (1857–1939), who later coined the term schizophrenia, afforded pictorial descriptions of affect and behaviors—or lack of such—in his patients:

> *... The patients appear lazy and negligent because they no longer have the urge to do anything either of their own initiative or at the bidding of another. They can spend years in bed. In mild cases, where wishes and desires still exist, they will nevertheless do nothing toward the realization of these wishes ...*
>
> *... The most severe schizophrenics live in their own rooms as if in a dream, at times moving about like automatons, without any external goal; at other times, they remain silent and motionless, their contact with the external world is reduced to an intangible minimum ...* (199, pp. 70-94).

The word apathy stems from the Greek "*apatheia*," for which the direct translation is "without feeling or passion" (200). In current daily language, apathy describes a lack of feeling or emotion, interest, or concern, which is similar to—but not an exact reflection of—the current concept of apathy in the field of psychiatry. In the psychiatric literature, apathy may also be

called “avolition,” “amotivation,” or “avolition-apathy.” There is no general agreement regarding any discrepancies between the terms, and for most practical purposes, they are considered analogous and used interchangeably in the literature (4, 39). The definition of apathy applied in the current thesis stems from the seminal works of Robert Marin, which states that apathy is a “*reduced goal-directed behavior due to reduced motivation, not attributed to diminished level of consciousness, cognitive impairment or emotional distress*” (201, 202). Marin argued that observing goal-directed behavior alone was insufficient when evaluating apathy (202). In concert with Marin, the current conceptualization of apathy comprises these behavioral aspects, as well as their emotional and cognitive concomitants (4). When assessing apathy, it is recommended that the interest and desire for—as well as the actual initiation and persistence of—goal-directed behavior be evaluated (4, 157).

Apathy may be present in various mental illnesses other than psychotic disorders, such as major depression, bipolar disorder, and post-traumatic stress disorder (25). Moreover, Marin called apathy “a neuropsychiatric syndrome,” reflecting the fact that apathy transgresses the boundaries between psychiatric and neurological illnesses (202, 203). In fact, the term apathy is more commonly used in the context of neurology than in psychiatry. Apathy is frequently present in neurodegenerative disorders such as Alzheimer’s (204), Parkinson’s (205), or Huntington’s diseases (206) and after traumatic brain injury or cerebral stroke (207, 208). It is not known whether apathy in neurodegenerative disorders and mental disorders other than psychotic disorders is primary and intrinsic to the disorders or secondary to other factors (or both) (25). A central NIMH initiative regarding the convergence or divergence of mechanisms for symptom development across diagnostic categories is the Research Domain Criteria (RDoc) project. RDoc aims to link the overarching phenotypes to their underlying biology at the level of genes, cells, neurocircuits, physiology, and behavior, thereby improving the classifications afforded by the DSM and ICD diagnostic systems (209-211). Within the RDoc project, apathy relates to the “positive valence system” that comprises the fundamental brain–behavior processes involved in motivation and reward (4, 212).

1.3.2 Etiology and mechanisms

Traditionally, etiological and mechanistic research has explored the underpinnings of negative symptoms as one single dimension. Lately, the focus of attention has shifted toward the negative symptom domains, whereas only a minority of studies have focused on apathy as an individual subsymptom. Thus, the insights into the mechanisms contributing to the formation of apathy stems mostly from the research attending to the experiential domain (157). The

determinants and mechanisms underlying the development of apathy in schizophrenia are still poorly understood (213). Still, it has been argued that psychological, cognitive, and reward processing factors may all be relevant (162, 214). Moreover, environmental etiological factors have been extensively studied in relation to psychotic disorders in general (84, 215). However, such factors, which may be biological (e.g., malnutrition or exposure to toxins or infections during pregnancy) or psychosocial (e.g., childhood adversity or social deprivation), have received less attention in relation to broad negative symptoms (216) and apathy specifically.

Understanding the mechanisms of motivation and reward has become central for research into the underpinnings of apathy in psychotic disorders and capitalizes on the theory, methods, and measures from affective and cognitive neuroscience (162, 217). Motivation and reward-related processes involve several interacting facets, where an impairment in one or more facets may propagate forward into the system. These facets comprise (simplified): 1. *consummatory hedonic* experience (i.e., the in-the-moment "liking" of a reward), 2. *anticipatory hedonic* experience (i.e., predicting and "wanting" a reward), 3. *reinforcement learning* (i.e., learning from previous rewards), 4. *reward and effort valuation* (i.e., a cost–benefit analysis), and 5. *development and execution of an action plan* to attain a reward (218-220). Evidence has suggested that the facets involve partly distinct brain regions, with key roles designated to the nucleus accumbens, striatum, and palladium within the basal ganglia and the orbitofrontal, anterior cingulate, and dorsolateral prefrontal cortices (221).

Research has shown that several motivational facets are impaired in schizophrenia, especially when the negative symptoms from the experiential domain like apathy are prominent (218, 219). In people with schizophrenia, in-the-moment liking (i.e., consummatory hedonic experience) appears intact in laboratory settings, but a putative positive stimulus may also result in more negative emotions compared with healthy controls (217, 222). This has been argued to result in a positive versus negative emotion imbalance that could impede motivated behavior (214). Furthermore, people with schizophrenia have a reduced inclination to foresee that an event will be pleasurable and have less feelings of pleasure when anticipating a reward (217, 218, 220). The evidence additionally suggests impairments in the capacity to compute the value of a reward, in the willingness to exert a high effort to attain a reward, and in creating an action plan for goal attainment (218-220). Finally, the relevance of and relations to cognitive impairments in schizophrenia have been questioned: some studies have implied that apathy may be related to impaired executive functioning or that the capacity to withhold emotional

information in working memory is reduced (162). However, the findings are contradictory, and currently, the relations between diminished motivation and cognitive impairments in schizophrenia are uncertain (162, 164, 221).

The development and maintenance of apathy (or experiential domain symptoms) are further suggested as being influenced by psychological mechanisms. One model implies that negative symptoms develop as part of a psychological defense against an anticipated failure in task performance (223). Defeatist performance beliefs (DPBs) like "Why bother, I'll just fail again" are theorized as resulting from repeated experiences of failure because of the early cognitive impairments in schizophrenia (185, 223). DPBs have shown positive associations to broad negative symptoms (186) and the experiential domain specifically (224, 225). Other psychological models pose a role for negative expectancy appraisals (226), reduced self-efficacy (227), and self-stigma (228). A link between apathy and reduced social cognition has also been questioned, yet the results are mixed, and research currently implies that social cognition is more relevant for the expressive domain (162).

The patterns of familiality and heritability for apathy remain largely unexplored, and currently, the findings are inconsistent for the negative symptom dimension: several, but not all (229), epidemiological studies have suggested the familiality of negative symptoms in schizophrenia, with reported heritability estimates of 0.38 (182) and 0.55 (230). The findings from family studies have also supported a genetic component to negative symptom etiology: compared with the relatives of healthy controls, the relatives of a proband with schizophrenia (hereafter: proband) have more negative-like symptoms (181). Further, negative symptoms in the proband predicts higher levels of negative-like symptoms in relatives (231). If the proband has severe negative symptoms (i.e., DS), their relatives likewise have more negative symptoms but also an increased risk for schizophrenia compared with the relatives of a proband with less severe negative symptoms (232). Further, the probands with a family history of schizophrenia show more severe and treatment-resistant negative symptoms compared with the probands without such family histories (233). Comparably, a study exploring psychotic experiences in a large community sample of adolescent twins suggested higher heritability 1) at the severe end of the negative symptom distribution and 2) for negative symptoms and paranoia compared with other psychotic experiences (234). Taken together, epidemiological research has indicated an association between negative symptoms and the genetic vulnerability for schizophrenia, suggesting that negative symptoms are credible candidates for molecular genetic research.

A review of GWASs in general population samples has displayed mixed results (184), but the most well-powered studies have implied a shared genetic influence between schizophrenia, psychotic experiences, and negative symptoms (184). Moreover, significant associations between negative symptoms and several concrete genetic variants have been shown in schizophrenia, but the findings lack replication, and the studies are hampered by limitations (235). In a schizophrenia GWAS, no SNPs showed genome-wide significant associations to symptom dimensions, but the SNP-related functional pathways for negative and positive symptom development were suggested as being partly distinct (236). Furthermore, studies exploring the associations between SZ PRS and negative symptoms have provided conflicting results. Whereas evidence of a positive association between SZ PRS and negative symptoms was found in one healthy adolescent sample (237), a negative association was reported in a similar population (238). In schizophrenia samples, some SZ PRS studies have failed to find a significant association with negative symptoms (239), while other studies have reported significant negative (240) or positive associations (241). A single study by Jonas et al. has previously explored the associations between SZ PRS and levels of apathy (or "avolition") in a first-admission sample of individuals with an affective, nonaffective, or substance-induced psychosis (242); during a 20-year follow-up, they found that the SZ PRS showed significant positive associations with levels of apathy.

In sum, the findings from molecular genetic studies have shown to be inconsistent. Importantly, except for the study on avolition by Jonas et al. (242), neither molecular nor epidemiological genetic studies have taken the heterogeneity of the negative symptom dimension into account. The putative discrete biological substrates for negative symptom domains or subsymptoms (162, 164) have been barely attended to. As a result, a genetic signal from a more homogenous subsymptom like apathy may have been obscured.

1.3.3 Development, predictors, and persistence

Apathy may arise long before psychosis onset and is highly prevalent in FEP and early course schizophrenia: in a FEP sample (hereafter: the "TOP apathy study") partly overlapping with the study samples comprising the data in the present thesis, 51% and 40% of the study participants had clinically significant levels of apathy at study inclusion and one-year follow-up, respectively (30, 38). In early course schizophrenia, two studies reported relevant levels of apathy in 30% and 77% of the study participants (243, 244). FEP studies further suggested that high levels of apathy may persist over time. In a 1-year (38) and 10-year follow-up study (29),

persistent apathy was found in 30% of the participants, whereas a 5-year follow-up suggested that experiential domain symptoms persisted in 16% (197).

The overall long-term development of apathy in FEP is uncertain because most studies to date include people with chronic illness (245-249), apply cross-sectional (245, 246), or short-term follow-up study designs (38, 248, 250) use rating scales that are not designed to map the individual apathy subsymptom (243, 244, 247, 251, 252) or instead investigate the broader experiential domain (34, 197). The only FEP study that has previously mapped the long-term development of apathy was part of the Early Treatment and Intervention in First-Episode Psychosis study (i.e., the TIPS study). The findings suggested two separate apathy trajectories: one with steadily decreasing apathy and another with stable and high levels during the 10-year follow-up (29). However, this TIPS study (hereafter: the "TIPS apathy study") did not introduce a specific apathy rating scale until the 10-year follow-up assessment; they applied a proxy measure based in two PANSS items at previous follow-up points, adding to the uncertainty regarding the interpretation of their findings.

Very few studies have explored the predictors of apathy development in FEP, but some have investigated the predictors of experiential domain development. Two studies found that higher levels of experiential domain symptoms at the one-year follow-up were predicted by 1) higher baseline experiential domain symptoms and reduced executive functioning (253) and 2) reduced premorbid functioning and higher baseline experiential and expressional domain symptoms (254). Significant positive associations between DUP and experiential domain symptoms at study inclusion (255) and at the two-year follow-up have also been described (256). In the TOP apathy study, higher apathy levels at one year were predicted by a long DUP and high apathy levels and a diagnosis within the schizophrenia spectrum at baseline (38). In the TIPS apathy study, however, no baseline or premorbid variables predicted apathy levels at the 10-year follow-up (29).

Taken together, current knowledge regarding the trajectories of apathy in FEP is scarce, but studies have suggested that a subgroup may experience a decline in apathy, while others could be prone to an unfavorable course with persistent apathy. In a short-term time horizon, the apathy course may be predicted from baseline, but in the long-term, the predictors are unknown. Identifying and attending to early predictors may have the potential to change the long-term apathy trajectory. However, currently, no studies in FEP have explored the long-term trajectory

of apathy and its predictors using a validated rating scale to assess the specific apathy subsymptom at all follow-up points, which is what we did in Study III.

1.3.4 Relation to depression

Depressive and negative symptoms repeatedly stand out as separable dimensions of psychopathology in schizophrenia (106, 111) and in FEP samples (128, 257). However, because of phenotypic similarity, distinguishing apathy as a part of the negative symptom dimension from depression is a complex undertaking (10, 167). Enabling a reliable discrimination is essential in research and to inform clinical therapeutic decisions. These issues are highly relevant in FEP, where apathy is frequent (30, 38) and depression is more prevalent than later in the course illness (137, 140). Notwithstanding this, most depression rating scales that are currently used in psychosis research and clinical practice do not readily separate negative symptoms from depression in the psychosis population (258). The Calgary Depression Scale for Schizophrenia (CDSS) was designed to enable a reliable discrimination from negative symptoms (259, 260). Evidence supports its superior properties in differentiating between depression and the negative symptoms of schizophrenia (258). Thus, the CDSS is regarded as the instrument of choice and was applied in the three studies included in the current thesis.

Adding to the putative relevance of depression in relation to apathy are perspectives from a review of secondary negative symptoms by Kirschner et al.; they proposed that the understanding of primary negative symptoms may profit from the study of secondary negative symptoms (10). The authors argued that the phenotypical similarity may indicate partly shared pathophysiology but that the underlying causal factors could differ depending on the primary or secondary status of the negative symptoms. Thus, the differentiation of causal pathways may be facilitated by also studying secondary negative symptoms (10). Nonetheless, most research has focused on primary negative symptoms, whereas secondary negative symptoms are comparably understudied (10), and studies concurrently investigating depression and primary negative symptoms like apathy are scarce (261).

Currently, the findings from two studies in schizophrenia have suggested significant positive associations between depression and expressional domain symptoms during a short-term follow-up (262) and that the associations between depression and apathy may increase in strength during a long-term follow-up (263). However, these studies were first-admission (263) and non-FEP-samples (262); one of them applied the CDSS, and neither used a specific measure for apathy, hence adding to the uncertainty regarding their interpretation. Furthermore, no

previous studies have simultaneously explored the early presence of persistent apathy and persistent depression in FEP. Thus, it is not known whether persistent apathy and persistent depression overlap in this population. Also, the associations between the two persistent symptoms and functional outcome—alone and together—have not previously been compared.

1.3.5 Relation to functional outcome

Beyond the effects of other negative symptoms, apathy has emerged as fundamental to the relationship with a poor functional outcome (5, 39) and may affect recreational activities, school or work, and self-care. The associations between apathy and a worse functional outcome have been demonstrated in chronic illness (244-246, 250, 264) and in cross-sectional and longitudinal studies in FEP (29, 30, 38, 251, 252, 256). Moreover, in line with the research literature on DS and PNS (169, 172), having persistent apathy is associated with even poorer functioning (38) than having apathy that fluctuates over time. Recent evidence further suggests that apathy does not pass unnoticed to individuals with schizophrenia (265). Adding to the burden of having apathy are associations with subjective distress in the individual (266) and reduced quality of life in FEP (29).

1.3.6 Assessing apathy

Several rating scales have been designed to assess apathy across neuropsychiatric disorders (267) and in schizophrenia (268, 269). However, broader rating scales like the PANSS and SANS—rather than more specific apathy scales—are often applied in psychotic disorders (268-271). Although the experiential and expressional domains are replicated in the PANSS and the SANS (24, 158), they do not adequately represent the apathy subsymptom as currently conceptualized (4, 156, 164). These older scales have first been criticized for including items that assess cognitive functioning, and second for only assessing overt goal-directed behavior, whereas the emotional and cognitive aspects of motivation are not explored (268, 272). Newer scales like the CAINS (159, 160) and the BNSS (273) were designed to overcome these and other limitations. The development of self-report instruments lags behind that of observer-rated scales (268), which is perhaps influenced by previous evidence questioning the reliability of self-reports of negative symptoms in psychotic disorders (274). However, a high correlation between newly developed self-report instruments and observer-rated scales—at least for experiential domain symptoms—stands in contrast to such a notion (275, 276).

Among the specific apathy scales, the Apathy Evaluation Scale (AES) was used in Studies I–III (41-43). The AES was developed by Robert Marin (201, 203) and is more commonly used in neurology than psychiatry. However, a transdiagnostic review deemed the AES as being

among the two most robust apathy scales for cross-disorder use (267). The scale comes in a self-report (AES-S), a clinician-rated (AES-C), and an informant-rated (AES-I) version, all mapping the levels of apathy during the past month. The actual behavior and cognitive and emotional engagement are evaluated. Marin also emphasized the need to differentiate between apathy and depression. The AES has demonstrated a satisfactory discriminant validity in the original studies by Marin and later in FEP as part of the TOP apathy study (201, 277). We applied the AES-C in Study II, and the AES-S in Studies I and III. For further description of the AES, see section 3.3.

2 THESIS AIMS

The overall aims of the current thesis were to explore the genetic underpinnings of apathy, to describe long-term apathy development after onset of the disorder, and to investigate the early predictors of this development in FEP. We aimed to examine the tendency of persistence and overlap between apathy and depression and their contributions to functional outcome in the short- and long-term perspectives in FEP.

In Study I, we investigated the cross-sectional associations between levels of apathy and SZ PRS, which represents the polygenic vulnerability for schizophrenia, in a sample of FEP and MEP combined compared with healthy controls. The specific aims were as follows: 1) to examine whether apathy levels were associated with SZ PRS in participants with schizophrenia spectrum disorders or in healthy controls and 2) to examine whether SZ PRS added to the explained variance in apathy levels compared with the premorbid and clinical characteristics in schizophrenia spectrum disorders.

In Study II, we investigated the cross-sectional and longitudinal associations between depression, apathy, and functional outcome in a one-year follow-up of FEP. The specific aims were 1) to explore the associations of current levels of depression and apathy with functioning at baseline and at one-year follow-up, 2) to describe the prevalence of persistent apathy and persistent depression and to what extent they overlapped during the one-year follow-up, and 3) to explore the relative contributions by persistent apathy and persistent depression to functioning at the one-year follow-up.

In Study III, we investigated the development of apathy, the predictors of apathy development, and associations to functioning in a 10-year follow-up study. The specific aims were 1) to describe the longitudinal development of apathy in a 10-year follow-up of FEP participants and a group of healthy controls, 2) to explore the early clinical or demographic predictors of apathy development in FEP, 3) to describe the prevalence of clinically significant apathy at the 10-year follow-up, and 4) to explore the associations between apathy and functional outcome at the 10-year follow-up.

3 METHODS AND MATERIALS

3.1 The Thematically Organized Psychosis study

The three studies included in the current thesis are based in cross-sectional and longitudinal data from the TOP study. The TOP study is a prospective, naturalistic, and ongoing multicenter study with the overall aim of increasing the insights into the causes, trajectories, and consequences of severe mental disorders. Since 2002, the participants with psychotic disorders have been consecutively recruited from the south-eastern health region of Norway, the majority from in- and outpatient clinics of the four major psychiatric hospitals in Oslo. Healthy controls from the same catchment areas were randomly drawn from Statistics Norway and invited to participate by letter. By September 2019, approximately 1900 participants and 1200 healthy controls were included. In 2010, a long-term follow-up study was launched. At the time when the present studies were conducted, approximately 150 FEP participants had been reassessed at a 10-year follow-up, and a subset was also reassessed at a 6- and/or at 12-month follow-up.

The NORMENT Center for Psychosis Research, in which the TOP study was embedded, is a translational research center with extensive national and international collaboration. This allows for the sharing of genetic data from participants with psychotic disorders and healthy controls across countries and research centers; data that are used in one of the present studies (Study I).

3.2 Participants

The study participants with a psychotic disorder according to the DSM-IV were consecutively recruited between 2004 and 2009. The majority had a FEP, while a subgroup in Study I had multiple episodes of psychosis prior to inclusion. A psychotic episode was defined as having a score of ≥ 4 on items p1 (delusions), p3 (hallucinatory behavior), p5 (grandiosity), p6 (suspiciousness/persecution), or g9 (unusual thought content) for ≥ 1 week on the PANSS (270). The participants who had not previously received adequate treatment for their psychotic episode were defined as having a FEP. Adequate treatment was defined as admittance to a mental hospital to treat psychosis or using antipsychotic medication in adequate dosage for a minimum of 12 weeks or until remission within those weeks. Some of the participants with a FEP were not able to give an informed consent because of their psychotic state, and the participants were thus eligible for inclusion within 12 months of the start of first adequate treatment. The participants who did not fulfill the first-episode criteria were defined as having multiple episode psychosis (i.e., MEP).

The general inclusion criteria were as follows:

1. Having a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, bipolar and major depressive disorders with psychotic symptoms, or psychosis not otherwise specified
2. Age between 18 and 65 years
3. Having an IQ ≥ 70
4. Speaking a Scandinavian language

The participants with neurological or medical illness that may cause psychosis or symptoms mimicking negative symptomatology were excluded. Participants were not eligible if they had a psychotic disorder because of substance use or had a moderate to severe head injury before inclusion or during the follow-up. Healthy controls that agreed to study participation were screened by phone using the Primary Care Evaluation of Mental Disorders interview at baseline and follow-up assessments (278). The inclusion and exclusion criteria were equal to that of the participants with psychotic disorders, except for the healthy controls, and their first- and second-degree relatives should not have a history of severe mental disorder. A broader personal assessment was then performed in those who met the inclusion criteria.

The studies were approved by the Regional Ethics Committee for Medical Research and the Norwegian Data Inspectorate; all studies were implemented according to the Ethical Principles for Medical Research Involving Human Subjects, the Helsinki Declaration (279). Biological data were collected and stored according to the TOP study's Biobank and Data Inspectorate Approval. Participation was voluntary, and all participants had to be able to give informed, written consent. The participants were informed that they could withdraw from the study at any time. Written consent was renewed at each follow-up point, and the participants were asked whether they could be contacted again. Only the participants who had agreed to future contact were later invited by letter to be reassessed. No information gathered during the study period was shared with their clinician, unless the participant explicitly agreed to and wanted such sharing. Sensitive data that could identify the participants were stored on computers without internet access or in locked containers in locked rooms. Only a selected group of employees were authorized access to information that could link anonymized IDs to specific participants.

In Study I, 281 participants with a schizophrenia spectrum disorder (defined as schizophrenia, schizophreniform, and schizoaffective disorders and psychosis not otherwise specified) were

included. The sample was a combined FEP (n = 186) and MEP (n = 95) sample. We defined "narrow schizophrenia" as having a schizophrenia diagnosis, that is, excluding schizophreniform and schizoaffective disorders, and psychosis not otherwise specified. In addition, 298 age- and gender-matched healthy controls were assessed at baseline. Only the participants (i.e., FEP, MEP and healthy controls) with European ethnicity were included in this specific study because of the PRSs' sensitivity to ancestry.

In Study II, a total of 125 FEP participants within a broad psychosis spectrum (i.e., schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, bipolar and major depressive disorders with psychotic symptoms or psychosis not otherwise specified) were included at baseline. Eighty-eight participants were reassessed at one-year follow-up. At one year, the participants were divided into four independent groups based on the persistence of depressive or apathetic symptoms during the follow-up: 1) participants with persistent depression but nonpersistent apathy (i.e., PDnA), 2) participants with persistent apathy but nonpersistent depression (i.e., PAnD), 3) participants with persistent depression *and* persistent apathy (i.e., PDPA), and 4) participants without persistent depression and persistent apathy (i.e., nDnA).

In Study III, a total of 198 FEP participants with a nonaffective psychotic disorder (i.e., schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, and psychosis not otherwise specified) were included at baseline. The majority were included from the Oslo region and a subset from the Innlandet region. At Innlandet, the participants were reassessed after 7 years, whereas in Oslo, reassessments were done after 10 years. We expected less variation in functioning and symptoms at a later phase of illness and assumed that the results of the analyses would not be significantly influenced by the differences in follow-up times. Thus, the 7- and 10-year assessments were merged and are hereafter called "10-year follow-up." Of those included at baseline, 77 were reassessed at the 10-year follow-up, and 98 participants from Oslo had an intermediary assessment at 6 and/or 12 months. Additionally, 198 healthy controls were included at baseline, of which 59 were reassessed at 10 years, and 82 had an intermediary assessment at 1 year. "Schizophrenia spectrum disorders" were defined as having schizophrenia, schizophreniform, or schizoaffective disorders. See the flowchart in Supplementary Figure 1 (42), section 8.

3.3 Clinical instruments

The participants were interviewed by medical doctors or psychologists using a comprehensive clinical protocol. Supplementary information was collected from medical charts from in- and outpatient treatment prior to inclusion and during the follow-up period and from close relatives or treating clinicians if necessary. The Structural Clinical Interview for DSM-IV Axis-I disorders (SCID-I, Module A-E) (280) was used to diagnose participants according to the DSM-IV (105). All interviewers completed a SCID-I training program based in the University of California, Los Angeles (281). Further, regular supervision by experienced clinical psychologists or psychiatrists was established. Diagnostic consensus meetings were held monthly and led by an experienced clinical psychiatrist and researcher. The interrater reliability of SCID-I diagnoses was satisfactory, with a mean kappa = 0.77 (0.60-0.94) (282).

In Studies I–III, premorbid functioning was measured using the Premorbid Adjustment Scale (PAS) (283). The premorbid phase was operationalized as the time from birth until six months prior to the onset of the first psychotic episode. The PAS scores were divided into social and academic domains of functioning and further into age-based intervals. Childhood (social and academic) scores represent the functioning from birth until 11 years of age, early adolescent scores from 12–15 years, late adolescent scores from 16–18 years, and adult scores from 19 years and older. A higher score indicates lower levels of premorbid functioning. In Studies I–III, we only applied the PAS childhood scores to minimize the chances of confounding by prodromal symptoms, which often emerge during adolescence. If the age at onset of the FEP was before the age of 11, the PAS childhood scores were not computed; thus, they were treated as missing in the analyses.

In Studies I and III, the age at onset of the first psychotic episode was depicted as age at onset (AAO).

In Studies I–III, the DUP was defined as the time in weeks from the onset of the first psychotic episode until the start of the first adequate treatment (284).

In Studies I–III, positive and negative symptoms were assessed using the PANSS, and the five-factor version by Wallwork et al. was applied in the analyses (106). The PANSS Wallwork version consists of 20 items divided into 5 symptom factors: positive, negative, disorganized, depressive, and excited. Only the positive, disorganized, and excited factors were applied in

analyses in Studies II and III because the other two showed collinearity with other measures of negative and depressive symptoms. The items included in the positive factor are p1 (delusions), p3 (hallucinatory behavior), p5 (grandiose ideas), and g9 (unusual thought content), while the disorganized factor includes p2 (disorganized thoughts), n5 (difficulty in abstract thinking), and g11 (poor attention). The excited factor includes p4 (hyperactivity), p7 (hostility), g8 (uncooperativeness), and g14 (poor impulse control).

In Study I, the PANSS Wallwork negative factor was applied in the follow-up analyses, and consisted of n1 (blunted affect), n2 (emotional withdrawal), n3 (poor report), n4 (passive, apathetic social withdrawal), n6 (lack of spontaneity and flow of conversation), and g7 (motor retardation). The rationale for this was that we assumed that our apathy measure (i.e., AES) would tap into the different aspects of the negative symptom dimension than the PANSS negative factor and, thus, that SZ PRS may be associated with one, both, or none of these negative symptom measures. For the same reason, we further applied a PANSS negative symptom two-factor model established by Liemburg et al. to represent the two negative symptom domains (expressive and amotivation) in Study I (158). The expressive domain comprises items n1 (blunted affect), n3 (poor report), n6 (lack of spontaneity and flow of conversation), g5 (mannerisms and posturing), g7 (motor retardation), and g13 (disturbance of volition). The amotivation domain comprises items n2 (emotional withdrawal), n4 (passive-apathetic social withdrawal), and g16 (active social avoidance).
Finally, in Study III, we used the PANSS g12 (insight) item to explore whether our self-reported apathy measure (i.e., AES-S) showed significant associations with a lack of insight, which could suggest that a self-report measure would not validly reflect apathy levels in our study sample.

Two versions of the AES (201) were used to assess apathy: the clinician report version, AES-C (Study II), and the self-report version, AES-S (Studies I and III). The AES has been extensively used to assess apathy across neuropsychiatric disorders (267). Over the last 15 years, the AES-C and AES-S have been validated in FEP in the TOP study cohort (277, 285). The original AES-C and AES-S have 18 identical items. However, factor analysis has shown that an abridged, 12-item version has a higher internal consistency (Cronbach's alpha = 0.9) and more accurately assesses apathy in FEP (277). Accordingly, we removed six items representing "social contact" and "insight" and applied the shortened AES-C and AES-S versions in Studies I–III. Færden et al. found that the abridged AES-C reliably and validly

assessed apathy in FEP, that it reliably differentiated patients from healthy controls, and that psychometric performance was stable across diagnostic groups (i.e., schizophrenia spectrum versus affective psychotic disorders) (277). In the TOP study sample, the AES-S has further shown a high concordance with the AES-C, with bivariate correlations at approximately $r = 0.6$ (285).

The AES-C starts with a brief semistructured interview, in which the participant describes a "typical day" during the last four weeks, and their activities, interests, or hobbies during the same time interval. Based on the interview, the clinician rates items like "Getting things started on her own is important to her" and "She is interested in learning new things" on a 1–4-point Likert scale. The number of activities or interests and the engagement and motivation reflected by thought content and the choice of wording is considered. A score of 1 means the item is "Not at all characteristic," while 2 means "Slightly characteristic," 3 means "Somewhat characteristic," and 4 means "Very characteristic." A higher sum-score indicates higher levels of apathy. A sum-score cut-off ≥ 27 (2 standard deviations above mean for healthy controls) has been used to depict clinically significant apathy levels in several studies using the 12-item version (29, 30, 38). In Studies II and III, we used the ≥ 27 cut-off to identify the fraction of participants with clinically significant apathy at each follow-up assessment. Further, in Study II, the cut-off score was used to identify participants with high levels of apathy at baseline and at the one-year follow-up (i.e., having persistent apathy).

In Studies I–III, we used the CDSS to measure depressive symptoms (260). The CDSS was developed to improve differentiation between depressive and negative symptoms in schizophrenia and has shown superior properties compared with other depression rating scales in the schizophrenia population (258). The CDSS has nine items reflecting depressed mood, hopelessness, self-devaluation/worthlessness, guilty thoughts of self-referral, pathological feelings of guilt, morning depression, early awakening, suicidality, and observed depression. Items are scored on a 0–3 Likert scale, with higher scores indicating more depressive symptoms. A sum-score > 6 predicts a major depressive episode with an 82% specificity and 85% sensitivity (260) and has previously been used as a cut-off score indicating clinically significant depression (14, 154). In Study II, we used a sum-score cut-off > 7 to identify clinically depressed participants. Although such a strict cut-off may increase the chance of false negatives, we prioritized specificity (91%) over sensitivity (85%) (260) to increase the

likelihood that true depression was present. Also, in Study II, a CDSS sum-score > 7 at baseline and 1-year follow-up was used to define participants with persistent depression.

In Studies II and III, we used the Global Assessment of Functioning Scale-split version, functioning subscale (GAF-F) to assess global functioning (i.e., functional outcome) during the week prior to interview (286). The scale ranges from 0 points (i.e., extremely impaired functioning) to 100 points (i.e., perfect functioning). The manual for scoring the GAF-F divides the 0–100 scale into 10 sections. The rater is guided by brief examples of typical levels of functioning for each section. Only problems with functioning caused by mental health issues should be considered.

In Studies I–III, the Alcohol Use Disorder Identification Test (AUDIT) (287) was used to measure alcohol use, and the Drug Use Disorder Identification Test (DUDIT) (288) was used to measure drug use. The AUDIT and DUDIT assess substance use during the preceding year. A higher score indicates more alcohol and drug use, respectively.

In Studies I and III, the use of antipsychotic medication (AP) was explored by participant interview and inspecting medical charts at inclusion and at follow-ups. Some participants used no AP. Others used one AP (i.e., AP1), while some participants used up to three types of AP simultaneously (i.e., AP1, AP2, and AP3). To estimate the individual's total load of AP, we first divided the actual daily dosage of AP 1, AP2, and/or AP3 by their respective defined daily dosages (DDD), as recommended by the World Health Organization (289). These fractions (AP1/DDD, AP2/DDD, and/or AP3/DDD) were then summed, resulting in a "Sum AP" variable. Sum AP was then included as a covariate in appropriate analyses.

3.4 Genotyping, variant imputation, and polygenic risk scores

For Study I, DNA was acquired from the blood or saliva of participants with psychotic disorders and healthy controls. DNA was analyzed in six succeeding batches between 2014 and 2017, at deCODE Genetics, Reykjavík, Iceland, using Illumina Human OmniExpress-12 and Infinium OmniExpress-24 chips and Illumina Global screening arrays. Genotype quality control was done using PLINK version 1.9 (290, 291). The genotyped participants were excluded if 1) more than 5% genotype data were missing, 2) there were mix-up samples (excess of heterozygosity was inspected), or if 3) they were represented twice (we retained one of the duplicates). Further, if the variants deviated severely ($p < 0.0001$) from the Hardy-Weinberg equilibrium, the minor

allele frequency (MAF) was < 5% or had a low yield (information about the variant was conferred by < 95% of chromosomes), they were also excluded.

Variants that were not genotyped in the above-mentioned process were imputed using MaCH (292). The European samples from the Phase III release of the 1000 Genomes project were used as the reference. If a variant was missing in the reference sample or strand alignments were ambiguous, it was eliminated from the sample dataset. Imputation was done in three stages: 1) ChunkChromosome: the dataset was divided into 2500 variant chunks with a 500-variant overlap; 2) MaCH: each chunk was phased (40 rounds, 400 states); and 3) Minimac: each of the phased chunks were imputed to the 1000 Genomes reference panel (20 rounds, 400 states) (293). Lastly, we eliminated variants with $r^2 < 0.2$ or MAF < 0.05. In a postimputation quality control, we excluded 1) the participants whose gender did not match the gender indicated by the X-chromosome marker homozygosity (n = 7) and 2) the participants who were relatives (identity by descent, $\hat{\pi} \geq 0.125$) (n = 4).

Using PLINK (290), a principal component analysis was carried out on a set of independent variants. This was done to inspect any allele clustering caused by population stratification, that is, that subgroups in the sample differ in allele frequencies because of differences genetic ancestry. The analyses resulted in 20 genetic principal components (PCs) that could be used as covariates in the subsequent analyses.

Polygenic risk scores were lastly computed based on the methodology developed by Purcell et al. (70). First, the TOP3-cohort (including our study participants) was removed from the dataset, and a meta-analysis using METAL (294) was performed on the remaining variants obtained from the PGC2. This meta-analysis produced unbiased effect sizes (ln (OR)) for all imputed variants. Then, the variants were pruned according to their LD state, using PLINK's clump option ($r^2 < 0.25$, 500 kb window), and the most significant variants from each LD block were selected. For each of the remaining variants, the specific effect sizes and allele counts were multiplied. The SZ PRS then resulted from summing the (*effect size* x *allele count*) products in each individual included in the TOP3 cohort, which also included the Study I participants. Based on the variants that were significantly associated with case control status at different *p*-value thresholds in the PGC2 reference sample, 16 SZ PRS were computed, from 5 x 10^{-8} to 1, at intervals of half an order of magnitude. Finally, one SZ PRS was selected for the following

analyses based on the *p*-value threshold that explained the most variance (Nagelkerke pseudo-r^2) in the case control status in the complete TOP3 cohort (p_T = 0.1).

3.5 Statistics

Statistical analyses for Studies I–III were performed using the IBM Statistical Package for the Social Sciences (SPSS), version 23 and 25.

For all the studies, variable distribution was inspected in the preliminary analyses. Descriptive statistics were computed as proportions, means, and standard deviations or medians and range depending on the level of measurement and distribution of the data. During further statistical analyses, violations of assumptions of homoscedasticity, linearity, multicollinearity, and independence of residuals were explored when appropriate. Significance levels were pre-set to 0.05, and analyses were two tailed. In Studies I–III, DUP was log10-transformed because of skewness, and in Studies I and II, AUDIT and DUDIT were log10-transformed. In Study III, prior to performing Pearson's bivariate product moment correlation analyses with the AES-S and GAF-F, the following skewed variables were transformed: PAS social, CDSS at 10 years, Sum AP at baseline, and AUDIT and DUDIT at baseline and 10 years (log10-transformed); CDSS at baseline, PANSS insight, and Sum AP at 10 years (square root transformed). In Study II, Spearman's rank-order correlation analyses was applied to inspect the associations between the skewed PAS childhood scores and GAF-F at baseline and at the one-year follow-up.

In Studies I–III, groups were compared in the following manner:

1) In Study I, independent Student's *t*-tests (for continuous variables) and Chi-square statistics (for categorical variables) were used to compare the demographic and clinical variables at baseline in the patients and healthy controls. Further, an independent samples *t*-test was applied to compare the SZ PRS in the healthy controls and participants with schizophrenia spectrum disorders, thereby validating the SZ PRS in our sample.

2) In Study II, Chi-square statistics were used to explore the likelihood of having persistent depression (yes/no) if the participants had persistent apathy (yes/no) during the one-year follow-up. Further, we investigated differences in GAF-F scores at the one-year follow-up between the four independent groups of participants with persistent apathy, persistent depression, both, or no persistent symptoms during the follow-up. Because of an unbalanced number of participants and heterogeneity of variance between groups and skewness of GAF-F scores within groups, we first applied a Kruskal–Wallis test to explore the overall between-groups differences in GAF-F scores. Six subsequent pairwise Mann–Whitney U-tests were

performed to compare which groups significantly differed from each other. Because of multiple comparisons, p-values were adjusted a.m. Bonferroni for six groups (level of $p = 0.05/6 = 0.008$).

3) In Study III, Chi-square statistics and Student's *t*-tests (or Mann–Whitney U-tests if the variable was not normally distributed) were used to compare categorical and continuous variables at baseline between the participants who completed reassessment at the 10-year follow-up and those who dropped out.

In Studies I–III, we applied bivariate correlation analyses (Pearson's or Spearman's Rho, depending on the variable distribution) in the following manner:

1) In Study I, we used bivariate correlation analyses to explore the associations between continuous clinical variables, the SZ PRS, and the AES-S score. As a follow-up of the primary analyses, bivariate correlation analyses were used to investigate the associations between the SZ PRS and 1) the AES-S in participants with a narrow schizophrenia diagnosis and in FEP and MEP participants separately, and 2) the PANSS negative symptom factor (Wallwork et al.'s) and the PANSS amotivation and expressive factors (i.e., the two negative symptom domains). Because the AES-S and the PANSS negative symptom factors were strongly correlated, and these analyses were follow-ups of the primary analysis, we did not adjust for multiple testing. Bivariate correlation analyses were finally performed between the 20 PCs, the AES-S, and SZ PRS. This was done to detect which PCs may confound the associations between SZ PRS and the AES-S score in the subsequent multiple regression analyses.

2) In Study II, bivariate correlation analyses were used to explore the associations between GAF-F at baseline and one-year follow-up and premorbid functioning, DUP, continuously distributed patient characteristics, concurrent AES-C, CDSS, and other symptom scores.

3) In Study III, bivariate correlation analyses were used to explore the associations between continuous clinical variables at baseline and 10-year follow-up, the AES-S at baseline and 10 years, and GAF-F at the 10-year follow-up.

For all studies, as a rule of thumb, the variables with bivariate associations at the $p \leq 0.1$ significance level with the dependent and/or relevant independent variables were introduced as covariates in the ensuing multiple regression analyses.

In Studies I–III, block-wise multiple hierarchical linear regression analyses were applied in the following manner:

1) In Study I, we first explored the independent contributions to the explained variance in AES-S scores by the SZ PRS in the participants with schizophrenia spectrum disorders while adjusting for confounding by PCs and batch number. Next, we added premorbid and clinical variables to this regression analysis to explore their contributions to the explained variance in AES-S while adjusting for secondary negative symptoms.
2) In Study II, to explore the independent contributions to the explained variance in GAF-F at baseline and one-year follow-up by AES-C and CDSS scores and concurrent clinical and demographic variables. The contributions from persistent apathy and persistent depression to the explained variance in GAF-F at the one-year follow-up were also explored using multiple hierarchical regression analyses while adjusting for relevant confounders.
3) In Study III, to explore the independent contributions to the explained variance in GAF-F at the 10-year follow-up by the AES-S and CDSS scores and other concurrent clinical and demographic variables.
As a rule of thumb, the variables were introduced into the regression model in order of lifetime appearance and with the AES and CDSS scores in the last steps after adjusting for relevant covariates. One exception is Study I, in which the SZ PRS was introduced into the equation in the last step.

In Study III, linear mixed models (LMM) analyses were applied to investigate the development of apathy and the predictors of this development in the 10-year follow-up. LMM is regarded as a robust statistical method in longitudinal studies when participant attrition causes missing and repeated measurement introduces dependencies in the dataset (295). The AES-S scores at four follow-up points were used as the dependent variable in the FEP participants. The following equation describes the overall model: $Y_{ij} = (\beta_0 + b_{0i}) + (\beta_{1ij} + b_{1ij}) * \text{time} + \beta_{2ij} * \text{time} * \text{time} + \beta_{3ij} * \text{predictor} + \beta_{4ij} * \text{predictor} * \text{time} + \varepsilon_{ij}$.
Y_{ij} represents apathy levels in an individual i = 1..., 198 at year j = 1..., 10. The estimates of the population's means (i.e., fixed effects) are depicted as $\beta_0 ... \beta_{4ij}$. The specific random intercept and random slope are represented by b_{0i} and b_{1ij}, respectively, and ε_{ij} is the error term. We first employed a growth model to describe apathy development and introduced the fixed effects of time and a curvilinear time trend to the equation. Next, the random intercept and a random slope were added, and the covariance structure (first-order autoregressive heterogeneous, ARH (1)) between them was inspected. The ARH (1) covariance structure assumes that correlations are stronger between repeated measurements that are adjacent in time

than measurements separated by longer time intervals. The best model fit was chosen based on the maximum likelihood. Based on theory and previous research, relevant baseline predictors and covariates of the development of apathy were next introduced. Variables showing significant bivariate associations ($p \leq 0.1$) to apathy development were kept for the ensuing analyses. The interaction terms with time were only explored for predictors showing bivariate, significant associations with apathy development. The predictor*time interaction effect describes whether the effect of the predictor on apathy development increases or decreases over time. In the final equation, we only kept the predictors, the predictor*time interaction terms, and the covariates with significant associations ($p \leq 0.05$) with apathy development. In the healthy controls, the AES-S scores from three follow-up assessments were used as the dependent variable. The principles for building the growth model were equal to that of the FEP participants.

4 SUMMARY OF THE RESULTS

For an overview of the sample characteristics at baseline in Studies I–III, see supplementary Table 1 in section 8.

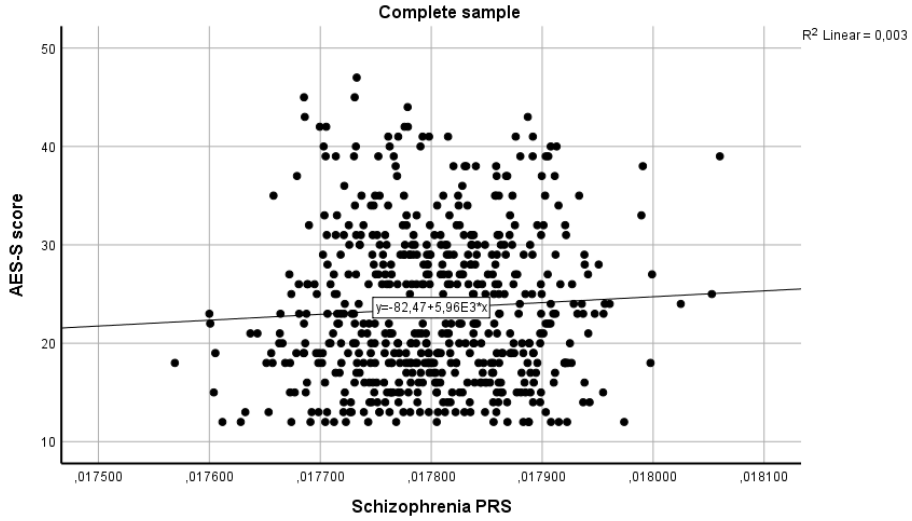
4.1 Study I

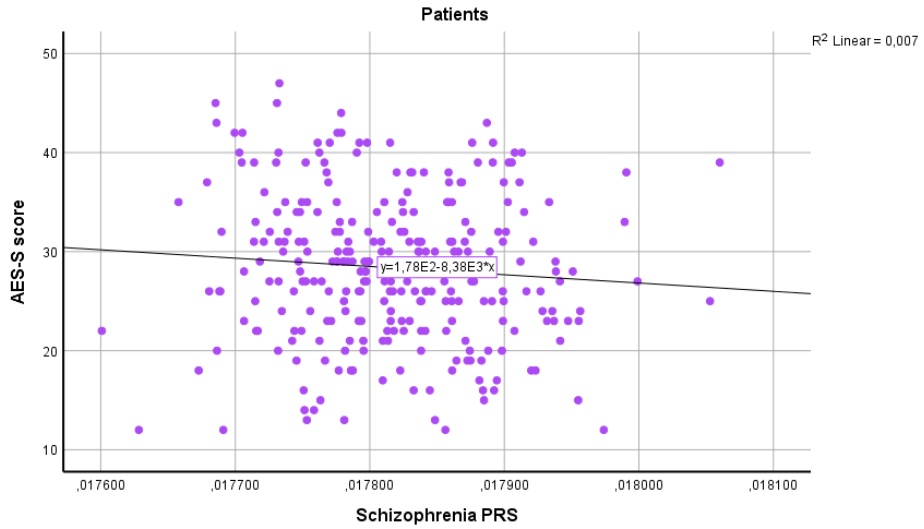
Associations between schizophrenia polygenic risk and levels of apathy in schizophrenia spectrum disorders and healthy controls

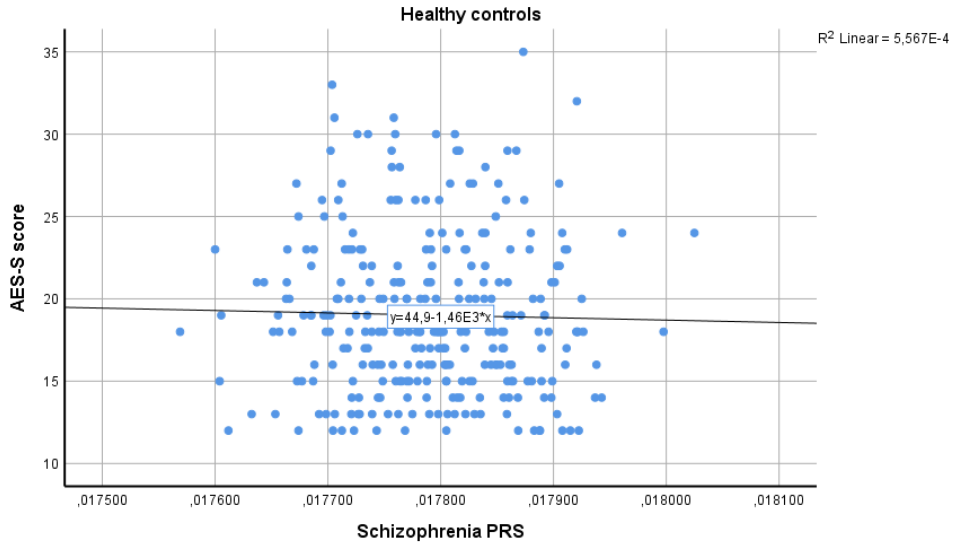
In this study, we investigated the associations between the genetic risk for schizophrenia and levels of apathy in schizophrenia spectrum disorders and in the healthy controls. The specific aims were 1) to examine whether levels of apathy were associated with SZ PRS in participants with schizophrenia spectrum disorders or in healthy controls and 2) to examine whether SZ PRS added to the explained variance in apathy levels when compared with premorbid and clinical characteristics in schizophrenia spectrum disorders.

We first found that the SZ PRS was significantly higher in those with schizophrenia spectrum disorders than in the healthy controls ($t = 4.2$, $p < 0.001$). The scatter plots of SZ PRS and AES-S scores in the complete sample, in healthy controls, and schizophrenia spectrum disorders separately are shown in Figure 1 (41).

Figure 1. Scatter plots of schizophrenia PRS and apathy scores (AES-S) in the complete sample, in individuals with schizophrenia spectrum disorders (i.e., patients), and in healthy controls*







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In the complete sample, the scatter plot seemingly displayed a positive association between the SZ PRS and apathy scores. However, as indicated by the scatter plots in the patients and controls separately, this was a result of case control status only. Accordingly, the SZ PRS did not show significant associations with the levels of apathy in patients (r = - 0.08, p = 0.160) or in the healthy controls (r = - 0.02, p = 0.685). Follow-up analyses in the participants with a narrow schizophrenia diagnosis (r = - 0.08, p = 0.307), in those with a FEP (n = 186, r = - 0.09, p = 0.214), or in those with a MEP (n = 95, r = - 0.02, p = 0.814) did not show any significant associations. Likewise, no significant associations were found between the SZ PRS and measures of the broader group of negative symptoms (i.e., PANSS negative symptom factor)

(r = -0.06, p = 0.340), the PANSS amotivation factor (i.e., experiential domain) (r = -0.06, p = 0.286), or the PANSS expressive factor (i.e., expressional domain) (r = -0.06, p = 0.294).

In the multiple regression analyses with AES-S as the dependent variable, while adjusting for genotyping batch and six PCs, the SZ PRS did not significantly contribute to the explained variance in apathy scores in the participants with schizophrenia spectrum disorders (R^2 change = 0.002, p = 0.512). Likewise, no significant contribution from the SZ PRS to the explained variance in apathy scores was shown (R^2 change = 0.002, p = 0.482) when the PRS was added to the equation after relevant clinical variables, while adjusting for PCs, genotyping batch, and secondary negative symptoms. Together, a low premorbid social functioning, long DUP, and higher PANSS positive and CDSS scores all showed significant associations in the direction of higher apathy scores. The complete model explained 27% of the variance in the apathy scores.

In sum, Study I indicated no significant relations between the polygenic vulnerability for schizophrenia and levels of apathy or the broader group of negative symptoms in schizophrenia spectrum disorders, nor with the levels of apathy in healthy controls. There was no indication that the lack of significant associations was a result of confounding factors. Consequently, environmental factors may be more important for the development of apathy in schizophrenia spectrum disorders than the summed effect of common genetic variants. However, because of the small effect sizes of each common genetic variant associated with schizophrenia, an adequate statistical power of the current SZ PRS relies on large sample sizes, both in the PGC discovery samples and test samples at hand. Therefore, our results should be interpreted with some caution.

4.2 Study II

Consequences of persistent depression and apathy in first-episode psychosis—a 1-year follow-up study

In this study, we investigated the persistent symptoms of apathy and depression, along with the associations with functioning of these persistent or nonpersistent symptoms during the first year after a FEP. The specific aims were as follows: 1) to explore the associations between current levels of depression and apathy with functioning at baseline and one-year follow-up, 2) to describe the prevalence of persistent apathy and persistent depression and to what extent they overlapped during the follow-up, and 3) to explore the relative contributions by persistent apathy and persistent depression to functioning at the one-year follow-up.

In cross-sectional analyses, higher apathy scores (i.e., AES-C) showed consistent and significant associations with lower levels of concurrent GAF-F scores at baseline (r = - 0.47, p < 0.01) and one-year follow-up (r = - 0.64, p < 0.01). In comparison, the CDSS scores only showed significant negative associations with functioning at the one-year follow-up (r = - 0.47, p < 0.01).

In the multiple hierarchical regression analyses with baseline GAF-F as the dependent variable, we adjusted for gender, premorbid academic functioning, and PANSS excited and positive factors, finding no significant contributions from the baseline CDSS scores to the explained variance in functioning. However, the DUP and PANSS disorganized factor both showed significant negative associations with baseline GAF-F. When baseline AES-C was introduced in the last step, higher apathy scores significantly added to the explained variance in GAF-F (R^2 change = 0.117, p < 0.001), here in the direction of lower levels of functioning. The final model at baseline explained 38% of the variance in the GAF-F scores.

In the regression analyses exploring contributions to the explained variance in GAF-F at the one-year follow-up, we adjusted for gender, premorbid academic functioning, DUP, and the concurrent PANSS disorganized factor. Here, the concurrent AES-C (R^2 change = 0.231, p < 0.001) and the PANSS positive factor scores showed significant negative associations with GAF-F. Further, the CDSS showed an independent negative association to GAF-F when introduced in the last step (R^2 change = 0.035, p = 0.015). The final model explained 52% of the variance in GAF-F at the one-year follow-up. We performed post-hoc analyses in participants with a nonaffective psychosis diagnosis at baseline (n = 103) and follow-up (n = 67). The same variables displayed significant associations to concurrent GAF-F scores, and their individual contributions to the explained variance in GAF-F were equivalent to the findings in the complete sample.

Among the 88 participants who were reassessed at the 1-year follow-up, we found that 32% had persistent apathy and 19% persistent depression (see Table 1). However, relative to the prevalence of apathy and depression at baseline, their tendencies of persistence (i.e., prospective consistency) were both considerable, 57% for apathy and 49% for depression. In the subset of participants with a nonaffective psychosis diagnosis, the prospective consistencies were similar, here both for apathy and depression (Table 1).

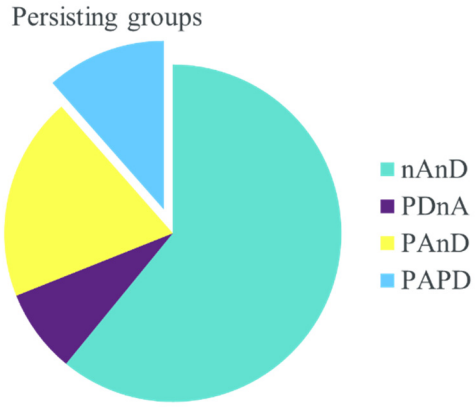
Table 1. Prevalence and persistence of apathy and depression in the complete FEP sample and in the subset with a nonaffective psychosis diagnosis at baseline and follow-up.

	Baseline		One-year follow-up	
Sample	Complete	Nonaffective	Complete	Nonaffective
N	125	103	88	67
Apathy				
Prevalence [a]	58% (72/125)	54% (56/103)	44% (39/88)	51% (34/67)
Persistent apathy [b]	-	-	32% (28/88)	-
Prosp. consistency [c]	-	-	57% (28/49)	61% (34/56)
Depression				
Prevalence [a]	41% (51/125)	33% (34/103)	25% (22/88)	25% (17/67)
Persistent depr. [b]	-	-	19% (17/88)	-
Prosp. consistency [c]	-	-	49% (17/35)	50% (17/34)

Abbreviations: Prosp. consistency = prospective consistency; persistent depr. = persistent depression.
[a] Cross-sectional prevalence of clinically significant apathy, defined as a sum score ≥ 27 on the Apathy Evaluation Scale, clinician version (AES-C) *or* cross-sectional prevalence of clinically significant depressive symptoms defined as a sum score > 7 on the Calgary Depression Scale for Schizophrenia (CDSS).
[b] Persistent apathy = clinically significant apathy at baseline and one-year follow-up; Persistent depression = clinically significant depressive symptoms at baseline and one-year follow-up.
[c] Fraction of those clinically apathetic or depressed at baseline that remained so at one-year follow-up.

Dividing the complete follow-up sample into four independent groups (Figure 2), 8% had persistent depression but nonpersistent apathy (i.e., PDnA group); 21% had persistent apathy bot nonpersistent depression (i.e., PAnD group); and 60% had no persistent symptoms (i.e., nAnD group). In addition, 11% had both persistent depression and persistent apathy (i.e., PAPD group), which was an overlap significantly higher than expected by chance according to Chi-square statistics (X^2 (1, n = 88) = 7.08, p = 0.008, phi = 0.284).

Figure 2. Persistent symptoms groups at the one-year follow-up in FEP



Abbreviations: nAnD = nonpersistent apathy + nonpersistent depression (60%); PDnA = persistent depression + nonpersistent apathy (8%); PAnD = persistent apathy + nonpersistent depression (21%); PAPD = persistent apathy + persistent depression (10%).

At the one-year follow-up, there was an overall difference in GAF-F scores between the four independent groups, with one, both, or no persistent symptoms of apathy and depression, as shown by a significant Kruskal–Wallis test (X^2 (3, n = 88) = 33.2, $p < 0.001$). The ensuing pairwise Mann–Whitney U-tests revealed that the participants with no persistent symptoms (i.e., nAnD group) had significantly higher levels of functioning than the three groups with one or both persistent symptoms. We removed 20 participants from the nAnD group without clinically significant symptoms of depression and apathy at baseline and follow-up; this resulted in a minimal numerical change in the mean GAF-F scores (GAF-F = 58.6, SD = 16.0 after removal; GAF-F = 60.9, SD = 15.3 before removal). Thus, we regarded it unlikely that these participants inflated the mean GAF-F in the nAnD group and thereby caused the between-group differences in functioning. Finally, the three persistent symptoms groups all had severely impaired functioning (Table 2). The group comparisons revealed no significant differences between having persistent depression only, persistent apathy only, or both persistent apathy and persistent depression.

Table 2. Median GAF-F scores in the persistent symptoms' groups at the one-year follow-up

Group	1. nAnD	2. PDnA	3. PAnD	4. PAPD	Statistic*
N	n = 53	n = 7	n = 18	n = 10	
GAF-F FU	61.0	39.0	39.5	39.5	1 > 2, 3, 4

Abbreviations: GAF-F = Global Assessment of Functioning Scale, functioning subscale; FU = one-year follow-up; nAnD = nonpersistent apathy + nonpersistent depression; PDnA = persistent depression + nonpersistent apathy; PAnD = persistent apathy + nonpersistent depression; PAPD = persistent apathy + persistent depression
* Mann–Whitney U tests showed significant GAF-F differences between the group with non-persistent symptoms (nAnD) and the three groups with persistent symptoms. There were no significant differences between the persistent symptoms' groups. We adjusted for multiple comparison (level of $p = 0.05/6 = 0.0083$).

In a subsequent regression analysis with GAF-F at the one-year follow-up as the dependent variable, persistent depression showed significant negative associations with GAF-F (R^2 change = 0.049, $p = 0.008$), even after adjusting for persistent apathy, gender, premorbid academic functioning, DUP, and PANSS disorganized factor at the follow-up. This suggested that there may be an independent, add-on effect from persistent depression to the reduction in functioning at the one-year follow-up, hence elaborating on the results from the pairwise group comparisons (Table 2), where no statistically significant differences in the GAF-F scores were found between the PAPD group (having both types of persistent symptoms) and the PAnD and PDnA groups.

We concluded that there was a high prevalence and significant overlap of persistent symptoms of apathy and depression in the early phase of a FEP. Having one or both persistent symptoms corresponded with severely impaired functioning at the one-year follow-up. Further, compared with depression, apathy was more stably significantly associated with reduced functioning in the cross-sectional analyses.

4.3 Study III

Trajectory and early predictors of apathy development in first-episode psychosis and in healthy controls: A 10-year follow-up study

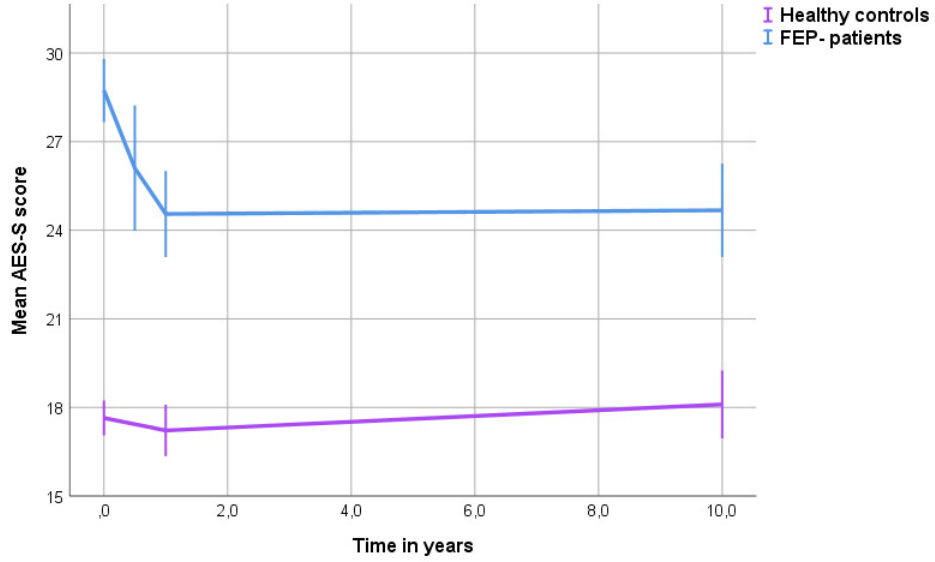
In this study, we explored the development of apathy in the long term after a FEP as compared with healthy controls. We investigated the baseline predictors of apathy trajectory, and the prevalence of apathy and associations to functioning at the 10-year follow-up. The specific aims were as follows: 1) to describe the longitudinal development of apathy in a 10-year follow-up of FEP participants and a group of healthy controls, 2) to investigate the early clinical or demographic predictors of apathy development in FEP, 3) to describe the prevalence of

clinically significant apathy at the 10-year follow-up, and 4) to explore the associations between apathy and functional outcome at the 10-year follow-up. For details on the participants, see the flow chart of study participation in FEP and healthy controls in Supplementary Figure 1 (42) in section 8.

The growth model showed that in FEP participants, the mean levels of apathy (i.e., AES-S scores) decreased during the first year of follow-up and stabilized thereafter (Figure 3) (42). This curve was best described by a combination of a linear and curvilinear time trend (i.e., "time" plus "time*time"). The linear effect of time was negative, indicating reductions in apathy with time, whereas the curvilinear time trend was positive (both, $p < 0.001$), indicating that the early reductions in apathy leveled off over the years. There were significant differences in apathy levels between individuals at baseline, as demonstrated by a significant random intercept ($p < 0.001$). However, the random slope did not significantly contribute to the model, suggesting little variation in the development of apathy between individuals over time. The covariation between the random intercept and random slope was nonsignificant.

Conversely, in the healthy controls, the mean apathy levels were low and stable throughout the follow-up (Figure 3) (42), as shown by a nonsignificant effect of time in the growth model ($p = 0.215$). However, there was significant variation in apathy levels between the healthy control individuals at baseline and in apathy development over time, as indicated by a significant random intercept ($p < 0.001$) and slope ($p = 0.019$), respectively. The apathy development in the individual was not associated with the individual apathy level at baseline, as signified by a nonsignificant covariance between the random intercept and slope ($p = 0.106$).

Figure 3. Development of apathy (AES-S) in a 10-year follow-up in FEP and healthy controls*



* Reproduced with permission from Springer and the European Archives of Psychiatry and Clinical Neuroscience under the Creative Commons Attribution 4.0 International License: http://creativecommons.org/licenses/by/4.0/. No changes have been made to the original figure.

In the FEP participants, a long DUP ($p = 0.014$) and higher CDSS scores ($p < 0.001$) at baseline showed significant positive associations with apathy development during the 10-year follow-up. The interaction effect between DUP and time was nonsignificant, implying that the effect of DUP did not significantly increase or decrease over time but held throughout the follow-up period. The effect of baseline CDSS scores on apathy development decreased over the years, as shown by a negative and significant interaction effect with time ($p = 0.001$). Moreover, the results indicated that baseline apathy levels had an enduring effect on apathy development, here in the direction of higher apathy levels during the follow-up. This was suggested by the combination of a significant random intercept, a nonsignificant random slope, and a nonsignificant covariation between them. There was a significant effect of the site of inclusion ($p = 0.048$), even after adjusting for DUP (which was significantly longer at Innlandet; $t = -4.4$, $p < 0.001$), with indications of higher apathy scores during the follow-up at Innlandet.

Finally, at the 10-year follow-up, the prevalence of clinically significant apathy in FEP was 37%. The levels of concurrent PANSS positive and disorganized symptoms and a schizophrenia spectrum diagnosis showed significant negative associations with GAF-F at the 10-year follow-up. When we adjusted for these variables in the multiple hierarchical regression analysis and further controlling for CDSS scores (R^2 change = 0.053, $p = 0.440$), the concurrent apathy scores

still showed significant negative associations to functioning. The final model explained 54.5% of the variance in GAF-F, with an independent 5% ($p = 0.006$) added by the apathy scores.

In conclusion, the mean levels of apathy were stable and low in the healthy controls. Yet significant interindividual variation was found in the apathy levels at baseline and in long-term apathy development. In FEP, there were signs of a critical period for the development of apathy, with declining apathy levels during the first year, followed by long-term stability. Our data imply that the individual apathy level at baseline in FEP may predict the development of apathy in the long term. Considering the significant independent associations found between high levels of apathy and impairments in everyday functioning at the 10-year follow-up, this may signify an especially vulnerable subgroup of patients at this early stage of the disorder. Moreover, treatment delay and higher levels of baseline depression predicted higher apathy levels in the forthcoming years.

5 DISCUSSION

5.1 Main findings

In the three naturalistic studies comprising the present thesis, we first found that the polygenic risk score for schizophrenia was not significantly associated with the levels of apathy in people with schizophrenia spectrum disorders or in the healthy controls. In people with schizophrenia spectrum disorders, the polygenic risk score did not contribute to the explained variance in apathy levels in the multivariate analyses. Further, in the prospective 1- and 10-year follow-up studies in FEP, we found that the mean levels of apathy decreased during the first year and then remained stable during the following years. Higher levels of baseline apathy and depressive symptoms and a long DUP predicted higher levels of apathy during the 10-year trajectory. The effects of DUP and baseline apathy were long standing, whereas the effect of baseline depression abated over time. In contrast, the mean apathy levels in the healthy controls were longitudinally stable and low.

However, although there was an overall decrease in apathy levels in people with FEP during the first year of follow-up, our data also indicated that a considerable fraction experienced persistent apathy or persistent depression during this year and that a significant subgroup had both persistent symptoms. Further, higher levels of apathy showed consistent, cross-sectional associations to reduced functioning at baseline, and at the 1- and 10-year follow-ups. In contrast, higher levels of depressive symptoms only had a significant add-on effect in the direction of reduced functioning at the one-year follow-up. Notwithstanding this, having early persistent depression or persistent apathy was equally detrimental to functioning at the one-year follow-up. Finally, our results were conflicting regarding the presence of significant additive, negative effects on functioning from having both persistent apathy and persistent depression.

In the following sections, I first discuss each study separately before I go on to discuss the results of Studies I–III together in section 5.5.

5.2 Genetic underpinnings of apathy

In Study I, we were the first to investigate the associations between SZ PRS and levels of self-reported apathy in people with schizophrenia spectrum disorders and in a group of age- and gender-matched healthy controls. The SZ PRS significantly discriminated between patients and healthy controls in our sample. Yet when patients and healthy controls were analyzed separately, no significant associations between the SZ PRS and levels of apathy were detected in either group. In the multivariate analyses exploring the contributions to explained variance in levels of apathy in schizophrenia spectrum disorders, SZ PRS was included together with

clinical variables while controlling for the confounding factors. The final model explained a total of 27.1% of the variance in apathy levels, but SZ PRS did not contribute significantly. I will hereafter discuss these nonsignificant results together.

The results contradicted our hypotheses but are in line with studies reporting nonsignificant associations between SZ PRS and the broad group of negative symptoms in schizophrenia (239, 296). Here, some methodological issues are worth mentioning. One of the studies (296) assessed negative symptoms with the original PANSS version (270) in a schizophrenia subsample and with a proxy measure developed from the Montgomery Aasbergs Depression Rating Scale and Becks Hopelessness Scale in an affective psychosis subsample. The other study (239) used selected items from the Comprehensive Assessment of Symptoms and History interview (297), which includes symptoms such as latency of speech, rigidity, and stupor but that does not have an item reflecting apathy. None of the above measures are likely able to capture negative symptoms according to current conceptualizations and may not map onto the same underlying construct (4), which could obscure a true association to the SZ PRS. In comparison, applying a specific apathy assessment scale that has been validated in FEP is an advantage of Study I (285). Second, the nonsignificant associations in these studies could result from insufficient statistical power. For instance, the study by Derks et al. (239) included approximately 300 patients and used the PGC1 discovery sample to compute the SZ PRS. The PGC1 included approximately 8,700 people with schizophrenia and 11,800 healthy controls, which are considerably smaller sample sizes than those of the PGC2, which was used in Study I (72).

Our results stand in contrast to the studies reporting statistically significant negative (240) or positive associations between SZ PRS and broad negative symptoms in FEP (241), in a schizophrenia sample (298), and in large cohorts of healthy adolescents (237, 299, 300). Another study in healthy adolescents reported nonsignificant associations between SZ PRS and positive symptoms but described significant negative associations with the negative symptom scores (238). Our results are also not in line with the only study exploring the associations between SZ PRS and levels of clinician-rated apathy (i.e., an apathy/asociality factor from the SANS) in people with schizophrenia (242). In this study by Jonas et al. (242), the authors found a significant positive association between SZ PRS and apathy at baseline and a persistent effect of SZ PRS in the direction of higher apathy levels during a 20-year follow-up. In sum, it is fair to say that the current evidence for an association between SZ PRS and negative symptoms is

unclear and that there is a dearth of studies investigating the associations to the apathy subsymptom.

There are several possible explanations for the nonsignificant results of Study I. First, our results may indicate that factors of nongenetic origin are more important than genetic factors in the development of apathy in schizophrenia spectrum disorders. I will return to these issues in the overarching discussion in section 5.5. Second, because of the small effect size of each schizophrenia-associated SNP, the power to detect associations related to an illness phenotype like apathy or broad negative symptoms depends on the size of the test sample and the PGC discovery sample (301). In our study, the SZ PRS was based in the PGC2 discovery sample and explained 4% of the variance in case control status in the study sample and 7.5% in the complete TOP sample (both at $p_T = 0.1$). Thus, although the present sample size was moderate for a clinical study, we may have lacked the power to detect a true association. In comparison, the above-mentioned studies had equivalent (239, 241, 242) or larger sample sizes (237, 238, 240, 296, 298, 300). By crude observation, however, patterns of significant or nonsignificant associations do not clearly follow sample size.

Another explanation for the nonsignificant associations between apathy and SZ PRS could be sample effects. Our study sample consisted of FEP and MEP participants with schizophrenia spectrum disorders. Among the other studies exploring associations with negative symptoms in psychotic disorders, one had a FEP sample (241), whereas the majority included individuals with multiple episodes or chronic schizophrenia (239, 240, 296). First, it could be possible that the phenotypic expression of a genetic risk for schizophrenia varies depending on illness phase and that the genotype-phenotype associations differ accordingly, for example, between FEP and MEP or across different age groups. This was also proposed by Jones et al., who found strong indications of a relation between SZ PRS and negative (but not positive) symptoms in a large cohort of healthy adolescents (237), where negative symptoms could be part of a prodromal phase in those who later develop a psychotic disorder. Further, sample effects may be at play if those with chronic illness or multiple episodes were prone to a more severe illness trajectory because of a stronger genetic propensity for schizophrenia. Similarly, a selection toward more severe illness could be relevant in first-admission samples (because not all people with a FEP need admission to a psychiatric ward). This may be reflected in the above-mentioned study by Jonas et al. (242), who reported that SZ PRS was positively associated with baseline apathy and predicted higher apathy levels during the following two decades. In their first-

admission sample, the participants had increasing apathy levels from year 5 to 20 of the follow-up and a steady decrease in functioning, with even stronger trends in those with a high SZ PRS. These are opposite trends both for the development of apathy and for functioning compared with the observations in FEP in the TIPS apathy study (29) and in Study III, potentially indicating a skew toward more severe illness in Jonas et al.'s sample. Moreover, compared with the noncompleters in Jonas et al.'s study, the completers at 20-year follow-up who provided their DNA had higher baseline apathy scores and more often used antipsychotic medication across the follow-up period (242). Thus, the completers may have had more severe illness and may not be representative of the general first-admission schizophrenia population. Finally, sample effects could result if people with a broad range of psychotic disorders were included rather than those with a schizophrenia diagnosis exclusively, where the former strategy could attenuate or obscure a genetic signal from a more genetically homogeneous population. For the above reasons, we investigated sample effects in our study by rerunning analyses in FEP and MEP separately and in those with a "narrow schizophrenia diagnosis" (i.e., schizophrenia) only. However, the results were equivalent to the findings in the complete sample; hence, such confounding influences are less likely.

Further, an explanation for the nonsignificant associations between SZ PRS and apathy in Study I could be that the schizophrenia-associated common genetic variants are expressed as a broader negative phenotype, that is, as broad negative symptoms or the expressive and experiential domains, resulting in weak or nonsignificant associations to a specific apathy measure like the AES-S. Moreover, if the AES-S captured an admixture of primary and secondary negative symptoms, hence causing measurement bias, a negative finding could be the result. Therefore, we probed these questions and first found no significant associations between the AES-S and the measures of substance use (AUDIT and DUDIT) or dosage of antipsychotic medication (Sum AP). The apathy score did show significant associations with sources of secondary negative symptoms (depressive and positive symptoms). However, when we explored the contribution from the SZ PRS to the explained variance in apathy levels while adjusting for these confounders in multiple regression analyses, the results were not altered. Similarly, there was no indication of significant associations between SZ PRS and the two negative symptom domains (158) or broad negative symptoms as measured by the PANSS (106).

Moreover, another concern could be the use of a self-report measure to assess apathy. Here, both underreporting and overreporting of apathy may potentially threaten the validity of our

results. Some researchers have advocated that people with psychotic disorders are not able to reliably self-report negative symptoms (274). Other studies do find a high correlation between the self-reported and the clinician-reported assessments of broad negative symptoms (276) and experiential domain symptoms (275), although one study reported a slightly higher tendency of underreporting in those with schizophrenia spectrum disorders compared to healthy controls (265). Regarding the AES-S specifically, it has shown high a concordance with the AES-C in FEP in parts of the present TOP sample (285). Still, the AES-S is not validated in MEP, which represents a limitation to Study I.

In Study I, the significance threshold level ($p_T = 0.1$) for the inclusion of SNPs in the SZ PRS computation was chosen a priori, here based on the SZ PRS' performance in discriminating patients from healthy controls in the complete TOP sample. However, it is conceivable that a different threshold level, including a higher or lower number of SNPs, would have been superior in predicting the apathy phenotype in our study sample. Still, a hypothesis-free inspection of the associations to apathy at several SNP significance levels would increase the risk of type I errors and require a stringent adjustment for multiple testing. Because of the sample size, we abstained from doing so.

Further, apathy is a highly transdiagnostic phenotype present across psychiatric disorders (25) and prevalent in neurodegenerative disorders (37, 204, 205). If the genetic vulnerability for apathy was not related to schizophrenia specifically but to a joint genetic architecture for apathy across disorders, this could explain why we found nonsignificant associations to SZ PRS. However, the probability of a transdiagnostic genetic liability for apathy development is lessened by recent evidence of little overlap between the genetic underpinnings of psychiatric and neurological disorders and across different neurological disorders, which could suggest more distinct etiologies in these conditions (302). Of note, similar apathy phenotypes may also result from different underlying genetic factors or mechanisms (i.e., equifinality) (25, 303).

In sum, research has suggested that the associations between the current SZ PRS and negative symptoms are unstably present, inconsistent, or nonexistent. In Study I, we attempted to reduce sample heterogeneity and, likewise, negative symptom heterogeneity by using a specific psychometric scale to assess the levels of apathy. Nonetheless, we were not able to detect a genetic signal for a neurodevelopmentally linked and biologically plausible phenotype like apathy in schizophrenia. The methodological pitfalls of using PRS to predict complex traits are

many (304). Although the present sample size is an obvious issue and a genetic contribution cannot be ruled out, our results may indicate that environmental etiological factors are important for the development of apathy. However, this remains an avenue for further study.

5.3 The first year: apathy and depression—early persistent symptoms

The main findings of Study II were that persistent depression was present in 19% and persistent apathy in 32% of the 1-year follow-up FEP sample and that a significant subgroup had both persistent symptoms. Relative to baseline prevalence rates, the prospective consistencies were 49% for depressive symptoms and 57% for apathy, indicating the tendency for the symptoms to persist in the individual. Having persistent depression or persistent apathy or both persistent symptoms was associated with severely impeded functioning, significantly differing from participants with no or fluctuating symptoms of apathy and depression during the first year. The cross-sectional associations with functioning were consistently significant and negative for apathy at both follow-ups, whereas the associations between functioning and depression varied.

The 19% prevalence of persistent depression at one-year follow-up is similar to 3 FEP studies reporting a prevalence ranging from 14–26% during the 12–18 months immediately prior to and after psychosis onset (14, 143, 144). Of note, the applied depression rating scales and cut-offs differ between studies: among the studies using the CDSS, one had a sample partly overlapping with Study II and applied a sum score cut-off of ≥ 6. They reported a higher prevalence of persistent depression (i.e., 26%) (14) than another study using a higher sum score cut-off of ≥ 7 (i.e., 22%) (144). In Study II, we employed a strict CDSS sum score cut-off of >7 to ensure high specificity and good discrimination from the symptoms of apathy (260). However, this strategy may have left some truly depressed participants out and deflated the prevalence rates. The last study by Cotton et al. found persistent depression in 14% at the 1-year follow-up in a larger sample of FEP participants with nonaffective psychotic disorders (143). Depressive symptoms were measured with the Clinical Global Impressions-Severity of Illness Scale-Bipolar Illness (CGI-BP). The psychometric properties of the CGI-BP in discriminating depressive and negative symptoms were not reported. Importantly, their study design was retrospective, and depression ratings were based on the case notes from treating clinicians. Of those with clinically significant depressive symptoms at study inclusion, only 29% had a comorbid MDD diagnosis and 56% used antidepressant medication. This may indicate that depressive symptoms were underreported or underdiagnosed, which could be

reflected in the lower prevalence rates of persistent depression compared with the other studies, including Study II.

Second, similar to Study II, one of the above studies included a broad psychosis sample (144), whereas two studies excluded affective psychotic disorders (14, 143). This may have resulted in higher depression prevalence rates in the studies including affective psychoses. To explore such sample effects because of diagnosis in Study II, we performed post-hoc cross-sectional analyses in the nonaffective subsample and found that the prevalence rates of clinically significant symptoms of apathy and depression were numerically similar but with a crudely observed trend toward a lower prevalence of baseline depression and a higher prevalence of one-year follow-up apathy in those with a nonaffective diagnosis (Table 1). In sum, our data supports previous findings (144, 152), suggesting that a cross-diagnostic subgroup of FEP may be more prone to depression and persistent depression.

We found persistent apathy in 32% of participants at the 1-year follow-up. This is in line with the TIPS apathy study, where 30% were suggested as having persistent apathy from baseline and across the 10-year follow-up, and thus also during the first year after the FEP (29). In contrast, a 5-year follow-up study by Norman et al. found a prevalence of persistent apathy of 16% (197). This study and the TIPS study were both early intervention studies, but the study designs and applied psychometric scales differed, which is likely relevant for interpretation.

In the five-year follow-up by Norman et al. (197), trained clinicians assessed experiential domain symptoms monthly using the SANS, noting weekly fluctuations within each month. Thus, scorings were very frequent compared with the six follow-up assessments in the TIPS apathy study (29). The likelihood that Norman et al. captured symptom fluctuations below clinically significant levels may have been higher and could explain the lower prevalence of symptom persistence in their sample. The TIPS apathy study used an apathy proxy measure based on 2 PANSS items (n2, emotional withdrawal; n4, passive-apathetic social withdrawal) at all follow-ups and then introduced the AES-S at the 10-year assessment (29). They retrospectively reconstructed the apathy trajectory of participants with clinically significant apathy as measured with the AES-S at 10 years (i.e., 30%), and found that these participants had likely been having persistent apathy. The PANSS n2 and n4 items were significantly correlated with the AES-S at 10 years in the TIPS apathy study (r = 0.49 and r = 0.48 respectively; both $p < 0.01$) (29). Similarly, the PANSS n2 and n4 have shown significant

correlations with the AES-S at baseline in parts of the present TOP sample ($r = 0.34$, $p = 0.01$; $r = 0.37$, $p < 0.05$, respectively) (285). Of note, the strength of the correlations between different clinician-rated (e.g., the PANSS) and self-reported (e.g., the AES-S) measures of amotivation may vary considerably (269). The overall shared variance was recently reported to be 11.6% ($r = 0.34$, $p < 0.001$) in a meta-analysis of 23 studies in schizophrenia (269). In sum, applying the specific AES-C at baseline and at the one-year follow-up, thus adds robustness to the findings of persistent apathy in Study II.

We further found that approximately 49% of those depressed and 57% of those apathetic at baseline were still depressed and apathetic at the 1-year follow-up, respectively. Although the sample size in our study was modest and we had (nonselective) attrition during follow-up, these numbers tell a more nuanced and alarming story at the individual level, indicating nonremission in frequent for both symptoms in the early course of illness. Of note, prospective consistencies were numerically similar (i.e., 50% for depression and 61% for apathy) in the nonaffective subsample.

When we divided the follow-up sample into 4 independent groups based on their persistent apathy and/or persistent depression status, we found that 60% had no persistent symptoms (nAnD group) and that 20 individuals in the nAnD group were below cut-off levels for both symptoms at both assessment points. Further, 8% had persistent depression only (PDnA group) and 21% had persistent apathy only (PAnD group). In addition, 11% had both (PAPD group), which was more than expected by chance. Hence, our data showed that 40% of participants had at least a single persistent symptom at the 1-year follow-up, and that in close to 30% of these, both phenotypes persisted, indicating a vulnerable subgroup that may, but must not, go unnoted. To the best of our knowledge, no other studies have explored the overlap between persistent depression and persistent symptoms of apathy or of the experiential domain. Of note, the group sizes in the current study were small, and the findings should be interpreted with some caution because a low statistical power could result in type II, but also in type I, errors (305). A spurious overlap could be attributed to measurement bias if the AES-C and CDSS did not properly discriminate apathy from depression or if the assessment of one phenotype systematically affected the evaluation of the other phenotype done by the same rater. However, both the CDSS (258) and the AES-C have shown adequate discriminative validities (201, 277).

We further found a significant negative association between cross-sectional depressive symptoms and GAF-F after adjustment for confounders and apathy levels (i.e., an independent add-on effect) but only at the one-year follow-up. In contrast, higher levels of apathy had significant and independent associations to a worse functional outcome at both assessment points. The results were equivalent in the nonaffective psychosis subsample. Although we cannot infer causality because of the naturalistic design and cross-sectional analyses, the findings of a consistent link between apathy and reduced functioning adds to a growing number of studies that signifies apathy as key to impeded functioning in psychotic disorders (37, 39). Regarding depression, some studies that simultaneously address the impact on functioning by depression and apathy report independent effects from *both* symptoms in FEP or chronic illness (29, 249, 250), while other studies only find a significant contribution from apathy (246, 252, 256, 306). However, the constitution of samples (e.g., affective and/or nonaffective psychotic disorders), stage of illness (e.g., FEP or chronic), nature of analyses (e.g., cross-sectional or longitudinal), and assessment scales (e.g., PANSS depressive factor or CDSS) vary considerably between studies and complicate comparisons. In FEP, two recent systematic reviews and meta-analyses reported dissimilar results: one found a significant association between early depressive symptoms and reduced long-term functional outcome (13), while the other did not (307). Taken together and compared with apathy, our findings are in line with current evidence, suggesting more uncertainty in the relations between depressive symptoms and functioning in psychotic disorders.

We found that functioning was significantly, severely, and equivalently impeded at the 1-year follow-up in all groups with persistent symptoms compared with those with no symptom persistence. These group differences could have been inflated by individuals in the nAnD group without depression and apathy at both assessment points. Yet this seems unlikely because the mean GAF-F scores were only slightly lower when these individuals were removed from the nAnD group. Although group comparisons did not reveal worse functioning in those with both persistent symptoms, the follow-up multiple regression analysis did demonstrate a statistically significant add-on effect of persistent depression to that of persistent apathy, maybe because of the increased statistical power of this analysis.

No other studies have concurrently investigated the associations between functional outcome, persistent apathy, and persistent depression in FEP. However, our findings are in line with FEP studies describing significantly poorer functioning in those with persistent depression during

the first 12 (14, 154) and 18 months of follow-up (143). One of these studies was part of the TIPS study cohort (154), additionally finding that the early persistent depression trajectory predicted worse functioning across the following five to nine years. Similarly, persistent apathy has previously shown associations with poorer functioning in the TOP apathy study sample, hence partly overlapping with the current study (38) and in the TIPS apathy study (29).

5.4 A 10-year perspective on apathy development

The main findings in Study III were that the mean levels of apathy significantly declined during the first year after a FEP, thereafter following a stable trajectory until the end of follow-up, indicating an early, critical period for apathy development. At the 10-year follow-up, 37% of FEP participants experienced clinically significant levels of apathy, as measured with the AES-S. Although apathy levels showed significant variation between individuals at baseline, the 10-year trajectory was less heterogeneous, and individuals were alike in the overall tendency of an early apathy decline and subsequent stability. In the healthy controls, however, the mean apathy levels were overall stable and low and varied significantly between individuals at baseline and in the trajectories over time.

The broad group of negative symptoms were previously reported to be stable or even increasing over time (11, 189). Recent research suggests that all negative subsymptoms may improve, even in people with chronic schizophrenia (27, 308), and that negative symptoms show substantial variability especially in the early phase after a FEP (32, 33, 190-192). Only the TIPS apathy study has previously set out to explore the long-term development of apathy in FEP (29), and one additional study by an der Heiden et al. explored apathy development in a first-admission schizophrenia sample (263). In line with our findings, both studies reported an overall reduction in apathy levels during the 10- and 11-year follow-ups, respectively. The TIPS apathy study found two diverging apathy trajectories that crystallized between year one and two of follow-up. The “apathy group” followed a steady course and had clinically significant levels of apathy at the 10-year follow-up assessment. The “nonapathy group” experienced a continuous, steady decline toward the 10-year assessment (29). In addition, 30% of their participants had clinically significant levels of apathy at 10 years (i.e., the apathy group). In comparison, the study by an der Heiden et al. reported that the initial decrease was followed by stable apathy levels, starting between two and five years after study inclusion (263).

Some differences in study designs and samples are worth mentioning. Whereas an der Heiden et al. included a first-admission sample, which may be prone to more severe illness (263), the

TIPS study was an early detection study aiming to reduce the delay between psychosis onset and first treatment (309). The median DUP in the TIPS apathy study was 6 weeks, compared with 75 weeks in Study III. It is conceivable that our "delayed entry" into the FEP illness trajectory explains why we observe an apathy reduction during the first year, whereas the decline becomes evident later in the follow-up in the TIPS cohort. Moreover, compared with the TIPS study, our sample may comprise participants who are more prone to high apathy levels, as a long DUP shows a strong, early, and persistent association with higher levels of broad negative symptoms in psychotic disorders (195). This is probably not a fruitful explanation for the early apathy decline in Study III but could have contributed to the long-term apathy stability and to a numerically larger fraction of participants with clinically significant apathy at the 10-year follow-up in Study III (~40% in Study III vs. ~30% in the TIPS apathy study).

Prominent negative symptom researchers (310) have argued that observing a decline in negative symptoms could be the result of a reduction in secondary negative symptoms or a regression toward the mean effect (e.g., a tendency that a very high initial score in an individual tends to be followed by a score closer to the mean) rather than a true change. Our data suggest that a regression toward the mean effect is not likely. Because there was no significant interindividual variation in apathy trajectory (i.e., the random slope) and the covariation between baseline apathy levels (i.e., the intercept) and the following trajectory was also nonsignificant, a person with a high apathy offset appears to have a similar liability for a declining course during the first year as a person with a lower baseline apathy level. Moreover, except for depression, no baseline sources of secondary negative symptoms (i.e., positive symptoms, alcohol or drug use, dosage of antipsychotic medication, etc.) showed significant associations with apathy development. For depression, the significant negative interaction effect (CDSS*time) indicated that the positive association between depression on apathy development abated over time. Our results further indicated that the effect of CDSS in the direction of higher apathy levels lasted beyond the first year, where the decrease in apathy levels appeared to take place. The above does not rule out confounding factors but makes confounds less probable.

Importantly, Study III corroborates on two studies because part of the TOP apathy study was conducted using partly overlapping samples with Study III (30, 38): Færden et al. found clinically significant levels of apathy in 51% at baseline and a significant reduction to 40% at the 1-year follow-up. This may be in line with our findings of a stable trajectory from the 1-

year follow-up in Study III, resulting in a 37% prevalence of clinically significant apathy at the 10-year follow-up. Of note, our samples were not identical, and a direct comparison of numerical values across studies should be performed with some caution. The TOP apathy study applied the AES-C, whereas we used the AES-S in Study III, which could reduce reliability and comparability if the participants did not reliably self-report apathy levels. However, individuals with chronic schizophrenia (245) and FEP may rate their apathy levels reliably and validly using the AES (30, 285), though conflicting results have been reported for other assessment scales (265). Lending support to the validity of our findings are nonsignificant associations between AES-S scores and the PANSS insight item in Study III, along with a high concordance between the AES-C and AES-S in FEP (285).

Taken together, the results imply that there may be a critical period for the development of apathy during the first year after FEP (122). Thus, an overall decrease in apathy levels in the long-term course after the onset of psychosis is suggested in FEP individuals recruited very early after onset (29), in those recruited later (Study III), and those who might be prone to more severe illness (263). This serves to strengthen the validity and generalizability of our joint findings although increasing apathy in the long-term course was described in the first-admission SZ PRS study of apathy by Jonas et al. (242). If present, early variability in apathy levels may not have been sufficiently displayed in the TIPS apathy study (29) because they dichotomized apathy groups at the 10-year assessment and explored the group trajectories in a retrospective manner. Of note, fluctuations in apathy trajectory between the 1- and 10-year follow-up are not captured by Study III, which is a limitation. Notwithstanding this, applying a specific, validated apathy scale, a prospective study design and a linear mixed model analysis handling missing data and dependencies because of repeated measurements adds robustness to the findings of Study III.

We found that a long DUP was significantly associated with higher levels of apathy over time and that the effect was long lasting. The is in line with the findings in the broad group of negative symptoms in FEP. Two systematic reviews and meta-analyses reported that treatment delay was associated with higher levels of negative symptoms in the short and longer term (120, 195). The link between DUP and apathy in FEP appears to be more uncertain. Two cross-sectional studies (255, 256) and the one-year follow-up of the TOP apathy study (38) reported significant positive associations between DUP and levels of apathy, while two studies reported nonsignificant associations (29, 254). Compared with the longer DUP in Study III and in the

TOP apathy study, two were early intervention studies (29, 254), and thus, their nonsignificant associations could be attributed to a brief DUP with less predictive power and that the negative effect of a longer DUP on apathy development was obscured.

We found a positive association between baseline depressive symptoms and levels of apathy during the follow-up, an effect that decreased with time. Our results are in line with a FEP study reporting that baseline depressive symptoms predicted an early high and increasing negative symptom trajectory (33); however, our results contradict another study finding that baseline depressive symptoms predicted an early high and then decreasing negative symptom trajectory (190). The TIPS apathy study found no significant associations between baseline depressive symptoms and apathy levels at 10 years (29). The 11-year follow-up study by an der Heiden et al. found that the cross-sectional positive associations between apathy and depressive symptoms grew stronger over time, yet only in females (263). Likewise, a study in non-FEP reported positive associations between the change in depression scores and development of experiential domain symptoms during a nine-month follow-up (262).

Based on the significant longitudinal associations between baseline depressive symptoms and long-term apathy development in Study III, we cannot infer causality because of the naturalistic study design, yet our findings suggest that the two phenotypes could be more intimately related. Methodologically, an association could result from measurement bias if the AES-S and CDSS did not adequately discriminate apathy from depression, as previously noted in section 5.3.

We found that higher baseline apathy levels had an enduring effect in the direction of higher apathy levels throughout the follow-up. This was in accord with our hypothesis and may allude to a subgroup of individuals with persistently high apathy. A group with persistent apathy was also suggested in the TIPS apathy study (29), though they did not find that baseline apathy predicted apathy levels at 10 years. In the TOP apathy study, high baseline apathy likewise predicted higher apathy levels at the one-year follow-up (38).

Further, premorbid functioning was not significantly associated with apathy development in the present study. This was unexpected because impaired premorbid adjustment could be a phenotypic expression of the neurodevelopmental disturbance hypothesized to underpin negative symptoms (176). However, it may be that the effect of a reduced premorbid social functioning (which was significantly correlated with AES-S at baseline) was carried forward

by other variables in the equation, for example, by the baseline apathy levels. Having a schizophrenia spectrum diagnosis at baseline did not improve model fit.

Finally, in cross-sectional analyses at the 10-year follow-up, we found that a schizophrenia spectrum diagnosis and higher concurrent depressive, positive, and disorganized symptoms were significantly associated with lower levels of functioning. When we adjusted for these factors in the multivariate analyses, concurrent levels of apathy had an independent significant add-on effect toward a poorer functional outcome, while depressive symptoms did not. Together with the findings from Study II, this suggests a consistent and independent cross-sectional association between higher levels of apathy and reduced functioning in the early—as well as the later—illness phases in FEP, whereas the associations between concurrent depressive symptoms and functioning are more ambiguous. Although we cannot infer causality, the results regarding apathy and functioning concur with the findings in Study II, with the TIPS apathy study (29), and a growing body of research (4, 39).

5.5 Overarching discussion

In the three studies comprising the present thesis, we have learned that the 10-year trajectory of apathy in FEP is characterized by an early decline followed by long-term stability and that clinically significant levels of apathy are still prevalent after 10 years. Even though the overall decline in apathy occurs during the first year, subgroups with equally and severely impeded functioning experience that apathy persists during this period, alone or together with persistent depressive symptoms. Further, we found no evidence to support that the common genetic variation increasing risk for schizophrenia contributes to the development of apathy. However, three factors predicting an unfavorable apathy course in FEP were present at baseline or before that: namely a long DUP, high levels of apathy, and high levels of depression. This calls for attention because apathy was found to be consistently and independently associated with reduced day-to-day functioning throughout the long-term follow-up period in FEP. In contrast to the FEP participants, the healthy controls showed low yet not ignorable levels of apathy throughout the 10-year follow-up, supporting a continuous distribution of apathy into the general population.

These findings are valuable and relevant at the individual level, for the organization of health care and for treatment within mental health services specifically. First, the initial apathy decline was brought to a halt after one year and was followed by a stable plateau. This is in line with an early critical period for the development of apathy in FEP, which is theorized to include the

early treated and untreated phase of the illness (119, 122). During this period, apathy could be more fluid and malleable to targeted, secondary prevention. At these early stages of a FEP, outcomes can generally be improved by optimizing treatment response, attending to comorbidities and the person's well-being, social skills, and functioning, and by secondary prevention of illness progression (123). At present, psychosocial and antipsychotic treatments have not proven clinically effective in reducing negative symptoms overall (35, 36). Thus, although not directly investigated in the present studies, it stands to reason that attending to the early predictors of an unfavorable apathy course could afford an alternative route to improve the long-term apathy trajectory (123).

In line with evidence for an early critical period, we also found that apathy development was predicted by a long DUP, that is, by treatment delay. This has not previously been shown for the long-term apathy development in FEP (29) but concurs with the associations between DUP and higher levels of broad negative symptoms (195) (and with a worse general symptomatic outcome (120)). The mechanisms underlying the associations between DUP and higher negative symptoms in FEP are still unknown. One hypothesis is that a lengthy psychotic illness has neurotoxic effects on the brain, but the support for this hypothesis from evidence is uncertain (311). A long-standing untreated psychosis may further result in "psychosocial toxicity" (121), meaning a disruption of family, social, or academic networks and activities because of illness-related factors. Such factors may take time to restore or change. It is possible that societal, interpersonal, and intrapsychic factors and an interaction between them may contribute to cementing a passive, apathetic, or withdrawn lifestyle (216) that endures after the start of treatment.

We were not able to discern at which points in the timeline from psychosis onset the delay to treatment arose. A large fraction of a long DUP may relate to delays in help-seeking and in entry into early intervention services (123, 312). Although efforts to reduce DUP have produced mixed results (313), some studies report that the factors causing delay are moldable by targeted information campaigns to increase mental health literacy and facilitate access to early intervention services. These interventions have resulted in substantial reductions in DUP in some early intervention studies (309, 312), followed by early and sustained reductions in negative symptoms compared with nonintervention regions (314-316). It has been suggested that reducing treatment delay may affect core neurobiological deficit processes in schizophrenia, thereby halting negative symptom progression (314). However, some have

proposed that an early illness phenotype with severe negative symptoms itself causes a delay in contacting mental health services. Other authors have argued that a short DUP is associated with better symptom outcomes because of lead-time bias (i.e., that early detection creates an illusion of early treatment effect). For more on this, please see the study by Jonas et al. (317) and the following debate (318, 319). Notwithstanding this, a systematic review and meta-analysis of randomized controlled trials found that early intervention programs had a superior effect compared with treatment as usual (TAU) on a broad range of outcomes. This included effects on negative symptoms in FEP and early phase schizophrenia spectrum disorders (320), though some studies indicated that the treatment effects taper off (321, 322). A recent study from Hongkong found that an extended early intervention program was more effective in reducing motivational impairment than standard care in FEP (254), which could be promising for this patient group—if healthcare follows the evidence (323).

In Study III, we found that higher baseline apathy predicted higher apathy levels at the 10-year follow-up and that the effect was enduring. Those with a high baseline apathy score equally experienced a decline during the first year, yet the level of the resulting apathy plateau was likely higher than that of the group mean. This alludes to a subgroup with persistent apathy that starts out high and perhaps stays at clinically significant apathy levels over time. The finding corresponds with the results in Study II, where 57% of those apathetic at the baseline remained so, and 32% had persistent apathy at the 1-year follow-up. Thus, our studies suggest that individuals prone to persistent apathy may be detected very early in the course of the disorder because of their high apathy symptom load, which is clinically important and will be discussed in section 5.8. The group with persistent apathy may similarly be found among those with persisting experiential domain symptoms in the context of DS (172) and PNS (169, 174). In FEP, some have advocated that the criteria for PNS are met, here mostly because of the persistence of experiential—rather than the expressional domain—symptoms (324), although not all studies have supported this stance (325).

In Study III, baseline depressive symptoms predicted higher levels of apathy during the 10-year follow-up, albeit the effect declined with time. This may indicate that the two phenotypes, in addition to being phenotypically alike, could be more closely related. Further support for such a notion could come from Study II, where a significant group of participants had overlapping persistent symptoms of apathy and depression. The present thesis cannot specify the nature of such a relationship, and it is not known whether the phenotypic similarity and co-occurrence of

symptoms speaks of partly shared underlying mechanisms or etiology. However, some lines of evidence afford interesting perspectives.

First, a systematic review aiming to tease apart depressive and negative symptoms in schizophrenia suggested that apathy—together with anhedonia and energy loss—were shared across negative symptoms and depression. Blunted affect and alogia were found to be more specific to negative symptoms, and suicidal thoughts and a low mood were more specific to depression (326). In the NIMH RDoC system, reduced motivation both as part of negative symptoms in psychotic disorders and as part of depression has been explored within the frames of the positive valence system domain (211, 219, 327). The mechanisms underlying motivational deficits (i.e., in this context, brain reward circuits) are complex, as described in several conceptual models (328), and have been studied both in depressive disorders and schizophrenia (25, 162, 219, 221).

Together, the components of reward circuits translate a desire for a reward into goal-directed actions to pursue an enjoyable outcome (219, 221). Research has indicated similarities, but also discrepancies, in the motivational deficits in depression and schizophrenia, which may indicate partly separate paths to reduced goal attainment. People with depression are suggested as having reduced feelings of pleasure *in the moment*, that is, when facing an enjoyable event (i.e., reduced "liking"). This consummatory anhedonia could result in a reduced incentive for seeking out future pleasurable events, may propagate forward into the brain's reward circuits and translate into reduced goal-directedness (219). To the contrary, people with schizophrenia have been suggested as having an *intact* in-the-moment liking. However, impairments are seen in the anticipation of future rewards (i.e., they have reduced "*wanting"*), as well as in reward learning, in the construction of an action plan, and in the willingness to exert effort to attain the reward. Moreover, it has been suggested that impairments in emotion regulation may result in a state of higher negative—relative to positive emotion—in schizophrenia and that the net level of positive emotions necessary for facilitating motivated behavior is not reached (214). Cognitive impairments in working memory and executive functioning may contribute to these problems, yet the findings have been mixed (25, 163, 329).

Importantly, however, heterogeneity across people with schizophrenia has been proposed by Strauss and Cohen, depending on the symptom profile and stage of illness (25). In-the-moment liking may *also* be impaired in those with high levels of apathy and in those with FEP or at

high-risk for psychosis. In the FEP and high-risk populations, reduced in-the-moment liking has been hypothesized to be driven by a high prevalence of depression (and anxiety) in the early phase of the illness (25). Thus, concurrent depression may be a more salient predictor of apathy trajectory in early illness phases compared with in chronic schizophrenia, where in-the-moment liking may be intact.

A similar line of reasoning may be provided by the *negative symptom reserve* (27), a novel concept that bares resemblance to the notion of a cognitive reserve in psychotic disorders (330). It was proposed as a model to explain that individuals with an efficient premorbid brain functioning may have a "negative symptom reserve" that buffers against the development of negative symptoms during psychotic illness (27). In this perspective—and related to our findings—it is conceivable that a person with FEP and with a low "motivational reserve" (i.e., because of apathy) would be more vulnerable to a concurrent condition that may lower motivation further (i.e., depression). Moreover, psychological mechanisms such as DPBs (185, 223) have shown associations with the development and maintenance of broad negative (186) and experiential domain symptoms (224, 225) and could perhaps intensify in the face of pessimism and low mood of a concurrent depression (185). Finally, one theorized common underlying factor for reduced motivation in schizophrenia and depression is inflammatory aberrancies. Evidence has suggested that inflammatory markers, which may be abnormal in schizophrenia and in depression, may affect reward system circuitry in the brain, causing decreased activation and connectivity of the ventral striatum (331).

The findings of overlapping persistent depression and persistent apathy and the role for depression as a predictor of a more unfavorable apathy development touch upon the schism between affective and nonaffective psychotic disorders (124, 125) and the distinction between primary and secondary negative symptoms (10, 167). Depression has often been understood as a super-imposed, comorbid condition in psychotic disorders (9). Evidence has supported that depression in schizophrenia may be a psychological reaction to the psychosis because of feelings of shame, humiliation, and entrapment or negative beliefs about symptoms and illness implications (145, 332, 333). It is also possible, that being apathetic and having a withdrawn lifestyle with few stimuli makes one more prone to become depressed. However, a more profound role for depression has been proposed for a subgroup of patients (139, 145, 152), especially early in the course of the disorder (137). This stance may be supported by the polygenic overlap between schizophrenia, bipolar, and major depressive disorders (76, 125),

high rates of depression during the prodrome (45, 138, 139, 142, 144), similar prodromal phenotypes of schizophrenia and major depressive disorders (138), concurrent exacerbation and decrease of positive and depressive symptoms during illness course (141, 142), and positive associations between depressive, negative, and positive symptoms (12). It has been proposed that depression in the early critical phase contributes to the development of psychotic symptoms in schizophrenia through a pathway of increased stress, inflammation, and brain structural changes (137).

Study III showed three early predictors of the 10-year apathy trajectory. However, despite the high heritability in schizophrenia (18, 19), Study I did not indicate that apathy development was influenced by the common genetic variants associated with schizophrenia. Hence, the paths to developing apathy in psychotic disorders may be more strongly influenced by biological and/or psychosocial environmental factors (187). Research has identified several environmental factors associated with an increased the risk of developing schizophrenia, for example, pregnancy- and birth complications, such as maternal infection, malnutrition, or bleeding, and childhood trauma, urbanicity, and immigration (84). However, Strauss recently argued that the relation between environmental factors and negative symptoms specifically is underexplored, which could partly explain the slow or absent progress in the development of effective treatments (216). However, some psychological factors have shown associations to broad negative symptoms and/or experiential domain symptoms: these comprise a reduced self-efficacy (227, 334), increased negative expectancy appraisals (i.e., beliefs of reduced likelihood of future success and limited cognitive resources) (226), a reduced capacity to resist stigma (228), and, perhaps the most studied, DPBs (185, 224, 226, 334, 335). DPBs showed positive associations with negative symptoms in 70% of the included studies in a meta-analysis in chronic schizophrenia spectrum disorders, although the cumulative effect size was small (r = 0.24) (186). Similar positive associations between DPBs and negative symptoms have also been described in FEP (334).

Based on our results, a genetic foundation for the development of apathy cannot be precluded. Still, the nonsignificant associations should not be reduced to an issue of power failure alone. When interpreting the results, one must bear in mind that the fraction of schizophrenia heritability embedded in the SZ PRS—the SNP heritability (h^2_{SNP})—is the proportion of heritability attributed to common genetic variants, which is estimated to account for approximately 50% (66) of the observed 64–81% heritability in family and twin studies (18,

19). Thus, a substantial proportion of heritability is not accounted for, that is, the missing heritability (336). Of note, these heritability estimates are not expected to align perfectly because the heritability observed in epidemiological studies accounts for both common *and* rare variants inherited in families (79). Still, the unexplained heritability gap could be because of an overestimation of schizophrenia heritability in the population and an underappreciation of the effects of the shared environment, which is reported to account for 4–11% of the propensity to develop schizophrenia (18, 19).

Conversely, an underestimation of SNP heritability in current GWAS studies may be relevant if true causal variants are not detected because of a low LD with tag-SNPs. Moreover, one would expect that SNP-based heritability estimates will increase (65, 337) when larger discovery sample sizes enable the detection of new SNPs and the en masse effects of genome-wide significant variants, as well as SNPs at lower levels of significance, are included (336). Taken together, the current SZ PRSs only represent the added effects of a fraction of the hypothesized relevant SNPs for schizophrenia. The SZ PRS tool and SNP-based heritability estimates also do not account for rare heritable variants, de-novo mutations, gene*gene interactions, gene*environment interactions, or epigenetic effects, all of which are all believed to be of relevance for the development of these disorders (338).

In some somatic illnesses, PRSs have already shown clinical utility in identifying high-risk individuals who may profit from illness-screening or preventive measures (339). Even though the SZ PRS consistently discriminates healthy individuals from those with schizophrenia (64), the discrimination between phenotypes within the schizophrenia category is challenged by extensive heterogeneity across people sharing the diagnosis (3, 65). Furthermore, considerable sharing of common and rare genetic variants across psychiatric disorders (76-78) suggests profound connections and perhaps fewer specific mechanisms. Finally, equifinality may be relevant, that is, that multiple mechanistic pathways may underlie similar phenotypes such as negative symptoms or apathy (25). As noted in section 5.2., measurement bias may further result in imprecise phenotyping, for example, if the diagnostic evaluation is not properly performed (in discovery and test samples) or the psychometric scales used to assess negative symptom phenotypes are not in accordance with current conceptualizations. Similarly, lumping test samples together based on diagnosis but across different negative symptom rating scales (299) may be a parsimonious approach and necessary to increase power but could threaten the validity and reliability of findings.

We finally found that the associations between high levels of apathy and reduced functioning were consistently significant and independent at the baseline, 1-year follow-up, and 10-year follow-up in Studies II and III. Depressive symptoms only showed an additional significant and negative effect to the explained variance in functioning at the one-year follow-up. This did not coincide with higher mean CDSS scores at the one-year follow-up. Mean CDSS sum-scores were (by observation) higher at baseline, where the fraction of participants with positive psychotic symptoms was also higher (58%) than at the one-year follow-up (39%). The above could indicate differential associations with functioning for depressive symptoms but not for apathy and could perhaps be dependent on illness phase in FEP. Along this line of reasoning, different substrates for depression during the first psychotic episode (and in subsequent psychotic exacerbations) and depression in between psychotic episodes (e.g., a postpsychotic depression) have also been suggested (340, 341). Variations in the underlying substrates for depression during and between psychotic episodes may be reflected in differential relations to psychosis remission (341) and to predictors and psychological mechanisms (333). However, we did not investigate postpsychotic depression specifically in our studies, so any assumptions regarding the relations to functioning would be speculative.

This stands in contrast to the findings in participants with persistent apathy, persistent depression, or both, which had severely impeded functioning compared with those with no or fluctuating symptoms during the first year. The associations between reduced functioning and cross-sectional and persistent apathy were in line with our hypotheses and were also found in the TOP (38) and TIPS apathy studies (29). This underlines the clinical importance of the baseline predictors of a high-level apathy trajectory to identify people at risk for a severely reduced functional outcome. We did not expect persistent depression to be equally detrimental to functioning as persistent apathy. Considering the unstable cross-sectional associations between depressive symptoms and functioning, individuals with persistent depression may comprise a vulnerable subgroup in FEP. It is conceivable—yet unknown—that the quantity or quality of risk factors differ or that a partly different etiology or mechanisms underlies the development of persistent depression compared with fluctuating depressive symptoms.

Finally, the results were inconclusive regarding an additional effect of persistent depression to that of persistent apathy on functioning at one year. Group comparisons did not support an additive effect, whereas multiple regression analyses controlling for confounding variables

suggested that persistent depression significantly and independently added to the explained variance in GAF-F at follow-up. Here, replication in a larger FEP sample is needed.
Taken together, according to our results, persistent apathy and persistent depression affect a substantial fraction of people during the early critical period of FEP and are equally associated with grave reductions in functioning. According to previous research, both phenotypes may further set the stage for long-term functional impediments (29, 154).

5.6 Ethical considerations

The participants in Studies I–III represent a particularly vulnerable population. As patients, they may have been subject to involuntary admittance to psychiatric wards or to compulsory treatments. Sharing their thoughts or beliefs with clinical staff (about such as delusions or hallucinations) may have resulted in increased dosages of medication and in side effects. Because of such experiences and because of, for example, suspiciousness being part of the illness, their trust in mental health professionals may be weak or absent. The establishment of a trustworthy relationship to research personnel in the study of people with psychotic disorders is critical.

In the TOP study, this was first done by ensuring that our research complied with the Helsinki Declaration and the Norwegian Health Research Act and that it was approved by the Regional Ethics Committees and the Norwegian Data Inspectorate. All participation was voluntary. The participants were informed and signed written consent. Research personnel should always evaluate whether the participant understands the information and the consequences of study participation and that their decision-making capacity is preserved. Participants could later, without further explanation, withdraw their consent and demand that the data be deleted, without consequences to treatment. The collected information was not shared with treating clinicians without explicit consent from the participant. Except for the time dedicated to participation and any pain during blood sampling, there were no other disadvantages to study participation.

Finally, in genetic studies, participants are informed that specific mutations for treatable or nontreatable conditions in the individual will not be analyzed. In our SZ PRS study, only participants with European ethnicity were included (see the reasoning in section 5.7.1). It is, however, imperative to increase the inclusion of diverse ethnicities in genetic research as a way to ensure equal opportunities in the progress of etiological knowledge and treatment development (342).

5.7 Methodological considerations

5.7.1 Representativity and generalizability

In Norway, the health care system is catchment area based and publicly funded and should be available to all, independent of their socioeconomic status. The majority of study participants in Studies I–III were recruited from four catchment areas in Oslo that are regarded representative of the city's socioeconomic variation. Study inclusion was consecutive and depended on referral from general practitioners or treating clinicians in outpatient and inpatient psychiatric treatment facilities. Self-referral was also possible. This enabled the inclusion of study participants that were likely representative of the heterogeneous FEP population.

Nonetheless, representativity may have been compromised because of a comprehensive and time-consuming study protocol that may have been too demanding for those with severe symptoms. To compensate for this, individuals in an acute psychotic exacerbation were eligible for participation within 12 months of the start of the first adequate treatment and could be recruited in a more stable phase. Still, it is possible that people less influenced by psychotic symptoms were more likely to participate from baseline. Conversely, and perhaps more relevant at the 10-year follow-up in Study III, former participants who were in full recovery and with a busy daily schedule may have been subject to attrition because of time restrictions. However, the variation in the reported symptom scores (e.g., depressive, positive, and negative symptoms) and levels of functioning was considerable among those who were included, suggesting that representativity was preserved.

Finally, because study participation was voluntary and likely required a certain degree of motivation, we cannot preclude that the eligible individuals who were severely affected by apathy did not agree to be referred or did not consent to participation after referral. Among those who did participate in the longitudinal studies (Studies II and III), no significant differences were found in baseline apathy levels between completers and noncompleters. Importantly, we do not know the number of eligible patients who were not asked or declined study referral. According to Norwegian law, researchers are not allowed to access medical records or keep data on patients before consent to study participation is given.

In Study I, we selected participants with schizophrenia spectrum disorders and healthy controls with European ethnicity only. This was necessitated by the heterogeneity of LD patterns and

allele frequencies between ethnicities and by the predominance of European ethnicity in the PGC discovery samples, which may affect SZ PRS performance (342, 343). Participant selection based on ethnicity is ethically questionable yet difficult to avoid at present. Thus, the lack of significant associations between SZ PRS and apathy is perhaps not generalizable to a non-European population.

In longitudinal studies, participant attrition may threaten the representativity of follow-up samples. We did not discover selective attrition at the one-year follow-up in Study II. At the 10-year follow-up in Study III, however, being male ($X^2 = 4.50$, $p = 0.034$), having a non-European ethnicity ($X^2 = 7.45$, $p = 0.006$), and having a lower PANSS general symptom score ($t = -2.10$, $p = 0.037$) at baseline were associated with study dropout. No significant differences between completers and noncompleters were found for the variables most relevant, including the PAS, AAO, DUP, PANSS negative, AES-S, GAF-F, and CDSS or other sources of secondary negative symptoms. Because male gender is associated with higher levels of negative symptoms and symptom persistence (169, 172), the long-standing effect of baseline apathy in the direction of higher apathy levels during the follow-up might have been even stronger had there not been a selective attrition of males. We investigated the baseline differences between European and non-European ethnicities and between genders, finding that Europeans had significantly lower premorbid social functioning, higher AUDIT, and higher IQ scores. Moreover, men had significantly lower premorbid academic functioning, higher DUDIT, and lower CDSS scores and were more likely single. It is possible that the effect of baseline depression on apathy trajectory in Study III may have been weaker if men had comparably completed the follow-up at 10 years. Interestingly, although baseline differences between completers and noncompleters are often used to evaluate the likelihood of longitudinal selection bias, attrition does not necessarily affect the estimates of associations between the variables in longitudinal studies, even when significant baseline differences are present (344). Mindful of the above reservations, we assumed that the follow-up sample was likely representative of the heterogeneity present at baseline and that the findings were generalizable to other FEP populations.

The attrition rate at the long-term follow-up in Study III was 59%, which is a higher loss-to follow-up rate than in early intervention studies like the Danish OPUS study (i.e., 39%) and the TIPS study (i.e., 38%), where retention may have been promoted by more frequent assessments and by treatment interventions during the follow-up. The retention rate in Study III (i.e., follow-

up sample/(baseline sample minus diseased participants) = 41%) was somewhat lower than in other naturalistic FEP studies (345-347), of which one computed retention rate in a less strict manner (346). Of the 198 baseline participants in Study III, 77 were reassessed at 7 years (Innlandet Site) or 10 years (Oslo Site). Of the 121 noncompleters, 9 were deceased, 9 had moved abroad, 43 were untraceable, and 60 refused to participate.

In Study III, a fraction of the participants was included from the more rural Innlandet county. Participants from Innlandet and Oslo differed significantly because those from Innlandet had a longer DUP, higher baseline apathy levels, and more often had a schizophrenia diagnosis. Explanations for the differences in DUP could be a delayed referral and start of treatment because of less accessible mental health care at Innlandet. Although early intervention services have long been part of mental health care at Innlandet, the catchment area is large, and driving from one end of the region to the other takes approximately four hours. This could reduce the experience of accessibility of such services and thereby reduce help-seeking behavior. Societal stigma associated with mental illness may be higher in rural areas, or conversely, the tolerance for deviant behavior could be higher. Both scenarios could result in an increased threshold for help-seeking and treatment delay. Measurement bias is less likely because the personnel who included participants from Innlandet took part in the same training program for symptom assessments and diagnostic evaluation as those in Oslo. In sum, we are not able to disentangle what caused the differences, so the explanations remain speculative. We adjusted for the inclusion site in the linear mixed model analyses in Study III. Even though inclusion at Innlandet was a significant predictor of an unfavorable apathy trajectory, the overall results for the growth model and predictors were not changed. This indicates that that our main findings were valid, although the rural population may not be representative of the urban population and vice versa, at least for some parameters. Healthy controls were randomly selected from population registers in the same catchment areas as the participants from Oslo. Considering the above, they may not be representative of the healthy controls from Innlandet in Study III.

5.7.2 Internal validity—confounding factors

In Studies I–III, we aimed to identify and statistically adjust for the factors that could confound the associations between the dependent and independent variables of interest. In Study I, the associations between SZ PRS and apathy may be confounded by nonrandom genetic variation because of population stratification (e.g., because of ethnicity, co-sanguinity, or genetic drift) or because of different genotyping batches. Thus, we adjusted for these factors (i.e., PCs and genotyping batch) in the multiple linear regression analysis.

In Studies II and III, the cross-sectional associations between depression, apathy, and functioning could be influenced by, for example, demographic variables and sources of secondary negative symptoms. We identified potential confounding from gender, premorbid functioning, DUP, AUDIT, DUDIT, and positive and disorganized symptoms in Study II, with the addition of Sum AP in Study III. In Study III, the same confounding variables and inclusion sites (Innlandet or Oslo) were probed when the prediction model for apathy development in the 10-year follow-up of FEP was built. Sum AP was not adjusted for in Study II. Regarding possible confounding from AP side effects, see also section 5.7.4. The associations between the dependent, independent, and confounding variables were explored using Pearson's bivariate correlation, Spearman's rho, or Chi-square statistics. Only variables with significant ($p \leq 0.1$) associations to the independent and/or dependent variables were included in the ensuing multivariate analyses.

In Study II, because of the between-group heterogeneity of variance and group sizes and skewed distributions of GAF-F within groups, we applied a Kruskal–Wallis test, followed by pairwise Mann–Whitney U-tests, to compare GAF-F between persistent symptoms groups. Using these analyses, adjustment for confounders was not possible. However, confounds were adjusted for in the ensuing multiple regression analysis with GAF-F as the dependent variable, and persistent apathy and persistent depression as independent variables.

5.7.3 Challenges regarding the use of the AES

Some issues regarding the use of the AES-C and AES-S have already been discussed in the previous sections. A few additional concerns relevant for our studies should be mentioned.

Several negative symptom rating scales have been criticized for assessing an admixture of negative symptoms and functioning, with the risk of introducing a spurious association between these symptoms and the functional outcome. These problems were more pronounced in older scales, where ratings were based on reported or observed behavior only (157, 268). The AES was constructed to incorporate the emotional and cognitive aspects of motivation, as well as goal-directed behavior (201). However, the definition of apathy by Marin entails a reduced goal-directed behavior because of diminished motivation (202). Thus, there is perhaps an unavoidable entanglement of the concepts of "apathy" and behavior and, thus, "functioning," which complicates the differentiation between the symptom and its behavioral consequences. Nevertheless, in Studies II and III, the correlation coefficients between the AES-C or AES-S

and the GAF-F at baseline, 1- and 10-year follow-up ranged between 0.47 and 0.64, leaving 59–78% of nonshared variance, which supports that the AES and GAF-F do tap into partly different phenomena.

Moreover, during the participant interviews, a halo effect is possible if the assessment of apathy and depression is done by the same rater. This is most relevant in Study II, where both the AES and CDSS were clinician reported. Here, a halo effect cannot be precluded. However, to ensure the reliability and validity of the AES-C scores, assessments were performed by psychologists or medical doctors working as research assistants or PhD students in the TOP study. They were trained in the use of the AES-C; first, the AES-C was applied after watching a series of videotaped interviews with people with psychotic disorders. Second, the AES-C scorings were discussed in plenum under the supervision of an experienced apathy researcher and clinical psychiatrist. In Studies I and III, the measurements of apathy and depression were independent, because we used the AES self-report version, whereas the CDSS was performed by the research personnel.

Conversely, because of state effects, a participant with concurrent depressive symptoms may rate him- or herself as more apathetic than externally observed. This could result in a false association between apathy and depression and may be relevant to Study III, where the AES-S was used. Thus, when applying the CDSS and AES-S, it is perhaps more likely that depression could be mistaken for apathy than the opposite. However, the strengths of the correlations between the CDSS and the AES-S and AES-C have shown to be similar at baseline ($r = 0.42$ and $r = 0.42$, respectively, both $p \leq 0.001$) and the one-year follow-up ($r = 0.54$ and $r = 0.46$ respectively, both $p \leq 0.001$) in a validation study of the AES-S, here comprising parts of the present FEP sample (285). This may indicate that such confounding of the AES-S relative to the AES-C is not very probable. Moreover, inter-rater reliability for the AES-C was satisfactory at baseline in the TOP apathy study (30, 277) but was not evaluated at follow-up assessments, which is relevant to Study II.

5.7.4 Strengths and limitations

Several strengths and limitations have been shown in the previous discussion. The primary strengths of Studies I-–III are the longitudinal, prospective designs (Studies II and III) and highly phenotyped study participants. Moreover, the participants were interviewed by trained psychologists or medical doctors using widely acknowledged and standardized assessment scales. We measured apathy with a specific and transdiagnostic, robust scale (267), where both

the clinician-reported and self-report versions had been validated in FEP (277, 285). Depression was measured with the CDSS to ensure the best possible discrimination from apathy and other negative symptoms (258), and secondary negative symptoms were adjusted for in the analyses. The linear mixed model analysis is a robust method if data are missing or there are dependencies in the data because of repeated measurements.

Regarding the limitations, several sources of sampling effects and attrition bias have been described in previous sections. Further, the samples in Studies I–III were not identical but partly overlapped, which represents a limitation to the direct comparison of numerical values across studies. Conversely, similar results between study samples may lend these findings strength, as exemplified by the consistency of the negative associations between apathy and functioning in Studies II and III. Moreover, the included diagnostic categories differed between the studies. In Study I, we aimed to explore associations to SZ PRS in a genetically more homogeneous population, thus only including schizophrenia, schizoaffective and schizophreniform disorders, and psychosis not otherwise specified. In Study II, a broad psychosis spectrum was included from baseline, while in Study III, only individuals with nonaffective psychotic disorders took part. These differences may reduce the between-study comparability.

In Study I, reduced statistical power because of the sample size has been noted in previous sections. In Study II, true differences in GAF-F between groups with persistent symptoms of apathy, depression, or both may have been obscured because of small-sized groups. A larger overall sample size, more equally sized persistent symptoms groups and normally distributed GAF-F within these groups may further have allowed for the use of more robust statistical methods with adjustment for potential confounding factors (e.g., gender, DUP, positive symptoms, medication).

Missing data may threaten the reliability and validity of the results, especially if the fraction of missing values is high, affects the dependent variables, or is nonrandom. In Study III, the number of participants at the different follow-up assessments varied. However, there were no missing values in the AES scores in Studies I–III. A few scores were missing in the AUDIT, DUDIT, or CDSS scores at different follow-up points in Study III. When less than two scale items were missing, these were replaced by the mean value of nonmissing items in the specific participant at that specific follow-up assessment. This was done to better preserve interindividual and longitudinal variation in the scores (compared with, e.g., replacement by

the sample's concurrent mean score or a last-observation-carried-forward strategy), thereby reducing the risk of estimation bias. If more than two items were missing, the values were treated as missing in the analyses, which was relevant in less than five individuals for each scale at any follow-up point. The linear mixed model analysis is considered robust in handling the above limitations in Study III (295).

Secondary negative symptoms were adjusted for in the analyses. In Studies II and III, we used the Sum AP as a proxy for secondary negative symptoms because of side effects. The participants used a wide variety of preparations and combinations of antipsychotic medications, and a more fine-grained measure of side effects may have been superior to the present strategy. Yet the Sum AP was not significantly associated with the dependent or independent variables and did not contribute to the explained variance in the dependent variables in any of the analyses. This could indicate that secondary negative symptoms because of side effects were not prominent at the group level.

In negative symptom research, it is common practice to exclude participants with high levels of secondary negative symptoms to reduce the risk of *pseudo-specificity*, for example, a false conclusion of an effect of antidepressants in reducing negative symptoms, when in fact only depressive symptoms have decreased (310, 348). Conversely, it may be argued that too strict exclusion criteria may eventually compromise the validity and generalizability of the findings because a substantial proportion of individuals with FEP do in fact have significant depressive symptoms or use alcohol or other substances (140, 349, 350).

Finally, fluctuations in symptoms of apathy and depression may have occurred between the baseline and one-year follow-up in Study II. Thus, the operationalization of persistent apathy and persistent depression as high cross-sectional symptom levels at both baseline and the one-year follow-up is a simplification. However, the same operationalization has been used in other studies (154, 351).

5.8 Clinical implications

The clinical implications of our findings are primarily that in FEP, individuals at risk of high apathy levels and perhaps persistent apathy for the decade to come may perhaps be identified close in time to their first adequate treatment by their higher levels of apathy, more depressive symptoms, and a long DUP. The early and severe impact of apathy and persistent apathy on everyday functioning found in previous research and supported by our studies calls for the

attention of clinicians and researchers to acknowledge apathy as a pivotal part of the negative symptom dimension and a critical target for treatment intervention.

However, the early critical period for apathy development may afford a window of opportunity for secondary prevention. In clinical practice, countering the effects of reduced motivation in apathetic patients will probably require close and flexible cooperation between specialist mental health care systems, community health care, relatives, workplaces, and educational institutions. As a clinical psychiatrist, I would certainly be curious to understand the idiosyncrasies of prior and current interests, desires, skills or goals in the individual patient. May they be revived or strengthened? Likewise, identifying the individual's perceived obstacles to change or goal-attainment appears to be important. Here, prescribing medication that may increase the experienced effort needed to achieve a certain reward or outcome, by aggravating, for example, sedation and hypersomnia, should probably be avoided.

Moreover, the lack of currently effective treatments for apathy may serve as an incentive to address its early predictors. It can first be suggested that one should not turn one's back on the symptoms of depression in FEP but always explore for concurrent depression in those with apathy and vice versa. Although we did not directly investigate this, it is tempting to speculate whether treating depression properly and early may be facilitate a more favorable long-term apathy trajectory in a subgroup of people with FEP. However, this hypothesis remains to be tested. Importantly, such efforts would not be relevant for those who have apathy *without* concurrent depression.

The direction of the positive association between apathy and DUP cannot be concluded with certainty because of the naturalistic design of Study III. However, the long-lasting effect of a long DUP in the direction of higher long-term apathy levels may serve as one argument for the sustained attention and priority of early detection and intervention programs in psychosis. Increasing mental health literacy in the general population may accelerate help-seeking behavior and reduce DUP, given that low-threshold early intervention services are available. Importantly, an early referral also depends on the competence in primary health care workers to detect the symptoms and behaviors related to psychosis development. Moreover, compared with TAU, early intervention in psychosis has also shown to be associated with reduced depressive symptoms in FEP (140, 320), which adds weight to the above reasoning.

Finally, our results suggest that environmental factors may be more important than common genetic variants for the development of apathy in schizophrenia, yet as mentioned, the literature on environmental risk factors and negative symptoms appears to be limited. If in Study I, a true association between SZ PRS and apathy was not detected because of reduced statistical power, the SZ PRS in its current form is still not helpful as a clinical tool in the prediction an apathy phenotype at the individual level.

6 CONCLUSION AND FUTURE RESEARCH

Apathy is suggested to be at the heart of the deleterious impact of negative symptoms on day-to-day functioning in FEP, and disentangling its causes is imperative. However, etiological and mechanistic research—and thus treatment development for negative symptoms—have been stunted by several factors. First, negative symptoms have mostly been handled as a unifactorial construct. Hence, their heterogeneity has not been sufficiently appreciated, and any differences in causal paths and mechanisms underlying the domains and subsymptoms have not been explored until more recently (162). Second, the most frequently used scales to assess negative symptoms have included cognitive symptoms among the negative symptom items and have also favored the external observation of behaviors relative to the subjective experience of negative symptoms in the individual (272). Lastly, confounding by secondary negative symptoms has not always been sufficiently addressed. However, there has been much progress regarding these issues during the last 10-15 years.

The main conclusions to be drawn from our three studies are as follows:

1. The current SZ PRS shows nonsignificant associations with apathy in schizophrenia spectrum disorders, which means common genetic variation related to schizophrenia may not be relevant for the development of apathy. However, at the time of the first adequate treatment in FEP, clinical variables predicting an unfavorable long-term apathy trajectory are well in place.

2. Apathy decreases during the first year of a FEP, which may represent a critical period for apathy development and is thereafter followed by long-term stability. In healthy controls, mean apathy levels are lower and longitudinally stable.

3. Persistent apathy or persistent depression is frequent during the early critical period in FEP, may overlap in the individual, and can be associated with equally severe functional impediments.

4. In cross-sectional analyses, the levels of apathy show consistent and statistically significant associations with reduced functioning during the first decade of a FEP, whereas the associations between depressive symptoms and functioning shows more variation.

Future research could first profit from narrowing the scope on apathy (and other negative subsymptoms) specifically. In their seminal paper "Avolition and Occam's Razor," Foussias and Remington theorized that avolition (i.e., apathy) led to the emergence of the other negative subsymptoms (39). This notion was supported in a recent review (40): Strauss et al. argued that according to network analyses, apathy may be a *central symptom* in the "network of negative symptoms" in schizophrenia (40, 352). Network analyses display the interconnections between symptoms in a network of symptoms. The most strongly interconnected symptoms in the network are depicted as *central* and are thereby theorized to be important for the development and persistence of less central symptoms (353). If apathy is indeed a central negative symptom and has a strong influence on the presence of other negative symptoms, an improved understanding of the processes influencing apathy development may have ripple effects on the broader negative symptom dimension. According to the network theory, the effective treatment of a central symptom may cause a general decline in the other symptoms of the network (40).

At the level of etiology, associations between apathy and SZ PRS should first be explored in larger FEP samples. Further, attending to environmental causal paths, gene*environment interactions and epigenetic mechanisms to apathy development are important ways forward. Wray et al. recently argued, that the PRSs for common complex disorders may never be able to "establish of definitively predict future diagnoses". Yet, they suggested that PRSs may have role in prediction algorithms together with other risk factors (e.g., environmental factors and rare genetic variants) (354). Whether such prediction algorithms will be clinically useful in psychotic disorders or at the level negative symptom domains or subsymptoms, remains for further study.

Moreover, because our results indicate that the predictors of higher long-term apathy levels are present at baseline in FEP, the risk factors preceding psychosis onset are of great interest. Biological and psychosocial data collected in large birth cohorts like the MoBa study (i.e., the Norwegian Mother, Father and Child Study (355)), where registry data are also embedded, could provide a unique window into the very early etiological factors associated with reduced motivation in those who later develop a psychotic disorder. Methodologically, digital phenotyping using actigraphy or smartphone apps may be more appealing to youth with a FEP. Applying such tools could perhaps lower the threshold for research participation in those with reduced motivation, allow information to be gathered more frequently, and may reduce the risk

of recall bias. Given that the daily questionnaires of an app are not too comprehensive, longitudinal attrition may potentially be minimized.

Second, although similar phenotypes may not have identical biological correlates (356), the cross-diagnostic manifestation of the apathy phenotype suggests that broadening the scope could provide valuable knowledge (162). This may involve transdiagnostic research strategies, investigating distinct and common biological circuits, genetic, and environmental factors associated with apathy across the psychosis spectrum and other mental and neurodegenerative illnesses. A cross-disorder approach may similarly be relevant to shed light on further questions regarding the relations between apathy and depression because both are prevalent and may also overlap in, for example, Parkinson's (357) and Alzheimer's diseases (358, 359). Here, a related, transdiagnostic and ongoing initiative is the Psychiatric Ratings using Intermediate Stratified Markers (PRISM), which aims to investigate the mechanisms underlying social disengagement across Alzheimer's disease, MDD, and schizophrenia (360).

The overlap between groups with persistent apathy and persistent depression and the comparison of functioning between these groups in Study II requires replication in larger FEP samples. Further, questions of whether the early treatment of apathy in FEP would reduce the likelihood of persistent apathy or result in a more benign long-term apathy course remain to be explored. Moreover, if persistent depression in FEP is truly associated with a profound impairment in functioning, it would be relevant to investigate whether the identification and treatment of early, concurrent depression in FEP could reduce the risk of symptom persistence and of functional impairment.

One example of a treatment intervention that may be relevant for further study is cognitive behavioral therapy (CBT), which may help minimize the effects of defeatist performance beliefs: the associations between DPBs and experiential domain symptoms have been shown (224, 225), but the relations between DPBs and the specific apathy subsymptom and with depression in FEP appear to be understudied. This could represent an interesting avenue of future research. To the best of our knowledge, a cognitive model for the understanding and treatment of depression in FEP has yet to be developed. However, lending support from the evidence of a psychosis and affective continuum in the general population and across mental illnesses, one may theorize that there is at least no categorical difference between people with a FEP and those with an MDD (or you and me). Thus, traditional CBT (or other types of

psychotherapy) could be equally helpful for concurrent MDD or depressive symptoms in individuals with a FEP.

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8 APPENDIX

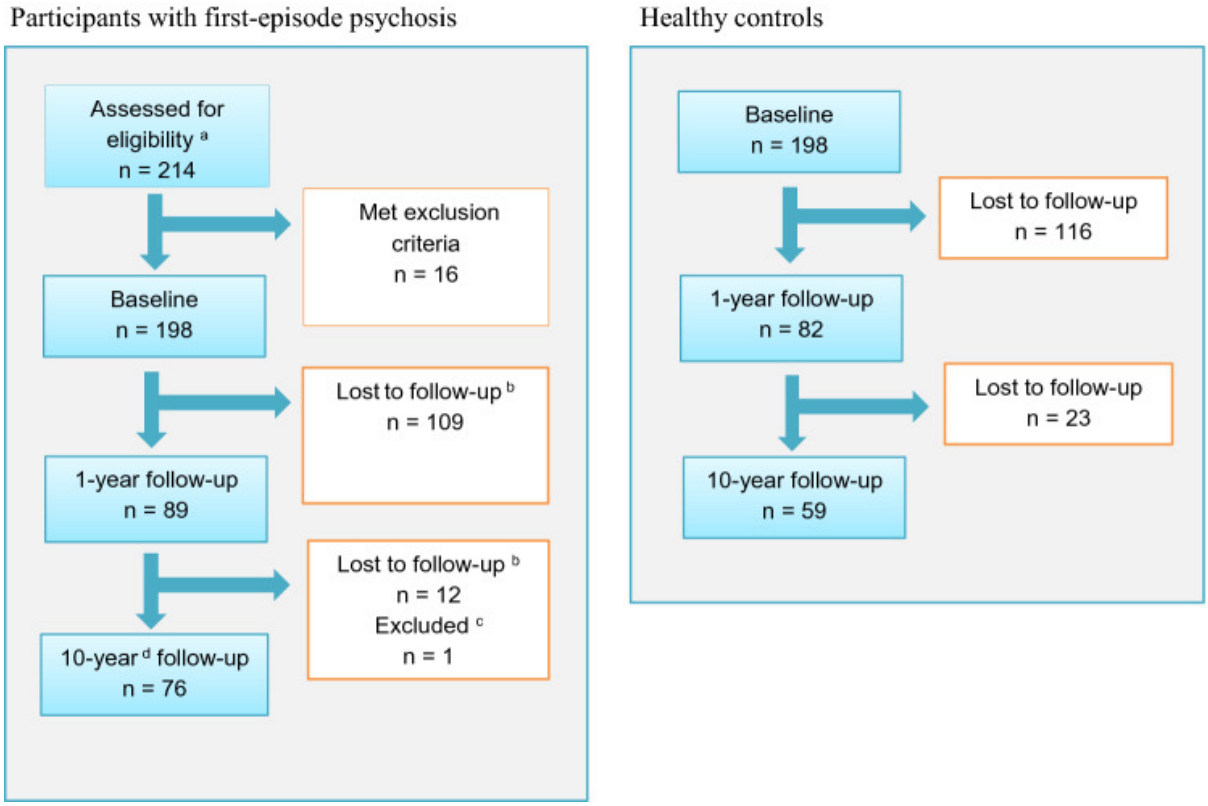
Supplementary Table 1. Sample characteristics at baseline in Studies I–III

	Study I		Study II		Study I	
Baseline variables[a]	Patients	HC	Patients	HC	Patients	HC
N (%)	281	298	125	0	198	198
Gender (female)	124 (44.1)	132 (44.3)	52 (41.6)	-	72 (36.4)	94 (47.5)
Age	29.3 (10.0)	30.4 (7.4)	28.1 (8.5)	-	27.2 (8.5)	32.6 (9.1)
Ethnicity European	281 (100)	298 (100)	95 (76.0)	-	155 (78.3)	196 (99)
FEP or MEP	FEP, MEP		FEP		FEP	
Diagn. distribution[b]						
Narrow schizophr.	163 (58.0)	-	-	-	-	-
PNOS, sch.affective, sch.form	118 (42.0)	-	-	-	-	-
Schizophr. spectrum		-	66 (52.8)	-	134 (67.7)	-
Affective psychosis		-	22 (17.6)	-	-	-
Other psychosis		-	37 (29.6)	-	64 (32.3)	-
Premorbid functioning						
PAS social childhood	1.25 (1.36)	-	1.43 (1.63)	-	1.41 (1.63)	-
PAS acad. childhood	1.67 (1.25)	-	1.67 (1.20)	-	1.73 (1.32)	-
DUP[c] (med./range)	40 (0-1040)	-	38 (1-1040)		75 (1-1560)	-
GAF-F	45.6 (12.5)	-	44.6 (13.6)	-	42.6 (12.5)	-
Symptom profile						
PANSS total	62.4 (16.7)	-	60.8 (14.1)	-	65.7 (16.1)	-
PANSS positive	14.9 (5.2)	-	14.8 (5.4)	-	16.2 (5.0)	-
PANSS negative	15.2 (6.2)	-	14.7 (6.1)	-	15.5 (6.6)	-
PANSS general	32.3 (8.4)	-	31.3 (7.1)	-	34.0 (8.3)	-
AES-S	28.4 (7.4)	19.0 (4.8)	-	-	28.7 (7.6)	17.6 (4.2)
AES-C	-	-	28.0 (7.5)	-	-	-
AES-C ≥ 27	-	-	72 (57.6)	-	-	-
AES-S ≥ 27	167 (59.4)	26 (8.7)	-	-	118 (59.6)	8 (4.0)
CDSS	5.6 (4.6)	-	6.6 (4.8)	-	6.8 (4.9)	-
CDSS > 7	-	-	51 (40.8)	-	-	-
AUDIT (med./range)	5.0 (0-36)	-	5.0 (0-33)	-	5.0 (0-38)	-
DUDIT (med./range)	0.0 (0-40)	-	0.0 (0-40)	-	0.0 (0-44)	-
Sum AP[d] (med./range)	1.0 (0.0-6.7)	-	-	-	0.9 (0.8)	-
SZ PRS ($p_T = 0.1$)	0.017817 (0.00007)	0.17790 (0.00008)	-	-	-	-

Abbreviations: HC = Healthy control; FEP = First-episode psychosis; MEP = Multiple episode psychosis; PNOS = Psychosis not otherwise specified; Sch.affective = Schizoaffective disorder; Sch.form = Schizophreniform disorder; PAS = Premorbid Adjustment Scale; DUP = Duration of untreated psychosis; med./range = median and range; GAF-F = Global Assessment of Functioning Scale–Functioning subscale; PANSS = Positive and Negative Syndrome Scale (Kay et al. 3-factor); AES-S = Apathy Evaluation Scale–Self-report version; AES-C = Apathy Evaluation Scale-Clinician version; CDSS = Calgary Depression Scale for Schizophrenia; AUDIT = Alcohol Use

Disorder Identification Test; DUDIT = Drug Use Disorder Identification Test; Sum AP = Sum antipsychotic medication; SZ PRS = Schizophrenia Polygenic Risk Score.
[a] Unless otherwise specified, values are given as N and percentages or means and standard deviations.
[b] In Study I, "narrow schizophrenia" was defined as a diagnosis of schizophrenia only. In Studies II and III, a "schizophrenia spectrum psychosis" included a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorders, and "other psychosis" included diagnoses of delusional and brief psychotic disorders and psychosis not otherwise specified. In Study II, "affective psychosis" included diagnoses of bipolar disorder type I and major depressive disorder with psychotic features.
[c] DUP in weeks.
[d] To compute the Sum AP, the dosage of each prescribed antipsychotic was divided by the defined daily dose (DDD) for that specific medication. The resulting ratios of each AP used (a maximum of three types /individual) were then summed. Thus, the Sum AP represents a proxy for the total load of AP prescribed to the individual.

Supplementary Figure 1. Participation in a 10-year follow-up of people with first-episode psychosis and in healthy controls*



[a] Patients with a first-episode psychosis were consecutively referred by their therapist in the clinical unit. Because we are not allowed by law to read the medical charts of patients before they give informed consent or o keep data on those who do not consent to be included, we have no possibility to report the number of eligible patients not asked by their therapist, said no to study referral, or did not want to give informed consent to enter the study after study referral.
[b] Of the ones lost to follow-up, 9 participants had died (all at the Oslo Site), 9 had moved abroad, 43 were untraceable, and 60 refused further participation.
[c] One participant was excluded because of a severe head injury btw. 1 and 10 years.
[d] At Innlandet, the mean follow-up time was 7.1 years. In Oslo, the mean follow-up time was 10.8 years. Thus, overall, the mean follow-up time was 9.0 years
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Associations between schizophrenia polygenic risk and apathy in schizophrenia spectrum disorders and healthy controls

Lyngstad SH, Bettella F, Aminoff SR, Athanasiu L, Andreassen OA, Færden A, Melle I. Associations between schizophrenia polygenic risk and apathy in schizophrenia spectrum disorders and healthy controls.

Objective: Apathy is a central predictor of a poor functional outcome in schizophrenia. Schizophrenia polygenic risk scores (PRSs) are used to detect genetic associations to key clinical phenotypes in schizophrenia. We explored the associations between schizophrenia PRS and apathy levels in schizophrenia spectrum disorders (n = 281) and matched healthy controls (n = 298), and further how schizophrenia PRS contributed in predicting apathy when added to premorbid and clinical factors in the patient sample.
Method: Schizophrenia PRSs were computed for each participant. Apathy was assessed with the Apathy Evaluation Scale. Bivariate correlation analyses were used to investigate associations between schizophrenia PRS and apathy, and between apathy and premorbid and clinical factors. Multiple hierarchical regression analyses were employed to evaluate the contributions of clinical variables and schizophrenia PRS to apathy levels.
Results: We found no significant associations between schizophrenia PRS and apathy in patients and healthy controls. Several premorbid and clinical characteristics significantly predicted apathy in patients, but schizophrenia PRS did not.
Conclusion: Since the PRSs are based on common genetic variants, our results do not preclude associations to other types of genetic factors. The results could also indicate that environmentally based biological or psychological factors contribute to apathy levels in schizophrenia.

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Key words: psychosis; schizophrenia; apathy; negative symptom; polygenic; genetic

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Significant outcomes

- There is no association between levels of apathy and the polygenic risk score for schizophrenia in patients with schizophrenia spectrum disorders and healthy controls. As opposed to clinical characteristics, polygenic risk scores do not contribute to predicting apathy levels in patients.
- Although the influence from genetic factors is not precluded, environmental factors may be important for the development of apathy.
- The schizophrenia polygenic risk score in its current form is of limited use in clinical settings.

Limitations

- Despite a moderate sample size for a clinical study, we may lack sufficient statistical power, with risks of type I as well as type II errors.
- The cross-sectional design precludes us from investigating associations to persistent negative symptoms.
- The apathy self-report measure is validated in healthy controls and first-episode psychosis patients, but not in multiple episode psychosis, and results should be interpreted with some caution.

Introduction

While the etiology of schizophrenia spectrum disorders remains largely elusive (1, 2), their heritability estimates are high (60–80%) (3, 4) and the hypothesis of an aberrant neurodevelopment as part of etio-pathogenesis is widely accepted (5–8). Improving our understanding of their underpinnings is imperative to develop new treatments and improve outcomes (1). Negative symptoms are core psychopathological phenomena in schizophrenia spectrum disorders (9). They frequently predate the onset of psychosis (10) and are associated with poor premorbid adjustment (11) and suggested to be closely related to neurodevelopmental disturbances (12–14). Due to lack of adequate treatments (15), high levels of negative symptoms predict poorer functional trajectories throughout the course of illness (16, 17).

Commonly used assessments of negative symptoms, such as the Scale for the Assessment of Negative Symptoms (18), the Clinical Assessment Interview for Negative Symptoms (19), and the Positive and Negative Syndrome Scale (20), are based on observations of behaviors, without links to biological underpinnings and thus without differentiation between primary negative symptoms and negative symptoms that are secondary to other causes, like positive symptoms or depression (i.e., secondary negative symptoms). The phenomenology of depressive symptoms may be similar to negative symptoms in schizophrenia spectrum disorders. However, telling them apart is facilitated by applying psychometric tools designed to improve this differentiation, like the Calgary Depression Scale for Schizophrenia (CDSS) (21). There is now consensus that negative symptoms comprise five symptom dimensions or negative 'sub-symptoms' (blunted affect, alogia, avolition/apathy, anhedonia, and asociality), clustering into two separate but related domains: the expressive and the experiential/amotivation domains (17). This differentiation is thought to reflect differences in their neurobiological substrates, and studies indicate that illness mechanisms may vary between the domains (17, 22).

Reduction of motivation and goal-directed behaviors is seen across several CNS and mental disorders. This phenomenon is called 'apathy' in neurology, but used interchangeably with 'avolition' in psychiatry. The study of apathy is facilitated by the availability of trans-diagnostic assessment scales, including self-report versions that are validated also in psychotic disorders (23), thus making larger-scale studies feasible. The mechanisms underlying avolition/apathy are not yet fully identified, but recent studies indicate complex disturbances involving the reward system (24), cognitive processes (22, 25), and defeatist attitudes (26, 27). In clinical studies of psychotic disorders, apathy appears as the strongest predictor of poor functional outcome relative to other negative sub-symptoms (28, 29).

Family studies show that negative symptoms are present in the families of individuals with schizophrenia (30–32), and the risk of other family members developing psychosis is higher if their index member with schizophrenia has severe negative symptoms (33). These findings suggest that negative symptoms are related to the genetic vulnerability for schizophrenia and thus are meaningful phenotypes in molecular genetic research (34). Positive symptoms also show familiality (30, 35), but less so than negative symptoms (31, 34). The heritability estimates of negative symptom-like traits in community samples are lower than the heritability for schizophrenia (36), but appear higher at the severe end of the negative symptom distribution and higher for negative symptoms relative to hallucinations (37). Research also suggests that the expression of negative symptoms is influenced by genetic variants (38, 39) and that the genetic variants and associated biological pathways underlying negative symptoms could be partly distinct from that of other symptom domains (40).

The genetic component of schizophrenia appears as highly polygenic (1) and mainly explained by aggregated, small effects of numerous single nucleotide polymorphisms (SNPs) scattered across the genome (41, 42). These SNPs currently map onto approximately 150 independent genetic loci (43, 44) and are often shared with several other phenotypes and across diagnostic categories (45–47). Schizophrenia polygenic risk scores (PRSs) (48) capitalize on the statistical power of the large genome-wide association studies (GWAS) from the Psychiatric Genomics Consortium (PGC) (43). Schizophrenia PRSs are computed based on the allele counts and effect sizes of SNPs associated with caseness in the PGC discovery samples and represent the en masse effects of common variants to schizophrenia risk in the individual. Studies using schizophrenia PRS have diverging findings regarding associations to the symptom dimensions of schizophrenia. Evidence supporting an association between schizophrenia PRS and positive symptoms is scarce (36, 49). Studies into negative symptoms are inconclusive, finding positive, negative as well as no statistically significant associations to schizophrenia PRS (36, 49). However, the interpretations of these studies have not taken into account the possibility of discrete biological mechanisms underlying the different negative sub-

symptoms and domains (17), which could disperse genetic signals. Linking genetic information to specific negative sub-symptoms could thus increase our ability to identify their biological substrates (39).

Aims of the study

In the present study, we investigated the association between schizophrenia polygenic risk score (PRS) and apathy in individuals with schizophrenia spectrum disorders and in healthy controls. The main research questions were as follows:

i Are schizophrenia PRSs associated with the level of apathy in patients and in healthy controls?
ii To what extent do schizophrenia PRSs predict the current level of apathy when added to premorbid and clinical characteristics in patients.

We hypothesized that higher levels of schizophrenia PRS would be associated with higher levels of apathy in patients and, to a lesser extent, in healthy controls. We also hypothesized that schizophrenia PRS would have an individual, but limited, explanatory effect in predicting the current level of apathy.

Methods

Participants

As part of the Thematically Organized Psychosis (TOP) Study at the Norwegian Center for Mental Disorders Research (NORMENT), 296 patients with schizophrenia spectrum disorders (schizophrenia, schizophreniform, and schizoaffective disorders, psychosis not otherwise specified) were consecutively recruited from in-patient and out-patient units of four major psychiatric clinics in Oslo. The hospitals' catchment areas serve approximately 485 000 inhabitants and are representative of the city population's variation in socioeconomic status. Participants were within 18–65 years of age. As allele frequencies vary widely between ethnicities (50), only participants of European ancestry origin were included.

General exclusion criteria were i) having an IQ below 70 ii) former moderate/severe head injury iii) present medical or neurological condition with associations to psychosis or apathy iv) psychosis caused by substance use. In total, 15 patients were excluded based on these criteria, leaving 281 for the analyses. Of these, 186 (66%) were first-episode psychosis (FEP) patients, while 95 (34%) had multiple psychotic episodes (MEP).

Persons randomly selected from the national population records from the same catchment areas (51) were invited by mail to participate as healthy controls (HC, $n = 350$). All were between 18 and 65 years old and with European ancestry. In addition to the general exclusion criteria specified above, HC were not eligible if they had a personal or family history of severe mental disorder. The mean age for HC was higher than for patients. They were matched with the patient group by randomly eliminating 52 HC with age above mean (28 women, 24 men), leaving 298 HC for the analyses. We did not match for intelligence or years of education due to the polygenic overlap between schizophrenia, cognition, and educational attainment (52, 53). Thus, matching for the intelligence quotient or educational years could introduce selection bias.

All participants gave informed, written consent according to the Declaration of Helsinki. The Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics approved the study.

Clinical assessment

Patients with schizophrenia spectrum disorders were evaluated by trained psychologists or medical doctors using comprehensive clinical interviews and neurocognitive tests. Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (54). The diagnostic inter-rater reliability was satisfactory, with a diagnostic agreement of 82% (95% confidence interval 0.60–0.94; $\kappa = 0.77$) (55). 'Narrow schizophrenia' was defined as a diagnosis of schizophrenia (excluding schizoaffective and schizophreniform disorders and psychosis not otherwise specified).

Premorbid functioning was assessed with the Premorbid Adjustment Scale (PAS) (56). PAS scores were divided into age-based intervals (childhood, early adolescence, late adolescence, adulthood) and into school (PAS academic) and social functioning (PAS social). To avoid including periods with prodromal symptoms, we only applied PAS childhood scores in the analyses. Duration of untreated psychosis (DUP) (57) was defined as the duration in weeks from psychosis onset (score ≥ 4 for ≥ 1 week on items p1, p3, p5, p6, or g9 in the Positive and Negative Syndrome Scale (PANSS)) (20) to first adequate treatment. Age at onset (AAO) depicts the age at onset of the first psychotic episode.

Symptom dimensions were assessed with the PANSS, with 20 items divided into five symptom factors (positive, negative, disorganized, depressed,

and excited) (58). We further employed a PANSS two-factor model for negative symptoms (59) where items n1, n3, n6, g5, g7, and g13 were grouped into the expressive domain and items n2, n4, and g16 into the experiential/amotivation domain. Functioning was assessed with the function subscale of the Global Assessment of Functioning Scale, split version (GAF-F) (60).

Apathy was assessed with the Apathy Evaluation Scale self-rated version (AES-S) (61), previously applied in neuropsychiatric (62) and psychotic disorders as well as in HC (63–65). We used a 12-item abridged version of the original 18-item AES-S. In a FEP subsample of the current sample, the AES-S was highly concordant with the AES clinician-rated version (23). This is in line with recent studies describing reliable self-reports of motivational symptoms in people with schizophrenia (66) even with longer duration of illness (67, 68). The AES-S items are scored on a 1-point to 4-point Likert scale with higher sum scores representing higher levels of apathy. We defined an AES-S sum score ≥ 27 (two standard deviations above mean in HC) to represent clinically significant levels of apathy, a cutoff applied also in previous studies (64, 69).

Depression was assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (21), a scale designed to enhance the differentiation between negative symptoms and depression in psychotic disorders. Alcohol and drug use were measured with the Alcohol Use Disorder Identification Test (AUDIT) and the Drug Use Disorder Identification Test (DUDIT) (70, 71) respectively. We estimated the current load of antipsychotic medication (AP) in each participant: The actual daily dose of an AP was divided by its Defined Daily Dose (DDD) (dose recommended by the WHO Collaborating Centre for Drug Statistics Method) (72). Then, if a participant used more than one AP, one ratio was computed for each and these ratios lastly summed to a 'Sum AP'.

Genotyping

DNA (obtained from blood or saliva) was analyzed in six succeeding batches between 2014 and 2017 at deCODE Genetics, Reykjavík, Iceland, using Illumina Human OmniExpress-12 and Infinium OmniExpress-24 chips and Illumina Global screening arrays.

The genotypes were quality controlled using PLINK (version 1.9; https://www.cog-genomics.org) (73, 74). Based on the genotyping, participants were excluded if they i) were represented in duplicate (one of the duplicates was retained), ii) were mixup samples (calculated investigating 'excess of heterozygosity'), and iii) had more than 5% missing genotype data. Variants were excluded if they deviated severely ($P < 0.0001$) from the Hardy–Weinberg equilibrium and had a minor allele frequency (MAF) <5% or low yield (<95% of chromosomes conferred information about the variant).

Variant imputation

Non-genotyped variants were imputed with MaCH (75) (http://www.sph.umich.edu/csg/abecasis/MACH) using the European reference samples in the Phase III release of the 1000 Genomes project. Variants not present in this reference sample or with ambiguous strand alignments were removed from the sample data set. Imputation was a three-stage process involving i) ChunkChromosome, dividing the data set into 2500 variant chunks with a 500 variant overlap; ii) MaCH, phasing each chunk (40 rounds and 400 states); and iii) Minimac, imputing each of the phased chunks to the 1000 Genomes reference panel (20 rounds and 400 states) (http://genome.sph.umich.edu/wiki/Minimac). Lastly, r^2 and MAF were estimated for all imputed variants; variants with $r^2 < 0.2$ or MAF < 0.05 were excluded. As part of postimputation quality control, participants were excluded if they i) were relatives (identity by descent, $\hat{\pi} \geq 0.125$) ($n = 4$) or ii) had a gender differing from that determined by the X-chromosome marker homozygosity ($n = 7$).

Population stratification analysis

To investigate the clustering of alleles due to ancestry/population stratification, we carried out a principal component analysis using PLINK (76) on a set of independent variants. This yielded 20 genetic principal components (PCs) to be used as covariates in the subsequent analyses.

Polygenic risk scores

Schizophrenia PRSs were computed using the methodology established by Purcell et al. (48). First, we performed a meta-analysis using METAL (http://csg.sph.umich.edu/abecasis/metal) (77) including all the Psychiatric Genetics Consortium's (PGC's) schizophrenia GWAS (PGC 2014) after removing the cohort in which the current study is based (TOP3). This meta-analysis resulted in unbiased effect sizes (ln (OR)) for all imputed variants. These variants were pruned according to their linkage disequilibrium state using PLINK's

clump option ($r^2 < 0.25$, 500 kb window), selecting variants with the lowest *P*-values from all linkage disequilibrium blocks. The schizophrenia PRSs then result from summing up the products (effect size*allele count) for all selected variants for each participant. Sixteen schizophrenia PRSs were computed including variants at *P*-value thresholds from 5×10^{-8} to 1, at intervals of half an order of magnitude. Of these, the PRS inclusion threshold leading to most explained phenotypic variance in case–control status (Nagelkerke pseudo-r^2) was selected for the ensuing analyses (*P*-value = 0.1).

Statistical analyses

All analyses from this point onward were performed using the IBM SPSS version 23. All variables were investigated concerning normality, outliers, collinearity, and homoscedasticity. DUP, AUDIT, and DUDIT were log10-transformed due to skewness. Independent-samples *t*-tests or chi-squared tests were used to assess differences between patients and HC, including validation of the expected PRS differences (Table 1). For all subsequent analyses, either parametric tests or their non-parametric alternatives were used as appropriate. Significance levels were pre-set to ≤0.05, two-tailed. For the first research question, associations between schizophrenia PRS and AES-S scores were explored in the complete sample and in patients and HC separately, using scatter plots and Pearson's correlation analyses. We did three sets of follow-up analyses in the patient group. First, we repeated correlational analyses in the subgroups of FEP ($n = 186$), MEP ($n = 95$), and patients with a narrow schizophrenia diagnosis ($n = 163$). Second, we repeated correlational analyses in the full patient group ($n = 281$), substituting AES-S scores with PANSS negative symptoms as

Table 1. Demographic and clinical variables

Variable of interest	Patients Mean (SD)	*n*	Healthy controls Mean (SD)	*n*	Statistic *t*, X^2
N (total)		281		298	
Women (*n*/%)	124 (44.1)	281	132 (44.3)	298	$X^2 = 0.002$, $P = 0.968$
Age	29.3 (10.0)	281	30.4 (7.4)	298	$t = -1.5$, $P = 0.128$
Education, years completed	12.3 (2.7)	266	14.4 (2.2)	297	$t = -10.1$, $P < 0.001$
Working/studying (*n*/%)	85 (30.4)	280	287 (99.0)	290	
PAS acad. child (median/range)	1.50 (0.0–5.5)	255	–		
PAS soc. child (median/range)	1.00 (0.0–6.0)	255	–		
Age at psychosis onset	24.2 (8.3)	270	–		
DUP (median/range in weeks)	40.0 (0–1040)	235	–		
Diagnostic distribution		281			
Narrow schizophrenia[†] (*n*/%)	163 (58.0)		–		
PNOS, sz.aff, sz.form (*n*/%)	118 (42.0)		–		
Symptom profile/functioning					
GAF-F	45.6 (12.5)	281	–		
PANSS total[‡]	62.4 (16.7)	276	–		
PANSS positive	14.9 (5.2)	278	–		
PANSS negative	15.2 (6.2)	277	–		
PANSS general	32.3 (8.4)	277	–		
PANSS 2-factor[§] expres.	11.7 (5.1)	278	–		
PANSS 2-factor[§] amotiv.	7.2 (3.3)	278	–		
AES-S	28.4 (7.4)	281	19.0 (4.8)	298	$t = 17.9$, $P < 0.001$
AES-S sum score ≥ 27 (*n*/%)	167 (59.4)	281	26 (8.7)	298	$X^2 = 167.3$, $P < 0.001$
CDSS	5.6 (4.6)	274	–		
AUDIT (median/range)	5.0 (0–36)	260	–		
DUDIT (median/range)	0.0 (0–40)	270	–		
Sum AP (median/range)[¶]	1.0 (0.0–6.7)	281	–		
SZ PRS ($P_T = 0.1$)	0.017817 (0.000074)	281	0.017790 (0.000077)	298	$t = 4.2$, $P < 0.001$

PAS, Premorbid Adjustment Scale, academic and social sub-scores (childhood ≤ 11 years); DUP, Duration of Untreated Psychosis; PNOS, Psychosis Not Otherwise Specified; Sz.aff., schizoaffective disorder; Sz.form, schizophreniform disorder; GAF-F, Global Assessment of Functioning Scale, functioning subscale; PANSS, Positive and Negative Syndrome Scale; AES-S, Apathy Evaluation Scale, self-report version; CDSS, Calgary Depression Scale for Schizophrenia; AUDIT, Alcohol Use Disorder Identification Test; DUDIT, Drug Use Disorder Identification Test; Sum AP, Sum (Actual Daily Dosage of Antipsychotic Medication/Defined Daily Dose) for a maximum of three antipsychotics used by each patient; SZ PRS, Schizophrenia Polygenic Risk Score.

Unless other is specified, values are means and standard deviations.

[†]Narrow schizophrenia = a diagnosis of schizophrenia (excluding schizoaffective and schizophreniform disorders and PNOS).

[‡]PANSS 3-factor (Kay et al.).

[§]PANSS 2-factor (Liemburg et al.).

[¶]*n* = 61/281 (22%) did not use any antipsychotic medication (AP). While 80% (176/220) used only one AP, the remaining 20% used two or three different APs.

one single factor (Wallwork's model) (58) and as two factors (Liemburg's model) (59). Third, we applied a multiple hierarchical linear regression analysis with AES-S as the dependent variable, adjusted for genotyping batch and six principal components, and entered the schizophrenia PRS at the last step. The relevant principal components were chosen based on significant bivariate correlations ($P \leq 0.1$ level) with schizophrenia PRS and/or the AES-S score. Since all these analyses were follow-up analyses of the primary, with a high degree of association between dependent variables, we did not correct for multiple testing. For the second research question, we did a series of blockwise multiple hierarchical linear regression analyses with AES-S as the dependent variable. Relevant premorbid and clinical predictors of apathy were chosen based on findings from previous research in psychotic disorders. Associations between AES-S, clinical predictors, and sources of secondary negative symptoms (depression, positive symptoms, and Sum AP) were then inspected using bivariate correlation analyses. Variables with a significant bivariate association ($P \leq 0.1$ level) to AES-S were entered into the regression model, adjusting for genotyping batch, principal components, and relevant secondary negative symptoms, then adding the schizophrenia PRS in the last block.

Results

Clinical and demographic characteristics of patients and HC are presented in Table 1. Patients had significantly fewer years of education and were less likely to be working or studying than HC. Twenty-two percent (61/281) of patients did not use any AP. Among the ones using AP, 80% (176/220) used one AP, while 20% used two or three different APs. Patients had higher mean apathy scores, and 59% had clinically significant levels of apathy, compared to 9% in HC. Schizophrenia PRSs were significantly higher in patients than in HC ($t = 4.2$, $P < 0.001$).

Associations between schizophrenia polygenic risk scores and apathy in patients and healthy controls

Scatter plots of schizophrenia PRS and AES-S scores in the complete sample, HC, and patients are shown in Fig. 1. Since patients had higher PRSs and higher apathy scores, the scatter plot of the complete sample gives an impression of an association between PRS and apathy. However, this is fully explained by the case–control status. The corresponding bivariate correlations are displayed in Table 2. We found no significant associations between schizophrenia PRS and apathy scores, neither in the patient sample ($n = 281$; $r = -0.08$, $P = 0.160$) nor in HC ($n = 298$; $r = -0.02$, $P = 0.685$). Follow-up analyses in the patient subgroups of FEP ($n = 186$, $r = -0.09$, $P = 0.214$), MEP ($n = 95$, $r = -0.02$, $P = 0.814$), and narrow schizophrenia diagnosis ($n = 163$, $r = -0.08$, $P = 0.307$) did not indicate any significant associations. Repeating correlational analyses in the full patient group ($n = 281$), applying PANSS negative symptoms as one single factor or as two factors, gave equivalent, negative results (Table 2). Multiple regression analyses, adjusting for batch and principal components, confirmed that the lack of significant associations between schizophrenia PRS and AES-S scores was not due to confounding effects (Table 3).

The contribution of schizophrenia polygenic risk scores to predicting current level of apathy when added to premorbid and clinical characteristics in patients

The bivariate correlations between AES-S, premorbid, and clinical characteristics are shown in Table 4. The variables entered in the multiple hierarchical regression analysis together explained 27% of the variance in apathy levels. There was not a statistically significant contribution from the schizophrenia PRS (Table 5).

Discussion

We found no statistically significant associations between schizophrenia PRS and levels of apathy neither in patients with schizophrenia spectrum disorders nor in healthy controls. Schizophrenia PRS did not contribute to the prediction of current levels of apathy when added to the premorbid and clinical characteristics.

To our knowledge, we are the first to investigate the relationship between schizophrenia PRS (as a measure of the polygenic contribution of common variants) and apathy (expected to be a biologically relevant negative sub-symptom). Using a broader measure of the negative symptom dimension than the AES-S could potentially have captured other aspects, associated with the PRS. However, follow-up analyses using different factor solutions for the PANSS negative symptom components produced equal results. Our findings are thus in line with the lack of associations found in several previous studies (38, 78, 79) and go against findings of negative associations (80) or positive associations in adolescents from the general population (81, 82), in FEP (83) or broader schizophrenia samples (84).

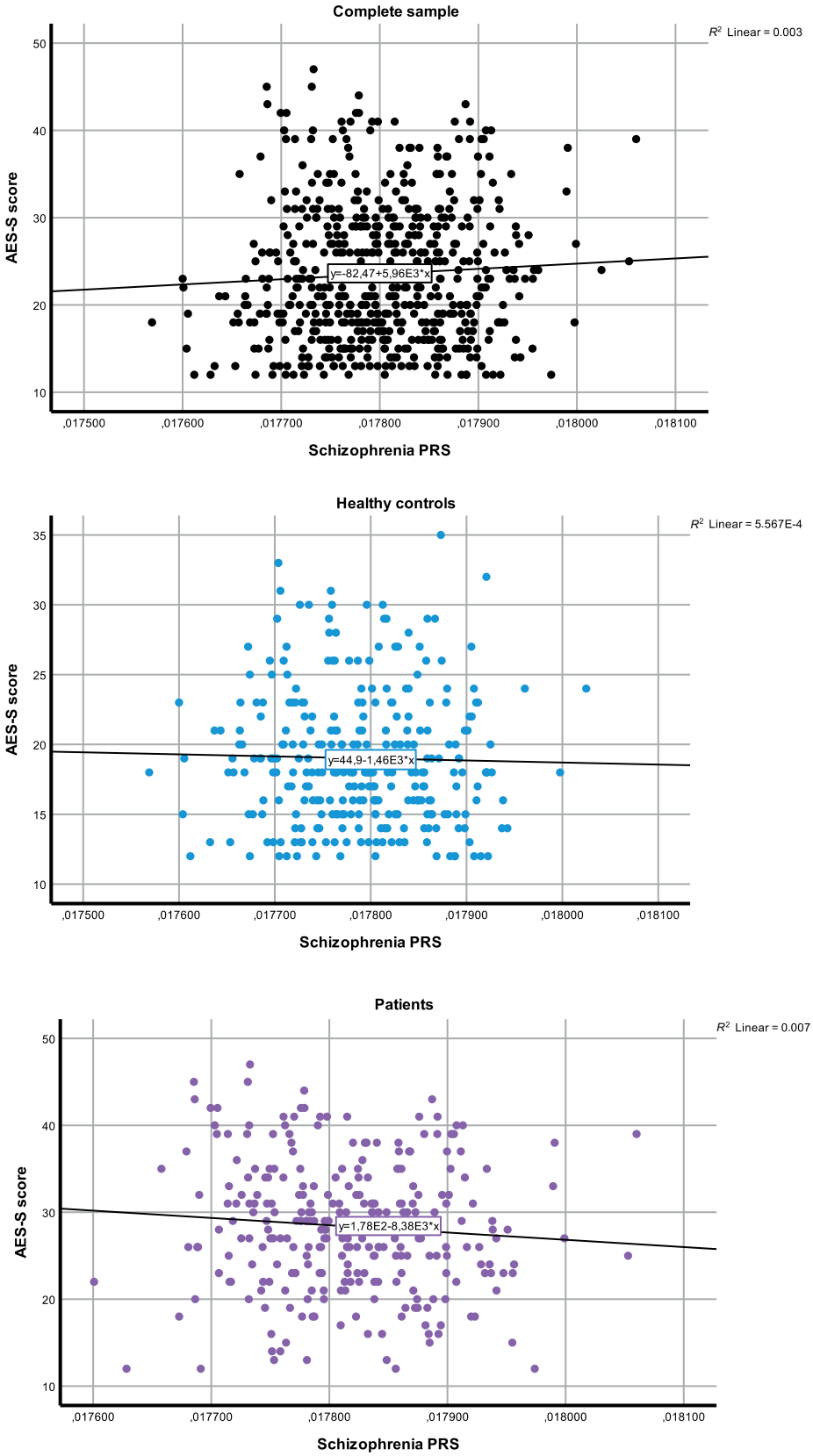

Fig. 1. Scatter plots of schizophrenia PRS and levels of apathy (AES-S) in the complete sample, healthy controls, and patients with schizophrenia spectrum disorders. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2. Bivariate correlations between schizophrenia polygenic risk scores ($P_T = 0.1$) and apathy levels in patients, healthy controls, and complete sample, and with PANSS negative symptoms as one single factor and as two factors in patients only

Clinical variable	Patients SZ PRS	*P*	Healthy controls SZ PRS	*P*	Complete sample SZ PRS	*P*
N	281		298		579	
AES-S[†], *r*	−0.08	0.160	−0.02	0.685	0.06	0.155
PANSS negative[‡]	−0.06	0.340				
PANSS neg. expressive[§]	−0.06	0.294				
PANSS neg. amotivation[§]	−0.06	0.286				

AES-S, Apathy Evaluation Scale, self-report version; SZ PRS, Schizophrenia Polygenic Risk Score; PANSS, Positive and Negative Syndrome Scale.

Unless other is specified, correlations are Spearman's rho.

[†]In patients, the AES-S showed significant correlations with PANSS negative symptoms as one factor ($\rho = 0.26$, $P < 0.001$), with PANSS negative expressive factor ($\rho = 0.18$, $P = 0.003$), and with PANSS neg. amotivation factor ($\rho = 0.42$, $P < 0.001$).

[‡]Negative symptoms as one single factor (Wallwork's model).

[§]Negative symptoms as two factors (Liemburg's model).

Our lack of findings could theoretically be explained by capturing an admixture of primary and secondary negative symptoms. However, bivariate correlation analyses between the AES-S and measures of substance use and antipsychotic medication load were non-significant (Table 4). Further, when we adjusted for positive symptoms and depression in the multiple regression analyses, results were not altered (Table 3 vs. Table 5). Moreover, even if cross-sectional studies may indicate a higher proportion of negative symptoms in chronic patient groups, longitudinal studies in FEP suggest that after an initial decrease, levels of apathy-like symptoms are quite stable over the first ten years of the disorder (64). The causes of secondary negative symptoms may, however, differ across FEP and MEP groups. While high levels of depressive symptoms may cause anhedonia and behavioral withdrawal in FEP, there is also a risk that treatment failures increase defeatist attitudes in MEP. Repeating our analyses in FEP and MEP separately did not influence our findings. Lastly, the use of a broad schizophrenia diagnosis may 'dilute' the PRS signal. Repeating the analyses in patients with a narrow schizophrenia diagnosis did not indicate that such sample characteristics influenced our findings. There are, however, hypotheses that patients with persistent, high negative symptoms (14) or the deficit syndrome (33, 85) are a specific clinical subgroup with a specific biological basis. Since our study was cross-sectional, we could not identify this group within our sample and might miss out signals of such a specific genetic basis. Lastly, as high levels of negative symptoms may be associated with a higher heritability (33, 37), one path of investigation could have been to explore the associations between apathy and PRS in a subgroup of patients with high apathy scores. However, our sample size had insufficient statistical power for subgroup analyses.

Our findings indicate a non-existent, weak, or unstably detectable association between the polygenic basis of schizophrenia and negative symptoms. However, the absence of significant associations may have some relevant explanations. First, common variants are estimated to explain at best 30–50% of schizophrenia's heritability (48, 86). A fair amount of schizophrenia's genotypic variance is thus not represented by the current schizophrenia PRS, including copy number variants (87–89), rare or de novo variants (90), and small deletions and insertions (42). Second, the current schizophrenia PRSs, based on the PGC2 discovery sample, only have the power to detect differences between cases and controls of 7.5% ($P_T = 0.1$) in the complete TOP study. The explained variance by the schizophrenia PRS ($P_T = 0.1$) in the current sample ($n = 579$) was 4.0%. In theory, the PRS threshold with the highest power to differentiate between cases and control subjects might not be the threshold with the highest association with apathy. However, to avoid

Table 3. Multiple hierarchical regression analyses exploring associations between schizophrenia polygenic risk scores and apathy levels[†] in patients ($n = 281$), adjusting for genotyping batch and principal components

	β	*t*	95% CI for B	*P*	R^2 change	Adjusted R^2	Sig *F* change
Constant		0.90	(−90.48, 327.85)	0.370			
Batch					0.026	0.009	0.191
PC					0.038	0.026	0.099
SZ PRS	−0.04	−0.66	(−16 296.13, 8148.12)	0.512	0.002	0.024	0.512

CI, confidence interval; PC, principal component; SZ PRS, Schizophrenia Polygenic Risk Score. Explained variance for the full model (R^2) = 0.066.

β, *t*, CI for B, and *P* refer to statistics from the final model. The model was adjusted for a total of six genotyping batches and six principal components; betas and 95% CIs are not reported for each batch/component for reasons of space.

[†]The AES-S score is the dependent variable.

Table 4. Bivariate correlations between apathy levels, and premorbid and clinical characteristics in patients ($n = 281$)

Clinical variable	AES-S	*P*
Gender, *r*	−0.06	0.326
IQ, *r*	−0.05	0.462
PAS acad. childhood	0.11	0.078
PAS social childhood	0.21	0.001
Age at psychosis onset	−0.08	0.181
DUP†	0.23	<0.001
PANSS positive‡	0.19	0.002
PANSS disorg.‡	−0.01	0.818
CDSS	0.48	<0.001
Sum AP†	−0.11	0.071
AUDIT†	0.05	0.415
DUDIT†	0.04	0.499

AES-S, Apathy Evaluation Scale, self-report version; IQ, intelligence quotient; PAS, Premorbid Adjustment Scale, academic and social sub-scores (childhood ≤ 11 years); DUP, Duration of Untreated Psychosis; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; Sum AP, Sum (Actual Daily Dosage of Antipsychotic Medication/Defined Daily Dosage) for a maximum of three antipsychotics used by each patient; AUDIT, Alcohol Use Disorder Identification Test; DUDIT, Drug Use Disorder Identification Test.
Unless other is specified, correlations are Spearman's rho.
†The variable was log10-transformed due to skewness.
‡PANSS 5-factor.

Table 5. Multiple hierarchical regression analyses exploring contributions to apathy levels† in patients from premorbid and clinical characteristics, together with schizophrenia polygenic risk scores

	β	*t*	95% CI for B	*P*	R^2 change	Adjusted R^2	Sig F change
Constant		0.90	(−118.38, 317.77)	0.369			
Block 1							
PAS soc. childh.	.11	1.79	(−0.06, 1.26)	0.074			
DUP‡	.09	1.36	(−0.40, 2.14)	0.177	0.081	0.072	0.000
Block 2							
PANSS positive	−0.01	−0.19	(−0.26, 0.21)	0.850			
CDSS	0.40	6.05	(0.44, 0.87)	0.000	0.146	0.212	0.000
Block 3							
Batch§							
PC§					0.043	0.218	0.329
Block 4							
SZ PRS	−0.04	−0.71	(−16 586.56, 7846.59)	0.482	0.002	0.216	0.482

β, t, CI for B, and *P* refer to statistics from the final model.
PAS, Premorbid Adjustment Scale, social subscale from childhood; DUP, Duration of Untreated Psychosis; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; PC, principal component; SZ PRS, Schizophrenia Polygenic Risk Score.
Explained variance for the total model (R^2) = 0.271.
†The AES-S score is the dependent variable.
‡Due to skewness, DUP was log10-transformed.
§The model was adjusted for a total of six genotyping batches and six principal components; betas and 95% CIs are not reported for each batch/principal component for reasons of space.

type I error, we abstained from exploring associations between the different PRS thresholds and the apathy scores.

As each common variant included in the PRS only confers small increments in risk, the sample sizes required to reveal true effects are large (91). Larger PGC discovery samples might thus detect additional common variants associated with schizophrenia, and increase the predictive power of the PRS (92, 93). The GWAS discovery samples are powered to accommodate for corrections for multiple testing, with a *P*-value threshold of 5×10^{-8}. The sample sizes needed to investigate a low number of hypothesis-based associations are lower. The current sample size is equivalent to some of the previous studies investigating associations between PRS and clinical phenotypes (78, 83), yet larger (94) or smaller than others (36, 38, 84). Although a larger clinical sample would increase statistical power for detecting associations between clinical symptoms and the current schizophrenia PRS, the low correlation coefficients found here indicate that even though this would be theoretically interesting, the low predictive power of the current PRS would not make it a valuable tool in standard clinical settings or for personalized medicine.

Third, a potential explanation could be that apathy is not a phenomenon specific to schizophrenia. Apathy occurs in several neuropsychiatric disorders (29) and a broad spectrum of mental disorders (25). Consequently, the common genetic variants associated with apathy may not be captured by the schizophrenia PRS but rather by a cross-disorder 'Apathy PRS', which theoretically could be identified by pooling large cross-diagnostic discovery samples. However, considering equifinality in complex disorders, the similarity of phenotypes does not necessarily correspond to a similar genetic makeup (25, 95). Rather, equivalent phenotypes may have separate etiologies. In the case of apathy, research implies that neurological and psychiatric disorders are fairly distinct genetically (96), which could question the utility of a future cross-disorder Apathy PRS.

Fourth, apathy could be elicited by environmental factors (97) or develop through a chain of illness-related events. This includes defeatist performance beliefs (DPB) (26, 98), where cognitive impairments and associated negative experiences of goal attainment become templates for negative beliefs about own performances, reducing motivation for future goal-directed behavior (22, 99). In a recent meta-analysis, 70% of included studies found significant, positive associations between DPB and negative symptoms (100). DPB are more strongly associated with the experiential/amotivation domain than the expressive domain in some (27, 101) but not all studies (100). Negative

Expectancy Appraisals (beliefs about a reduced likelihood of success, acceptance, and pleasure in the future) (101), reduced self-efficacy (102), and stigma and stigma resistance (103) are other suggested psychological models for reduced motivation. In this line of reasoning, apathy is conceivable as a downstream psychological effect of disturbances in cognitive functioning, another key characteristic of schizophrenia spectrum disorders, and not linked to the genetic basis of the disorder itself.

In sum, we found no significant association between schizophrenia PRS and the level of apathy in schizophrenia. The 'missing heritability' in schizophrenia, including the large amount of variance not explained by the current schizophrenia PRS, is substantial (104) and offers one possible explanation for our results. However, the clinical utility of the current PRS has been questioned in psychiatry (105). Precision medicine aims at understanding illness etiology and pathogenesis, enabling personalized treatment of the individual. In schizophrenia, PRSs so far seem to fall short on accuracy (106) and as a prediction tool at the level of clinical phenotypes.

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Declaration of interest

Author OAA has received speaker's honorarium from Lundbeck. All other authors declare that they have no conflicts of interest..

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Consequences of persistent depression and apathy in first-episode psychosis — A one-year follow-up study

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ABSTRACT

Background: Apathy and depression are prevalent in first-episode psychosis (FEP), have overlapping clinical features and are linked to social dysfunction, with indications that persisting symptoms have an even more negative impact. Our objective was to investigate the prevalence of persisting depression (PD), persisting apathy (PA), to what extent they overlap and their relative associations to functioning during a one-year follow-up.
Methods: One hundred and twenty-five participants with a FEP were recruited, and 88 (70%) were reassessed at follow-up. Functional outcome was assessed with the Global Assessment of Functioning Scale-split version, functioning sub-scale, apathy with the Apathy Evaluation Scale, Clinician version (AES-C), and depression with the Calgary Depression Scale for Schizophrenia (CDSS). Persisting depression was defined as a CDSS sum-score > 7 at baseline and follow-up, and persisting apathy as an AES-C sum-score ≥ 27 at baseline and follow-up. Multiple linear regression analyses were used to investigate symptoms' contributions to functioning. Differences in functioning between groups were explored with Kruskal-Wallis test and Mann-Whitney *U* test.
Results: We found PD in 17 (19%) and PA in 28 (32%) of participants. The likelihood of PD was increased if PA was also present ($p = 0.008$, phi = 0.28). Ten participants (11%) experienced overlapping PD and PA. Participants with PD ($r = -0.38, p = 0.004$), PA ($r = -0.51, p < 0.000$) or both ($r = -0.52, p < 0.000$) had poorer functioning at follow-up than participants without persisting symptoms.
Conclusion: PD, PA and overlapping PD/PA is highly prevalent and associated with severely impaired functioning in FEP. Correct identification of these patients is a prerequisite for initiating relevant treatment early in the course of illness.

1. Introduction

Functional disabilities are pronounced in schizophrenia and related psychotic disorders [1], and are often present at the start of the first psychotic episode. Negative symptoms have long been recognized as a central phenomenon in these disorders [2,3], with significant influence on the risk of disabilities [4].

Previously, affective symptoms have been considered positive prognostic factors in psychotic disorders [5]. However many, but not all [6, 7], recent studies link depression to reduced everyday functioning, quality of life and increased suicidality [8–11]. Depressive symptoms are highly prevalent both in the prodromal phase [8,12], during and between acute psychotic episodes in schizophrenia [13,14]. Being more common in early stages of illness, prevalence rates of depression range between 14 and 45% at baseline in first-episode psychosis (FEP) studies [5,15]. The wide variability may be explained by heterogeneity in study designs. Though depression is known to wax and wane throughout the course of the disorders [12,16], 14–26% of people with FEP are found to be continuously depressed in 12–18 months follow-up studies [6, 8, 17], i.e. having persisting depression (PD). Functional impairments are shown to be worse in people with PD than in people with fluctuating depression [6,8,18].

Clinical expressions of depression and negative symptoms can be phenomenologically similar [19,20], including loss of motivation and withdrawal from activities. However, differentiating depression from negative symptoms is essential in order to offer appropriate treatment [21,22]. During the last decade our understanding of the phenomena underlying negative symptoms has improved. Five different sub-symptoms can be grouped into two sub-domains: avolition/apathy (from here on called apathy), anhedonia and asociality, i.e. the "experiential domain", and blunted affect and alogia, i.e. "the expressive domain" [23]. Research on sub-symptoms is expected to give more

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knowledge about etiology and outcome, and harbors the potential for developing new treatments of negative symptoms [24].

Apathy, the best studied sub-symptom, is defined as a lack of goal directed behavior due to reduced motivation [25]. Studies indicate that beyond other negative sub-symptoms, apathy has a pivotal role in predicting poor functioning across psychotic disorders [2,26–28]. FEP-studies imply that apathy is prevalent early in the course of illness, with clinically significant levels (two standard deviations above mean in healthy controls) occurring in 50% at baseline assessments [29]. Between 16 and 30% have persisting apathy (PA) at short or long term follow-up [28,30,31]. Moreover, like for PD, PA has a stronger negative impact on functioning than fluctuating apathy [30,32,33].

In sum, persisting depressive and apathetic symptoms are of great concern as they seem to predict future functional impairment more strongly than fluctuating symptoms. Concurrently evaluating apathy and depression is necessary to assess their relative contributions to functional outcome. The prevalence of PD and PA in FEP and to what extent they overlap is not known, nor are their associations with functional outcome.

This study is a one-year follow-up of people with FEP. The aims are to explore:

1) the associations of current levels of depression and apathy with functioning at baseline and follow-up.
2) the prevalence of PD and PA and to what extent they overlap over the follow-up.
3) the relative contributions of PD and PA to functioning at follow-up.

As the associations between depression and functional impairment seem less unambiguous than for apathy, we hypothesized 1) that levels of apathy would be more consistently associated with reduced functioning in the cross-sectional analyses than depression 2) a more profound impact on functioning by PA than PD and 3) that PD and PA have additive negative effects on functioning at follow-up.

2. Materials and methods

2.1. Participants

Participants were consecutively recruited to the Thematically Organized Psychosis (TOP) study from four psychiatric units (inpatient and outpatient) in Oslo, Norway. We included 125 participants within a broad psychosis spectrum; schizophrenia, schizoaffective and schizophreniform disorders, bipolar I and major depressive disorders with psychotic symptoms, delusional disorder, brief psychotic disorder and psychosis not otherwise specified. This approach was chosen based on reports showing similar likelihoods of negative symptoms in schizophrenia spectrum and affective psychoses, and to avoid excluding participants based on diagnoses known to be unstable early in course of illness [31,34]. Participants were not considered FEP if they had previously been adequately treated for psychosis, defined as hospitalization or antipsychotic medication in adequate dosage for ≥ 12 consecutive weeks (or until remission within these 12 weeks). Participants were eligible for inclusion within 52 weeks following the start of first adequate treatment.

The Regional Committee of Research Ethics and the Norwegian Data Inspectorate approved the study. All participants gave an informed, written consent. At one-year follow-up, 88 (70%) participated.

Exclusion criteria were: Previous moderate/severe head injury, present medical or neurological condition with relationship to psychosis, not speaking a Scandinavian language, age outside the range of 18–65 years, IQ < 70 and psychosis due to substance use.

2.2. Instruments and measures

An extensive clinical assessment was performed by trained medical doctors or psychologists at baseline (BL) and follow-up (FU). Participants were diagnosed using the Structured Clinical Interview for the DSM IV (SCID-1) [35]. Interrater reliability of diagnostic categories was satisfactory, with an overall kappa of 0.77 [36]. Symptom levels were measured with the Positive and Negative Syndrome Scale (PANSS). We report on the Wallwork five factor model consisting of 20 items divided into positive, negative, disorganized, depressed and excited factors [37].

Functioning was measured with the Global Assessment of Functioning Scale-Split version [38], functioning sub-scale (GAF–F). Premorbid functioning was assessed with Premorbid Adjustment Scale (PAS) [39]. Scores from each interval (childhood: <11 years; early adolescence: 12–15 years; late adolescence: 16–18 years) were split into social and academic domains. As PAS-scores were highly correlated between age-intervals and the adolescence scores could be confounded by psychosis onset, we only used childhood scores in our analyses. Duration of Untreated Psychosis (DUP) was defined as the number of weeks from the first psychotic symptom (scored ≥4 on PANSS-items p1, p3, p5, p6 or g9) until first adequate treatment [40].

Apathy was assessed with the Apathy Evaluation Scale-Clinician version (AES-C) [41]. AES-C starts with an interview about hobbies, activities and descriptions of a "typical day" during the last month. Then, items like "She gets things done during the day" and "She is interested in learning new things" are scored from 0 through 4 on a Likert scale. Originally, AES-C has 18 items. We used an abridged 12-item version shown to have better psychometric properties in FEP. A sum-score ≥ 27 was set as cut-off for clinically significant apathy (2 standard deviations above mean in healthy controls) [42].

Depressive symptoms were measured with the Calgary Depression Scale for Schizophrenia (CDSS) [43]. CDSS outperforms other scales in differentiating between depression, extrapyramidal side-effects and negative symptoms in schizophrenia [21]. A major depressive episode is predicted with 91% specificity and 85% sensitivity at a cut-off of >7 [44]. To ensure a high specificity, we chose >7 as the cut-off for a clinically significant depression. Alcohol use was measured with Alcohol Use Disorder Identification Test (AUDIT) [45], and drug use with Drug Use Disorder Identification Test (DUDIT) [46].

2.3. Persisting symptoms groups

We divided the FU sample ($n = 88$) into groups based on the following criteria: 1) participants with a CDSS-score > 7 at both BL and FU were defined as having PD, 2) participants with an AES-C-score ≥27 at both BL and FU were defined as having PA, and 3) participants with depression or apathy above cut-off at only one assessment were defined as having non-persisting symptoms, together with the group with scores below cut-off at both BL and FU. We then defined four mutually exclusive groups:

$$\text{nAnD} = \text{non}-\text{persisting apathy} + \text{non}-\text{persisting depression}$$

$$\text{PDnA} = \text{persisting depression} + \text{non}-\text{persisting apathy}$$

$$\text{PAnD} = \text{persisting apathy} + \text{non}-\text{persisting depression}$$

$$\text{PAPD} = \text{persisting apathy} + \text{persisting depression}$$

2.4. Statistics

Analyses were carried out using the IBM Statistical Package for the Social Sciences (SPSS Inc.), Version 23. Violations of assumptions of normality, homoscedasticity, linearity and multicollinearity were

investigated. DUP, AUDIT and DUDIT were log-transformed due to skewedness. All tests were two-tailed, and alpha levels were set to 0.05.

For the first reseach question we used bivariate correlation analyses (Pearson's correlation or Spearman's Rho) to assess associations between patient characteristics, clinical symptoms and GAF-F at baseline (GAF-F BL) and follow-up (GAF-F FU). Multiple linear hierarchical regression analyses were used to investigate how current clinical symptoms contributed to the variance in GAF-F BL and GAF-F FU. Only independent variables with bivariate correlations at a significance level ≤ 0.1 were included, then entered in order of lifetime appearance and consecutively removed if no significant contribution was detected. The depressed and negative factors of the PANSS were not included in multiple regressions due to collinearity with the CDSS and the AES-C.

For the second research question, prevalence and prospective consistencies of PD and PA were calculated. A chi square test was used to investigate the likelihood of PD (yes/no), depending on apathy status (PA, yes/no) at FU. Because GAF-F FU-scores were not normally distributed within the persisting symptoms groups we used a Kruskal-Wallis Test to explore differences in GAF-F FU for the third research question. Post-hoc analyses using Mann-Whitney *U* test were done to compare pairs of groups: PAPD vs. PAnD, PAPD vs. PDnA, PAPD vs. nAnD, nAnD vs. PAnD, nAnD vs. PDnA and PDnA vs. PAnD. Alpha level was adjusted for the number of comparisons a.m. Bonferroni, i.e. $0.05/6 = 0.0083$. Last, a series of multiple hierarchical regression analyses were applied to further explore the relations of PD and PA to GAF-F FU.

For all three research questions, post-hoc analyses were performed in a subset of the sample consisting only of participants with non-affective psychosis diagnoses at BL ($n = 103$) and at FU ($n = 67$) (i.e. participants with major depressive disorder or bipolar disorder with psychotic features were excluded).

3. Results

Patient characteristics at BL and FU are presented in Table 1.

3.1. Contributions by depression and apathy to GAF-F at baseline and follow-up

Bivariate correlations between patient characteristics, clinical symptoms and GAF-F at BL and FU are displayed in Table 2.

The association between CDSS (as for the PANSS depressed factor) and GAF-F was significant at FU but not at BL.

AES-C was significantly associated with GAF-F at both BL and FU. All PANSS-factors had significant negative correlations with GAF-F at BL and FU, except for the excited factor. AES-C and CDSS inter-correlation was 0.349 ($p < 0.001$) at BL and 0.386 ($p < 0.001$) at FU.

Results from the multiple linear hierarchical regression analyses at BL and FU are shown in Table 3. Adjusting for gender, childhood academic functioning, PANSS excited and positive factors, only DUP, baseline AES-C and PANSS disorganized factor had significant associations with GAF-F BL, together explaining 38.3% of its variance. CDSS did not contribute significantly at BL. At follow-up, adjusting for gender, childhood academic functioning, DUP and PANSS disorganized factor, both AES-C and CDSS contributed to a lower level of functioning, and together with PANSS positive factor explained 52.1% of the variance in GAF-F FU. Further, the clinical variable entered into the regression first tended to contribute with the highest R^2-change, leaving less explained variance to the remaining variables. Entering AES-C first, it explained 41.2%, while CDSS explained 5.7% and PANSS positive factor 5.2% of the variance in GAF-F FU. Entering CDSS first, it explained 21.8%, PANSS positive 14.0% and last AES-C 16.3%.

Post-hoc analyses in the subset of participants with non-affective psychosis diagnoses at BL ($n = 103$) and FU ($n = 67$) showed that the clinical variables with significant contributions were identical, and that the fractions of explained variance in GAF-F BL and GAF-F FU were very similar to the ones in the sample as a whole. At baseline, DUP, PANSS disorganized factor and AES-C explained a total of 41.9% of the variance in GAF-F BL. At follow-up, PANSS positive factor, AES-C and CDSS together explained 58.4% of the variance in GAF-F FU (adjusting for the same variables as in the whole-sample analyses).

Table 1
Patient characteristics at baseline and one-year follow-up.

	Baseline	N	Follow-up	N
	n (%)		*n* (%)	
	mean (S.D.)		mean (S.D.)	
Gender (female)	52 (41.6)	125	37 (42.0)	88
Age	28.1 (8.5)	125	28.6 (8.2)	87
Years education	12.9 (2.9)	125	–	
IQ	102.9 (14.4)	113	103.5(14.6)	83
Ethnicity European	95 (76.0)	125	69 (78.4)	88
Working	49 (39.2)	125	–	88
Single	97 (77.6)	125	–	88
Diagnostic distribution		125		87
Sch. spectrum psychoses[a]	66 (52.8)		55 (62.5)	
Affective psychoses[b]	22 (17.6)		21 (23.9)	
Other psychoses[c]	37 (29.6)		11 (12.5)	
Premorbid functioning				
PAS social childhood	1.43 (1.63)	123	–	
PAS social early adolesc.	1.40 (1.41)	123	–	
PAS acad. childhood	1.67 (1.20)	122	–	
PAS acad. early adolesc.	2.07 (1.36)	122	–	
DUP median/range (weeks)	38 (1–1040)	125	–	
GAF-S	42.0 (12.2)	125	53.2 (17.2)	88
GAF-F	44.6 (13.6)	125	53.0 (16.5)	88
Clinical symptoms				
PANSS total	41.9 (10.0)	125	37.8 (9.7)	88
PANSS positive	9.7 (4.2)	125	8.1 (4.3)	88
PANSS negative	12.6 (5.7)	125	9.8 (4.2)	88
PANSS disorganized	5.4 (2.1)	125	5.0 (2.0)	88
PANSS depressed	8.6 (3.3)	125	7.1 (2.9)	88
PANSS excited	5.6 (2.0)	125	4.8 (1.5)	88
AES-C	28.0 (7.5)	125	25.0 (6.9)	88
CDSS	6.6 (4.8)	125	4.8 (3.9)	88
AES-C ≥ 27	72 (57.6)	125	39 (44.3)	88
CDSS>7	51 (40.8)	125	22 (25.0)	88
DUDIT, median/range	0.0 (0–40)	118	0.0 (0–40)	83
AUDIT, median/range	5.0 (0−33)	114	5.0 (0–29)	81

Abbreviations: PAS = Premorbid Adjustment Scale, divided into childhood and early adolescence scores, thereafter divided into social and academic sub-scores; DUP = Duration of Untreated Psychosis; GAF-S = Global Assessment of Functioning Scale-Symptom subscale; GAF-F = Global Assessment of Functioning Scale-Function subscale; PANSS=Positive and Negative Syndrome Scale (Wallwork 5-factor); AES-C = Apathy Evaluation Scale-Clinician version; CDSS=Calgary Depression Scale for Schizophrenia; DUDIT = Drug Use Disorder Identification Test; AUDIT = Alcohol Use Disorder Identification Test.

[a] Schizophrenia spectrum psychoses included schizophrenia, schizoaffective and schizophreniform disorders.

[b] Affective psychoses included bipolar I and major depressive disorder with psychotic features.

[c] Other psychoses included psychosis not otherwise specified, delusional disorder and brief psychotic disorder.

3.2. Prevalence and overlap of persisting symptoms at follow-up ($n = 88$)

Investigating the 88 participants who completed BL and FU assessments, 18 of the ones depressed at BL ($n = 35$) were in remission at FU, hence remission rate for depression was 51.4% (18/35). Twenty-one out of 49 participants with apathy above cut-off at BL were in remission at FU, i.e. remission rate for apathy was 42.9% (21/49). Prospective consistency was 48.6% (17/35) for depression and 57.1% (28/49) for apathy.

Seventeen (19.3%) had persisting depression (PD), while 28 (31.8%) had persisting apathy (PA). Seven (8.0%) had PD, but non-persisting apathy (PDnA), and 18 (20.5%) had PA but non-persisting depression (PAnD). Fifty-three (60.2%) had no persisting symptoms (nAnD), of which 20 were below cut-offs for depression and apathy at BL and FU. Ten (11.4%) had both persisting depression and persisting apathy

Table 2
Bivariate correlations between patient characteristics, current symptoms and GAF-F at baseline and one-year follow-up.

	GAF-F BL (N = 125)	GAF-F FU (N = 88)
	r	*r*
Gender	0.16	0.22*
Age	−0.01	−0.12
IQ	0.13	0.08
Premorbid functioning		
PAS social childhood (rho)	−0.14	−0.19
PAS acad. childhood (rho)	−0.19*	−0.19
Log10 DUP	−0.33**	−0.35**
Clinical symptoms		
PANSS positive	−0.36**	−0.50**
PANSS negative	−0.41**	−0.45**
PANSS disorganized	−0.42**	−0.34**
PANSS depressed	−0.15	−0.48**
PANSS excited	−0.16	−0.15
AES-C	−0.47**	−0.64**
CDSS	−0.16	−0.47**
Log10 AUDIT	0.09	0.08
Log10 DUDIT	−0.18	−0.17

Abbreviations: BL = baseline; FU = follow-up. PAS=Premorbid Adjustment Scale; log10 DUP = logarithm of Duration of Untreated Psychosis; GAF-F = Global Assessment of Functioning Scale-Function subscale; PANSS=Positive and Negative Syndrome Scale (Wallwork 5-factor); AES-C = Apathy Evaluation Scale-Clinician version; CDSS=Calgary Depression Scale for Schizophrenia; log10 DUDIT = logarithm of Drug Use Disorder Identification Test; log10 AUDIT = logarithm of Alcohol Use Disorder Identification Test.
* $p < 0.05$ (2-tailed).
** $p < 0.01$ (2-tailed).

(PAPD). Having PD was more likely in the presence of PA; $X^2(1, n = 88) = 7.08$, $p = 0.008$, phi = 0.284.

Post-hoc analyses in the subset of participants with non-affective psychosis diagnoses at BL and FU revealed a prevalence rate for BL depression of 33.0% (34/103), and a prevalence rate for BL apathy of 54.4% (56/103). At FU, the prevalence rates were 25.4% (17/67) for depression and 50.7% (34/67) for apathy, while in the total sample (n = 88) FU prevalence rate was 25.0% for depression and 44.3% for apathy. Hence, prospective consistencies were 50.0% (17/34) for depression and 60.7% (34/56) for apathy in the non-affective psychosis group, which is quite similar to the sample as a whole for both depression and apathy.

3.3. Contributions by persisting depression and apathy to functioning at follow-up

Mean GAF-F FU in the nAnD group was 60.9 (SD = 15.3), approximately 20 points above the groups with persisting symptoms (PDnA: M = 42.9, SD = 12.6; PAnD: M = 42.0, SD = 10.7; PAPD: M = 38.3, SD = 5.4). Removing the nAnD-group participants with depression and apathy scores below cut-off at both BL and FU only changed GAF-F FU slightly (M = 58.6, SD = 16.0), making it unlikely that they were causing the GAF-F FU-differences.

The Kruskal-Wallis test (Table 4) revealed significant differences in GAF-F FU across persisting symptoms groups ($X^2(3, n = 88) = 33.2$, $p < 0.000$). Post-hoc bivariate group comparisons identified highly significant differences between the nAnD-group and all other groups. No significant differences in GAF-F FU were seen between having PD only, PA only or both persisting symptoms. Removing the 20 participants with low levels of depression and apathy at BL and FU from the nAnD-group did not alter results ($X^2(3, n = 68) = 23.9, p < 0.000$), nor did excluding 21 participants with affective psychosis diagnoses at FU ($X^2(3, n = 67) = 28.7, p < 0.000$).

Results from the multiple hierarchical regression analyses on persisting symptoms and GAF-F FU are shown in Table 5. Controlling for gender, childhood academic functioning, DUP and PANSS disorganized symptoms at FU, positive symptoms, PA and PD had independent and significant associations to worse functioning at FU. The model explained 43.5% of the variance in GAF-F FU.

4. Discussion

4.1. Main findings

During the follow-up period 40% of participants had PD or PA. Among these, one third had both persisting symptoms. The likelihood of having PD was increased if they also had PA. The median GAF-F FU among participants without persisting symptoms indicated only moderate difficulties in functioning, significantly differing from the severe functional impairments in participants with PD, PA or both PD/PA. This might signify vulnerable FEP sub-populations with shared neurobiological or environmental risk factors.

4.2. Contributions by depression and apathy to GAF-F at baseline and follow-up

Baseline depression had no significant association to functioning at BL, although depression scores were higher than at follow-up. At follow-up, depression was negatively associated with GAF-F FU even after adjusting for positive symptoms and apathy scores. This supports our hypothesis of non-consistent cross-sectional associations between depression and functional impairment. The findings are reflected in previous research; some find no associations to functioning [7,27,47,48] while others describe an independent negative effect [28,30,49–51]. Comparing studies directly is hampered by methodological differences, like samples including a broad psychosis spectrum or schizophrenia

Table 3
Multiple hierarchical regressions: estimates of current symptoms' associations to functioning at baseline[a] and one-year follow-up[b].

Baseline variable[a]	β	*t*	95% CI for β	R^2 change	R^{2c}	*p*-Value
Constant	79.21	18.81	(70.88, 87.55)	–	–	0.000
Log10 DUP	−4.01	−3.54	(−5.04, −0,26)	0.107	0.107	0.001
PANSS disorganized BL	−1.99	−4.25	(−2.91, −1.06)	0.158	0.265	0.000
AES-C BL	−0.64	−4.80	(−0.91, −0.38)	0.117	0.383	0.000
Follow-up variable[b]	**β**	***t***	**95% CI for β**	**R^2 change**	**R^{2d}**	***p*-Value**
Constant	92.44	19.56	(83.04, 101.83)	–	–	0.000
PANSS positive FU	−0.97	−3.03	(−1.61, −0.33)	0.254	0.254	0.003
AES-C FU	−1.10	−5.34	(−1.51, −0.69)	0.231	0.485	0.000
CDSS FU	−0.87	−2.49	(−1.56, −0.18)	0.035	0.521	0.015

Abbreviations: BL = baseline; FU = follow-up; CI = confidence interval; log10 DUP = log-transformed Duration of Untreated Psychosis; PANSS=Positive and Negative Syndrome Scale (Wallwork 5-factor); AES-C = Apathy Evaluation Scale- Clinician Version; CDSS=Calgary Depression Scale for Schizophrenia.
[a] Dependent variable is GAF-F BL ($N = 125$).
[b] Dependent variable is GAF-F FU ($N = 88$).
[c] Adjusted for gender, PAS academic childhood, PANSS excited and PANSS positive factors.
[d] Adjusted for gender, PAS academic childhood, log10 DUP and PANSS disorganized factor.

Table 4
Kruskal-Wallis Test: differences in GAF-F FU between persisting symptoms groups (N = 88).

Groups	N (%)	GAF-F FU		Statistic	*p*-Value
		Mean rank	Median		
1. nAnD	53 (60.2)	57.2	61.0		
2. PDnA	7 (8.0)	26.6	39.0		
3. PAnD	18 (20.5)	26.9	39.5		
4. PAPD	10 (11.4)	21.6	39.5		
				X^2=33.2[a,b]	<0.000

Abbreviations: GAF-F = Global Assessment of Functioning Scale, Function subscale; FU = Follow-up.
nAnD = non-persisting apathy + non-persisting depression.
PDnA = Persisting depression + non-persisting apathy.
PAnD = Persisting apathy + non-persisting depression.
PAPD = Persisting apathy + persisting depression.
[a] $df = 3$.
[b] Post-hoc group comparisons using Mann-Whitney *U* test: 1 > 2,3,4 (PDnA vs. nAnD: $r = -0.38$, $p = 0.004$; PAnD vs. nAnD: $r = -0.51$, $p < 0.000$; PAPD vs. nAnD: $r = -0.52$, $p < 0.000$; PAPD vs. PAnD: $r = -0.10$, $p = 0.61$; PAPD vs. PDnA: $r = -0.01$, $p = 0.96$; PDnA vs. PAnD: $r = -0.02$, $p = 0.90$). Alpha level was adjusted for the number of comparisons a.m. Bonferroni, i.e. 0.05/6 = 0.0083.

only, differences in duration of illness, length of follow-up and the assessment tools applied.

A larger fraction were in a psychotic phase at BL (57.6%) compared to at FU (38.6%). Some lines of evidence indicate that depression during the acute phase often resolves with remitting psychotic symptoms [16], increases the chances of remission [52,53] and relate to different psychological phenomena than post-psychotic depression [54]. This could imply that the effect of depression depends on illness stage, and that neurobiological and psychological substrates of depression differ between phases of a psychotic illness [13].

We reproduced findings from a smaller, overlapping FEP-sample describing apathy as an early, stable predictor of reduced functioning [29,30], supported by research both in chronic [50,55] and FEP-samples [28,56]. Positive symptoms, depression and apathy explained over half of the variance in functioning at follow-up, underscoring their clinical relevance. The tendency that whichever symptom was introduced into the regression first explained the largest fraction of variance in GAF-F FU, points to some shared variance between them. This is in keeping with FEP-studies showing an overlapping ebb and flow of symptoms [16,57,58]; i.e. being depressed is linked to the likelihood of having more positive and negative symptoms [28], at least for a subgroup of patients [13]. This covariation pattern has been hypothesized to be an expression of a common neurobiological disease process underlying depression and psychosis [12].

4.3. Prevalence and overlap of persisting symptoms

PD was less frequent than PA, but prevalence of depression was also lower than prevalence of apathy at baseline. Approximately 49% of the depressed and 57% of the apathetic participants at baseline, remained so at follow-up. Relative to their BL prevalences, apathy thus appears slightly more prone to persist in our sample. Of note, our follow-up period was short. The tendencies of persistence might be different with prolonged or more frequent observations.

PD prevalence is similar to findings from previous FEP-studies, ranging between 14 and 26% [6,8,17]. Again methodological differences are relevant for interpretation. Some define depression by a single PANSS depression-item score, others by a summary-score, and the applied cut-offs for caseness differ. Excluding affective psychoses could decrease PD prevalence [6], though in the present study, the prospective consistency for depression was equivalent (50%) in the non-affective psychosis subsample.

Regarding PA prevalence, a five-year FEP follow-up study found persistingly reduced motivation in 15.7% [31], while a ten-year follow-up suggested 30% had persisting apathy [28]. Rather than exploring single sub-symptoms like apathy, more studies focus on persistent negative symptoms (PNS) [59] or deficit schizophrenia [60]. PNS' prevalences the first year in FEP range between 3.8 and 31.5% [61]. Using PNS criteria in our sample would have required applying thresholds for positive symptoms, depression and side-effects, consequently excluding participants with concurrent depression and altering PA prevalence.

Almost 30% (10/35) of all participants with persisting symptoms had both PD and PA. To our knowledge, no other studies have simultaneously investigated PD and PA. A 12-year FEP follow-up study found that the relationship between apathy and depression grew stronger with time, becoming highly significant only in females seven years after baseline assessments [62], but persisting symptoms were not investigated further.

As PD and PA prevalences in our sample were substantial, their coexistence in some participants could occur by chance. However, we revealed a significantly increased likelihood of PD if participants were also experiencing PA. First, a systematic trend towards an overlap could indicate shared environmental factors or psychological mechanisms, like defeatist performance beliefs [63]; being apathetic, striving to manage your every-day chores could make you more prone to depression. Second, phenotypic similarities between negative symptoms and depression could suggest partly shared pathophysiological mechanisms [20]. Signs of a temporal relationship, as symptoms undulate [16] or are persistingly present together, could strengthen such hypotheses. Shared genetic vulnerability in schizophrenia, bipolar and unipolar depression [64,65] and overlapping reward system impairments linked to striatum hypofunction in apathy and depression [20] further add to this idea. Some have argued that schizophrenia might lie at the severe end of a continuum of affective disturbances [12], and recently, depression was suggested to drive "forward further symptom dimensions through a stress-inflammation-structural brain change pathway" in schizophrenia [5].

Notably, the evaluation of depression and apathy could be biased if CDSS and AES-C items were too similar, consequently measuring different phenomena as one. CDSS was originally made to avoid misinterpreting negative symptoms or side-effects for depression in schizophrenia. Maybe only item nine, "Observed depression", could still be subject to confounding as raters might score an apathetic, withdrawn participant as depressed. Though Marin et al. found that the AES-C discriminated between depression and apathy [41], several AES-C items might be influenced by depression, like "She gets things done during the day" and "When something good happens, she gets exited". Overall, using CDSS and AES-C thus probably makes it more likely to mistake depression for apathy than the opposite, which is relevant as depression tends to be undertreated in schizophrenia [11,66]. Inconsistent recommendations for psychotherapy and medication [20], and the hierarchy of diagnostic systems might also contribute to downplaying the clinical importance of depression in FEP.

Table 5
Multiple hierarchical regression: estimates of persisting symptoms' associations to functioning at one-year follow-up[a].

Follow-up variable	β	*t*	95% CI for β	R^2 change	R^{2b}	*p*-Value
Constant	94.16	17.48	(83.45, 104.88)	–	–	0.000
PANSS positive	−1.35	−4.05	(−2.01, −0.69)	0.254	0.254	0.000
PA	−11.48	−3.62	(−17.78, −5.18)	0.132	0.386	0.000
PD	−9.65	−2.71	(−16.72, −2.57)	0.049	0.435	0.008

Abbreviations: PANSS positive = Positive and Negative Syndrome Scale- Wallwork positive factor, PA = persisting apathy, PD = persisting depression, FU = follow-up.
[a] Dependent variable is GAF-F FU (N = 88).
[b] Adjusted for gender, PAS academic childhood, log10 DUP and PANSS disorganized factor FU.

4.4. Contributions by persisting depression and apathy to functioning at follow-up

The median GAF-F FU of participants with one or both persisting symptoms was significantly lower than for participants without

persisting symptoms. Contradicting our hypotheses, group comparisons revealed no significant differences in GAF-F FU between having only one persisting symptom (PDnA or PAnD) or both (PAPD). On the other hand, PD and PA both contributed independently to worse functioning in regression analyses at follow-up. This discrepancy could be due to a loss of statistical power when comparing groups with Mann-Whitney *U* test, possibly not revealing true additive effects of PD and PA.

To our knowledge, PD and PA's relations to outcome in FEP have not previously been compared. Poorer functioning in the PA-subgroup has earlier been demonstrated in parts of the present sample [30]. Moreover, global functioning, social network, employment and quality of life were reduced among participants with PA in the 10-year follow-up mentioned above [28]. Comparably, PD early in the course of FEP has been linked to poorer functioning not only at 18 months FU [6], but also for the following 5–10 years [18]. Hence, there are indications that both of these early, persisting phenomena pave the way for an unfavorable illness course. PD and PA might thus represent separate phenotypes and especially vulnerable sub-groups, compared to fluctuating depression or apathy.

Reduced motivation and capacity of experiencing pleasure (i.e. hedonic capacity) exist across diagnostic categories in neuropsychiatric disorders including the broad psychosis spectrum [3]. Even in depression without psychosis such motivational impairments have been linked to reduced functioning [67,68]. Though separate mechanistic pathways towards similar negative symptom phenotypes are likely [3], it is conceivable that for depression and apathy within psychotic disorders, reduced motivation or hedonic capacity might represent one common path to poorer functional outcome. However, as PD added to explained variance in GAF-F FU after adjusting for PA in our study, PD seems to have an add-on, unique contribution, possibly unrelated to demotivation or due to different aspects of the complex motivational construct being hampered.

4.5. Strengths and limitations

This study's major strength is the longitudinal, prospective design. Further, AES-C is specialized for evaluating apathy across diagnostic borders [42,69]; likewise using CDSS reduces confounding [21].The study has several limitations: First, of the 125 included participants only 88 completed re-assessments. However, analyses revealed no significant baseline differences between drop-outs and completers. Second, concerning symptom evolvement, our definition of persisting symptoms is a simplification. Participants defined with PD or PA might have had symptom fluctuations between baseline and follow-up. However, previous studies have applied similar, parsimonious approaches [18,70]. Third, due to sample size and lack of statistical power, we were not able to investigate differences in clinical variables at BL or functional outcome at FU directly between participants with PA and participants who remitted from apathy during the follow-up (parts of the nAnD-group).

Fourth, the same rater conducted PANSS, CDSS and AES-C, introducing possible rating bias if evaluation of one scale influenced another scale. Fifth, some participants had a long DUP, possibly reflecting insidious onsets and more negative symptoms relative to positive. Prevalence of apathy might thus be inflated. Sixth, persisting symptoms group sizes were small, hence we cannot rule out type II error.

4.6. Conclusion

There is a high prevalence and significant overlap of PD and PA in FEP, all with negative impacts on functional outcome. Correct identification is valuable for early initiation of relevant psychological and medical treatment.

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ORIGINAL PAPER

Trajectory and early predictors of apathy development in first-episode psychosis and healthy controls: a 10-year follow-up study

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Abstract

Apathy is prevalent in first-episode psychosis (FEP) and associated with reduced global functioning. Investigations of the trajectory of apathy and its early predictors are needed to develop new treatment interventions. We here measured the levels of apathy over the first 10 years of treatment in FEP and in healthy controls (HC). We recruited 198 HC and 198 FEP participants. We measured apathy with the Apathy Evaluation Scale, self-report version, psychotic symptoms with the Positive and Negative Syndrome Scale, depression with the Calgary Depression Scale for Schizophrenia, functioning with the Global Assessment of Functioning Scale, and also estimated the duration of untreated psychosis (DUP). The longitudinal development of apathy and its predictors were explored using linear mixed models analyses. Associations to functioning at 10 years were investigated using multiple hierarchical linear regression analyses. In HC, mean apathy levels were low and stable. In FEP, apathy levels decreased significantly during the first year of treatment, followed by long-term stability. High individual levels of apathy at baseline were associated with higher apathy levels during the follow-up. Long DUP and high baseline levels of depression predicted higher apathy levels at follow-ups. The effect of DUP was persistent, while the effect of baseline depression decreased over time. At 10 years, apathy was statistically significantly associated with reduced functioning. The early phase of the disorder may be critical to the development of apathy in FEP.

Keywords First-episode psychosis · Follow-up · Course · Negative symptoms · Apathy · Avolition

Introduction

Negative symptoms are core features of schizophrenia spectrum disorders and recognized as markers of an unfavorable illness course and outcome [1]. The etiology and pathogenesis of negative symptoms are mostly unknown, and current available treatments are not sufficient [2–4]. Negative symptoms are traditionally seen as stable; however, more recent follow-up studies indicate both symptom persistence and significant fluctuations [5–8]. Some studies indicate that the most noticeable changes occur during the first year of follow-up [9, 10], supporting the notion of a "critical period" of symptom evolvement [11]. However, the current evidence for a critical period for negative symptom evolvement is inconclusive [12].

Recent research indicates that negative symptoms comprise five sub-symptoms, clustering into two domains with different associations to the outcome: The expressive domain (i.e. blunted affect and alogia) and the experiential domain (i.e. anhedonia, avolition-apathy and asociality) [13–15].

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These domains appear to have a continuous distribution that includes the general population [16]. There is evidence that avolition-apathy ("apathy" for short) is more strongly associated with a poor functional outcome than the other subsymptoms [1, 17]. Apathy is usually defined as a reduction in goal-directed behavior due to a lack of motivation [18]. The prevalence of apathy in the early stages of a psychotic disorder can exceed 50% [19, 20], and higher levels are associated with male gender, reduced premorbid functioning, a long duration of untreated psychosis (DUP) and a diagnosis of schizophrenia [15, 19, 21, 22].

Despite the high prevalence of apathy in early psychosis, most studies have included participants with chronic illness [23–25], applied cross-sectional or short-term follow-up designs [21, 26] and/or used psychometric tools not primarily made to assess apathy [23, 27, 28]. The long-term development of apathy from the first treatment and its predictors thus remain mostly unexplored [29]. The only study so far investigating longer-term apathy development in first-episode psychosis (FEP) is the TIPS study [30]. At 10-year follow-up (10YFU), the study used a specialized psychometric tool to assess apathy, the Apathy Evaluation Scale-self-report version (AES-S) [31] and found that 30% of participants had high apathy levels, as defined by the AES-S. Using items from the Positive and Negative Syndrome Scale (PANSS) [32] as a proxy for AES measures, the trajectories of apathy over the follow-up period were then investigated retrospectively, with findings of a reduction in apathy levels during the first 1-to-2 years of treatment and stable levels from that point onward. No baseline variables predicted apathy levels at 10 years, but the use of different measures at different time-points limits interpretation. The study also lacked a healthy control group to examine the development of apathy over time.

The main aim of the current study was thus to investigate the development of apathy prospectively over 10 years in a FEP sample, using the AES at all time-points and additionally including a healthy control group (HC). Our research questions were:

1. How does apathy develop over 10 years in FEP compared to HC?
2. Do early clinical or demographic characteristics predict the development of apathy in FEP?
3. How prevalent is clinically significant apathy at 10YFU?
4. What are the functional consequences of high apathy levels at 10YFU?

We hypothesized that apathy would be higher in the FEP population than in HC, be predominantly stable over the follow-up period with changes primarily taking place early on. We also hypothesized that premorbid functioning and DUP would predict baseline levels of apathy and that premorbid function, DUP and baseline levels of apathy would predict the development of apathy over time. Finally, we hypothesized that the level of apathy would be a significant contributor to reduced functioning at 10YFU.

Methods

Participants

Two-hundred and fourteen participants with FEP aged 18 to 65 years were consecutively recruited from outpatient or inpatient units of hospitals in the regions of Oslo and Innlandet, as part of the Thematically Organized Psychosis (TOP) study in Norway. Inclusions into the study took place between March 2004 and December 2007 in Oslo, and between December 2007 and October 2009 at Innlandet. Participants were reassessed after 7 years (7YFU) at Innlandet, and after 10 years in Oslo (10YFU). A subset of the Oslo participants also had an intermediate assessment (6 and/or 12 months).

All FEP participants met the diagnostic criteria of a non-affective psychotic disorder, i.e. schizophrenia, schizophreniform disorder, schizoaffective disorder ("Schizophrenia spectrum disorders") or delusional disorder, brief psychotic disorder or psychosis not otherwise specified. A psychotic episode was defined as having a score of ≥ 4 on items p1 (delusions), p2 (conceptual disorganisation), p3 (hallucinatory behavior), p5 (grandiosity), p6 (suspiciousness/persecution) or g9 (unusual thought content) for ≥ 1 week on the PANSS. Participants were not defined as FEP if they had previously received adequate treatment for psychosis (i.e. hospitalization or antipsychotic medication in adequate dosage for ≥ 12 weeks or until remission). Since some patients were not able to give informed consent during the acute phase, FEP participants were eligible for inclusion within 52 weeks of the start of first adequate treatment.

Exclusion criteria were: Not speaking a Scandinavian language, IQ < 70, current neurological or medical condition which could cause negative symptoms or psychosis, psychosis due to substance use, moderate/severe head injury prior to inclusion or during the follow-up period.

Based on these criteria, 16 participants initially deemed eligible were excluded, leaving 198 for analyses at baseline (BL) (Fig. 1). Of these, 98 (49%) had an intermediate assessment at 6MFU and/or at 1YFU. A total of 77 (41%) completed assessments at the long-term follow-up. One participant was excluded due to a severe head injury between 1 and 10YFU, leaving 76. Of the 121 lost to follow up, nine had died (all from Oslo), nine had moved abroad, and 43 were untraceable despite multiple attempts to contact them, and 60 said no to further participation.

The HC were 18–65 years old and were randomly selected from the national population registry of Norway [33], and invited to participate by letter. All HC were interviewed with the Primary Screening for Mental Disorders [34] at BL and follow-ups to ensure that they, or any first-degree relative, did not have a current or previous severe mental illness. The same exclusion criteria used for participants with FEP were applied, and 199 HC were included. One HC developed a severe mental illness during the follow-up and was excluded from analyses at both BL and follow-ups, leaving 198 HC at BL, 82 (41%) with intermediate measures (1YFU) and 59 (30%) at 10YFU (Fig. 1).

Clinical assessment

At each follow-up point, participants were interviewed by psychologists or medical doctors, applying a comprehensive clinical assessment protocol. The Structured Clinical Interview for Mental Disorders (SCID-I) was used to diagnose participants, according to the DSM IV [35]. All interviewers completed a SCID-assessment training program based in the University of California, Los Angeles [36]. Diagnostic consensus meetings led by experienced clinical researchers were held regularly, and inter-rater reliability was found satisfactory [37]. Medical charts from in- and outpatient treatments during the follow-up were inspected to supplement information given by the participants.

Premorbid functioning was measured with the Premorbid Adjustment Scale (PAS) [38]. Since the baseline assessments were done in the mid-2000s, the structured interview for PAS published in 2009 was not used [39]. Scores were divided into age intervals (childhood ≤ 11 years, early adolescence 12–15 years, late adolescence 16–18 years, adult > 18 years), and further into social and academic functioning within each interval. To reduce chances of prodromal symptoms influencing adjustment, we only used childhood scores in the analyses, and PAS scores for patients with age at onset less than 12 years of age were treated as missing. The age at onset (AAO) refers to the individual's age when the first psychotic episode started. Duration of untreated psychosis (DUP) was defined as the time in weeks from the first psychotic episode until first adequate treatment [40].

Psychotic and other symptoms were measured with the Positive and Negative Syndrome Scale (PANSS), divided into five factors (positive, negative, disorganized, depressed and excited) [41]. The Apathy Evaluation Scale self-report version (AES-S) was used to assess apathy [31]. A shortened 12-item version with superior psychometric properties in FEP was applied [42]. The AES-S has shown a high concordance with the clinician-rated version, AES-C, in a partly overlapping sample [43], and reliably distinguishes patients from HC [19, 25]. The AES-S maps one's interests and engagement during the last month. A higher score indicates higher levels of apathy. Following previous studies [19, 30], we used a sum-score cut-off of ≥ 27 points (two standard deviations above mean for HC) to indicate clinically significant apathy. To better distinguish between apathy as a part of negative symptoms and symptoms of depression [44], depression was measured with the Calgary Depression Scale for Schizophrenia (CDSS) [45]. Higher CDSS scores indicate higher levels of depressive symptoms.

Global functioning was measured with the Global Assessment of Functioning Scale-split version, functioning subscale (GAF-F) [46]. Scores range from 0 (extremely impaired) to 100 (perfect function). Alcohol and drug use the last year were measured with the Alcohol Use Disorder Identification Test (AUDIT) [47] and the Drug Use Disorder Identification Test (DUDIT) [48], respectively.

The current load of antipsychotic medication (AP), were represented by dividing the actual daily dosage of used antipsychotics with its Defined Daily Dosage (DDD) (dosage recommended by the WHO Collaborating Centre for Drug Statistics Method [49]). If a participant used two or three different AP, one ratio was computed for each AP, and the ratios subsequently summarized to 'Sum AP'.

Statistical analyses

Analyses were carried out in the SPSS version 25. Variables were inspected for outliers, normality, collinearity and heteroscedasticity. Tests were two-tailed, and significance levels pre-set to 0.05.

Site characteristics and follow-up intervals

Mean long-term follow-up time was 7.1 years at Innlandet and 10.8 years in Oslo. We expected higher stability of symptoms and functioning this late in the course of illness and thus assumed that the difference in follow-up time would not have a significant influence on the results of the analyses. The '10YFU' variables thus included measures from both 7 (Innlandet) and 10 years (Oslo). There could, however, be other systematic or random site differences. In our sample, patients from the rural communities at Innlandet had a longer DUP than Oslo (median $DUP_{Innlandet} = 104$ weeks; median $DUP_{Oslo} = 52$ weeks, $t = -4.4$, $p < 0.001$) and a significantly higher proportion meeting a schizophrenia spectrum diagnosis at baseline ($\chi^2 = 4.0$, $p = 0.045$). 'Inclusion site' was thus adjusted for in the multivariate analyses in the case of a significant bivariate association between "Inclusion site" and other covariates and/or outcome variables in initial analyses.

Missing data

We evaluated differences in BL characteristics between those who completed and those who did not complete the long-term follow-up using χ^2 test for categorical and t-tests or Mann–Whitney *U*-tests for continuous data (Table 5). Participants with a lower PANSS general symptoms score, male gender or non-European ethnicity were significantly less likely to complete the long-term follow-up assessments. No other significant differences were found.

The AES-S had no missing data in those who completed reassessment at each follow-up point. The GAF-F score was missing in one participant at 10YFU. For the CDSS, AUDIT and DUDIT, between one and five participants had missing scores for two or fewer items at one or more follow-up points. These missing items were replaced with item scores imputed as the mean value of the non-missing items for the scale in question for that participant at that specific follow-up. If more than two items were missing, which was the case in less than five participants, no imputations were done and the variable was treated as missing. Missing data did not exceed 4% for any BL data, except for the Sum AP, which had 7% missing.

Analyses

FEP and HC samples were analyzed separately for the first research question. We used a scatter-dot with a fitted regression line to explore the longitudinal development of apathy. To account for missing data and dependencies caused by repeated measurements, we then applied linear mixed models analyses [50]. In FEP, AES-S scores at four follow-up points were used as the dependent, continuous apathy variable. Longitudinal apathy development was described by employing a growth model, and maximum likelihood used to select the best-fitted model. Time was first introduced as fixed factor. We then explored whether a curvilinear function (time*time) improved model fit. Subsequently, random intercept and random slope were introduced, and an autoregressive heterogeneous (AR1H) covariance structure between them was inspected. The same procedure was then applied for HC separately, using the available three assessment points for the dependent, continuous apathy variable.

For the second research question, relevant early predictors and covariates of apathy development in FEP were chosen based on previous research and theory. We used Pearson's bivariate correlation analyses to investigate associations between predictors, covariates and the AES-S scores at BL and 10YFU. Variables with significant ($p \leq 0.1$) bivariate associations to apathy development were introduced into the linear mixed models analyses in order of lifetime appearance. Interaction effects with time were explored only for BL predictors with a significant association to apathy development. Such interaction effects describe whether the predictor's effect on apathy development increases or decreases with time. Predictors and covariates with non-significant estimates ($p > 0.05$) were removed from the final equation. The following equation describes the basic model:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_{1ij} + b_{1ij}) * \text{time} + \beta_{2ij} * \text{time} * \text{time} + \beta_{3ij} * \text{predictor} + \beta_{4ij} * \text{predictor} * \text{time} + \varepsilon_{ij}$$

Y_{ij} is apathy in an individual $i = 1\ldots, 198$ at year $j = 1\ldots, 10$. $\beta_0 \ldots \beta_{4ij}$ are the estimates of the population's means (i.e. fixed effects). The b_{0i} and b_{1ij} represent the specific random variation between individuals in BL apathy levels and in the slope of apathy development, respectively.

For the third research question, we employed Pearson's bivariate correlation analyses to evaluate the association between GAF-F at 10YFU and concurrent symptoms, diagnosis and demographic variables in FEP. Multiple hierarchical linear regression analyses were used to investigate associations to GAF-F further. Independent variables with significant ($p \leq 0.1$) bivariate associations to GAF-F were introduced in a block-wise manner, with the AES-S score in the final block.

Results

Table 1 displays the characteristics of HC and participants with FEP. A total of 198 FEP patients and 198 HC were included at BL. At 1YFU, 89 patients and 82 HC were reassessed, while 76 of the included patients and 52 of the HC were reassessed at 10YFU. At BL, 36% of the FEP patients and 48% of the HC were female. The mean age in FEP and HC was 27 years and 33 years, respectively. Among patients, 67% had schizophrenia, schizophreniform or schizoaffective disorder diagnosis (i.e. a schizophrenia spectrum disorder).

Development of apathy in HC

Development of apathy in HC is presented in Fig. 2. Mean apathy levels appeared stable over the follow-up period, as indicated by a non-significant fixed effect of time in the apathy growth model ($p = 0.215$). However, apathy levels varied significantly between individuals at BL and between individuals over time, as shown by a significant effect of a random intercept ($p < 0.001$) and random slope ($p = 0.019$),

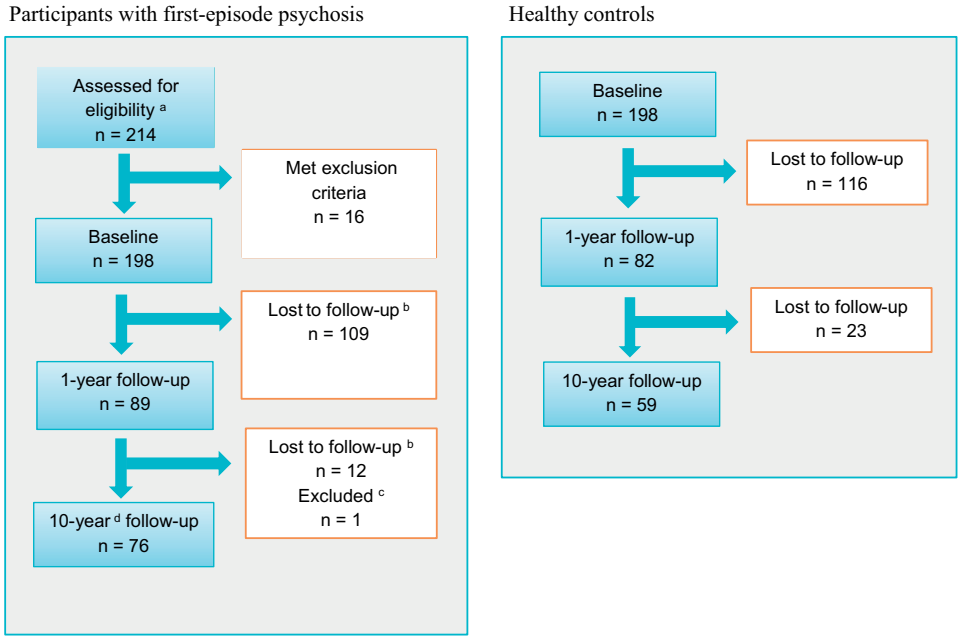

Fig. 1 Participation in a 10-year follow-up of people with first-episode psychosis and in healthy controls. [a]Patients with first-episode psychosis were consecutively referred to the study from their clinical units. Since Norwegian law does not allow researchers to access medical charts of patients before they give an informed consent or to keep data on those who do not consent, we have no report of the number of eligible patients that were not referred or said no to study referral. [b]Nine participants had died (all at the Oslo Site), nine had moved abroad, 43 were untraceable, and 60 refused further participation. [c]One participant was excluded due to a newly acquired severe head injury between 1 and 10 years. [d]At Innlandet, mean follow-up time was 7.1 years

respectively. The individual level of apathy at BL was not associated with the individual development of time, as indicated by a non-significant covariance between the random intercept and slope ($p = 0.106$). Gender and age did not contribute significantly to the model.

Development of apathy in participants with FEP

Apathy development in FEP participants is displayed in Fig. 2. The scatter-dot regression line indicated that apathy levels declined during the first year, levelling off thereafter. In the growth model, apathy levels decreased over the long-term follow-up, i.e. there was a significant, fixed effect of time (− 2 log likelihood = 2836.8; BIC = 2854.9, $p = 0.002$). When quadratic time (time*time) was added to the equation, the model fit was improved (− 2 log likelihood = 2818.8, BIC = 2842.9). The linear effect of time was negative, while the quadratic effect was positive (both: $p < 0.001$). Apathy levels significantly varied between individuals at BL, as indicated by a significant random intercept ($p < 0.001$). The random slope and the covariance between the random intercept and slope did not significantly improve model fit, which suggested that the development of apathy did not significantly differ between individuals over time, with an enduring effect of baseline apathy levels.

Early clinical and demographic predictors of apathy development in FEP

Bivariate correlations are presented in Table 2, followed by the linear mixed models analyses in Table 3. The AES-S level at BL was significantly associated with the PAS social and academic scores, DUP, concurrent CDSS, and the AES-S and CDSS at 10YFU. The AES-S level at 10YFU was significantly associated with gender, DUP, concurrent CDSS and PANSS disorganized symptoms.

In the linear mixed models analysis, DUP had a significant, positive association with the development of apathy. There was an enduring effect of DUP, as shown by a non-significant interaction effect of DUP*time. Baseline CDSS levels showed a significant, positive association with the development of apathy. The interaction term CDSS*time was negative and statistically significant, indicating that the effect of BL depression decreased with time. Gender, AAO, PAS, BL disorganized symptoms, AUDIT, DUDIT, Sum AP, or having a schizophrenia spectrum diagnosis did not contribute significantly to the model. The inclusion site was, however, significantly associated with apathy development, with higher apathy scores at the Innlandet site, also after correcting for other statistically significant variables in the equation.

Table 1 Characteristics of first-episode psychosis participants and healthy controls during follow-up

	Baseline		6MFU		1YFU		10YFU	
	FEP	HC	FEP	HC	FEP	HC	FEP	HC
N (%)	198	198	49 (24.7)	–	89 (44.9)	82 (41.4)	76 (40.7[e])	59 (29.8)
Gender female (n/%)	72 (36.4)	94 (47.5)	24 (49.0)	–	35 (39.3)	39 (47.6)	35 (46.1)	27 (45.8)
Age	27.2 (8.5)	32.6 (9.1)	28.2 (8.7)	–	27.6 (7.2)	–	35.9 (8.9)	39.9 (6.9)
Single (n/%)	146 (73.7)	–	–	–	–	–	41 (43.9)	12 (20.3)
Ethnicity European (n/%)	155 (78.3)	196 (99)	37 (75.5)	–	65 (73.0)	82 (100)	67 (88.2)	59 (100)
Working or studying (n/%)	71 (36.0)	–	–	–	–	–	59 (77.6)	–
IQ[a]	100.5 (13.8)	114.5 (9.5)	–	–	–	–	–	–
Premorbid functioning								
PAS social (median/range)	1.0 (0–6.0)	–	–	–	–	–	–	–
PAS acad. (median/range)	1.5 (0–5.5)	–	–	–	–	–	–	–
AAO psychosis	23.3 (8.1)	–	–	–	–	–	–	–
DUP weeks (median/range)	75 (1–1560)	–	–	–	–	–	–	–
Diagnosis (n/%)								
Schizophrenia spectrum[b]	134 (67.7)	–	–	–	–	–	58 (76.3)	–
Other psychosis [c]	64 (32.3)	–	–	–	–	–	18 (23.7)	–
Symptoms and functioning								
PANSS positive	16.2 (5.0)	–	12.3 (4.5)	–	13.0 (5.1)	–	12.5 (5.0)	–
PANSS negative	15.5 (6.6)	–	14.7 (5.2)	–	13.5 (5.0)	–	12.2 (5.0)	–
PANSS general	34.0 (8.3)	–	27.8 (7.7)	–	27.3 (6.9)	–	26.5 (8.1)	–
AES-S	28.7 (7.6)	17.6 (4.2)	26.1 (7.5)	–	24.6 (7.0)	17.2 (4.0)	24.7 (7.1)	18.1 (4.5)
AES-S ≥ 27 (n/%)	118 (59.6)	8 (4.0)	25 (51.0)	–	31 (34.8)	2 (2.4)	28 (36.8)	3 (5.1)
CDSS	6.8 (4.9)	–	3.8 (4.5)	–	3.8 (3.4)	–	2.8 (3.1)	–
AUDIT (median/range)	5.0 (0–38)	–	4.0 (0–31)	–	4.0 (0–29)	5.0 (0–14)	4.0 (0–28)	5.0 (1–12)
DUDIT (median/range)	0.0 (0–44)	–	0.0 (0–32)	–	0.0 (0–34)	0.0 (0–10)	0.0 (0–42)	0.0 (0–5)
Sum AP[d]	0.9 (0.8)	–	–	–	1.1 (0.89)	–	1.3 (0.9)	–
GAF-F	42.6 (12.5)	–	55.0 (16.1)	–	53.3 (16.6)	–	58.4 (16.3)	–

Unless otherwise specified, values are given in means (standard deviation)

6MFU six-months follow-up, *1YFU* one-year follow-up, *10YFU* ten-year follow-up, *IQ* intelligence quotient, *AAO psychosis* age at onset of first psychotic episode, *PAS* premorbid assessment scale, *DUP* duration of untreated psychosis, *PANSS* positive and negative syndrome scale, *AES-S* apathy evaluation scale-self-report version, *CDSS* calgary depression scale for schizophrenia, *AUDIT* alcohol use disorder identification test, *DUDIT* drug use disorder identification test, *GAF-F* global assessment of functioning scale, split version, Functioning subscale, *Sum AP* weighted sum of antipsychotic medication

[a]The average IQ for HC in the present sample are parallel to the findings reported by the Knowledge Centre for the Health Services at The Norwegian Institute of Public Health, evaluating the psychometric properties of the Wechsler Abbreviated Scale of Intelligence (WASI) in Norwegian study samples [79]

[b]Schizophrenia spectrum = Schizophrenia, schizophreniform and schizoaffective disorders

[c]Other psychosis = Brief Psychotic Disorder, Delusional Disorder and Psychosis Not Otherwise Specified (PNOS)

[d]The actual daily dose used (of each antipsychotic medication) was divided by the defined daily dosage (DDD) for that specific preparation. These ratios (for a maximum of three simultaneously used antipsychotics) were then summed and called Sum AP, a proxy for the total antipsychotic load in each participant

[e]Of the 198 included at BL, nine had died and nine had moved abroad. At 10YFU, $n = 77$ were reassessed. One of these was excluded from analyses at 10YFU due to a severe head injury since 1YFU. Retention rate was estimated based on the 189 participants who were alive and available to follow-up

Prevalence of clinically significant apathy at 10 years and the associations between apathy and global functioning

The prevalence of clinically significant apathy at 10YFU was 5% in HC and 37% in FEP participants (Table 1). Results from the multiple hierarchical linear regression analysis at 10YFU are shown in Table 4. Concurrent positive and disorganized symptoms, and having a schizophrenia spectrum diagnosis, had statistically significant, negative associations with GAF-F. After adjusting for these variables and concurrent depression, apathy added 5% to

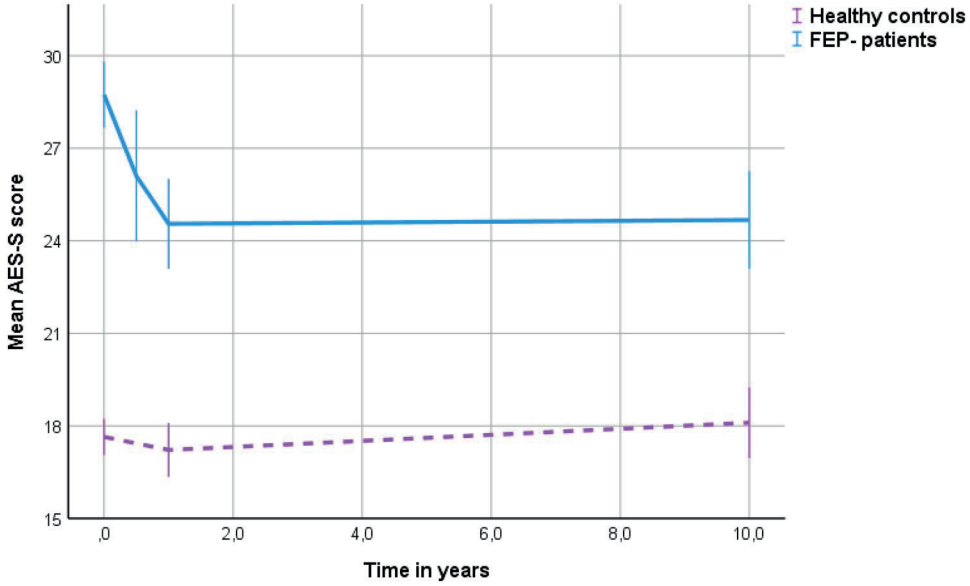

Fig. 2 Development of apathy (AES-S scores) in first-episode psychosis (FEP) patients and in healthy controls during the 10-year follow-up

the explained variance in GAF-F. Age, gender, AUDIT, DUDIT and Sum AP did not contribute significantly to the model.

Discussion

Main findings

We found a significant decrease in mean apathy scores during the first year of treatment in FEP, followed by long-term stability over the next 6 to 9 years. A high BL apathy score increased the likelihood of apathy scores above the group mean throughout the follow-up. Also, a long DUP and high BL depression score predicted higher apathy scores over the follow-up period. However, while the effect of BL depression levels decreased over time, the effect of DUP persisted. The mean apathy scores in the HC group were lower and stable over time, but with inter-individual variation both in BL levels and in later trajectories. Accordingly, the BL apathy score was not equally predictive of the later development of apathy in HC.

In FEP, a schizophrenia spectrum diagnosis together with concurrent positive- and disorganized symptoms together were significantly associated with poorer global functioning at the long-term follow-up. The level of apathy had an independent and statistically significant influence on global functioning also after adjusting for other clinical characteristics in the multivariate analyses.

Development of apathy in participants with FEP

The finding of an overall decrease in apathy levels in the long-term is in line with results from two previous follow-up studies from FEP [30] and first-admission schizophrenia participants [51]. In the FEP TIPS study, a group characterized by enduring high apathy levels was discernible in the second year of treatment. Another group with lower and decreasing apathy levels over time explained most of the overall reduction in apathy levels in the total sample [30]. The primary reduction in apathy levels both in the TIPS study and the current study took place within the first years of treatment. This finding supports that the notion of a critical period for symptom development in FEP, i.e. a time interval where symptoms may be more amenable to interventions, also comprises the development of apathy [11].

We also found that the individual variations in apathy levels already at BL were carried forward through the follow-up period, corresponding to the "persistently high apathy" group in the TIPS study [30]. Since the TIPS was an early intervention study, it recruited FEP with a short DUP during their first week of treatment [52], which may explain why symptom trajectories were less stable over the first years of treatment. Taken together this indicates that factors influencing apathy trajectories are in place well before the first adequate treatment of the psychotic illness. This notion is supported by findings of stable negative symptoms in ultra-high-risk populations [53].

Table 2 Pearson's bivariate correlation analyses between patient characteristics at baseline and 10 years, AES-S at baseline and 10 years and GAF-F at 10 years

Demographic and clinical variables	AES-S BL	AES-S 10Y	GAF-F 10Y
N	198	76	76
Inclusion site	0.22*	0.32**	− 0.07
Gender	0.00	− 0.24*	0.21
PAS social childhood[a]	0.19**	0.06	− 0.16
PAS acad. childhood[a]	0.14*	0.06	− 0.14
AAO psychosis	− 0.13	− 0.08	0.10
DUP[a]	0.19**	0.24*	− 0.32**
Schizophrenia spectrum BL[b]	0.10	0.04	− 0.34**
Schizophrenia spectrum 10Y[b]	0.11	0.03	− 0.36**
PANSS pos. BL	0.08	0.06	− 0.17
PANSS pos. 10Y[a]	0.11	0.18	− 0.56**
PANSS disorg. BL[a]	− 0.04	0.14	− 0.29*
PANSS disorg. 10Y[a]	0.05	0.39**	− 0.58**
AES-S BL	–	0.42**	− 0.16
AES-S 10Y	–	–	− 0.49**
PANSS insight BL (g12)	− 0.09	− 0.12	− 0.11
PANSS insight 10Y (g12)[a]	0.07	0.21	− 0.53**
CDSS BL[a]	0.44**	0.22	− 0.19
CDSS 10Y[a]	0.33**	0.59**	− 0.48**
AUDIT BL[a]	0.01	0.14	0.14
AUDIT 10Y[a]	− 0.16	0.10	0.02
DUDIT BL[a]	− 0.03	− 0.05	− 0.02
DUDIT 10Y[a]	− 0.03	− 0.08	− 0.09
Sum AP BL[a]	− 0.10	− 0.19	0.04
Sum AP 10Y[a]	− 0.10	− 0.06	− 0.18
GAF-F BL	− 0.26**	− 0.32**	0.39**

BL baseline, *FU* follow-up, *10Y* ten-year, *PAS* premorbid adjustment scale, *DUP* duration of untreated psychosis, *GAF-F* global assessment of functioning scale-function subscale, *PANSS* positive and negative syndrome scale, *AES-S* apathy evaluation scale-self report version, *CDSS* calgary depression scale for schizophrenia, *DUDIT* drug use disorder identification test, *AUDIT* alcohol use disorder identification test, *Sum AP* sum antipsychotic medication; the actual daily dose used (of each antipsychotic medication) was divided by the defined daily dosage (DDD) for that specific preparation. These ratios (for a maximum of three simultaneously used antipsychotics) were then summed and called Sum AP, representing the total antipsychotic load in each participant

*$p < 0.05$; **$p < 0.01$

[a]PAS social, DUP, CDSS 10Y, Sum AP BL, AUDIT and DUDIT (BL and 10Y) were log10-transformed, CDSS BL, PANSS insight 10Y and Sum AP 10Y were square root transformed due to skewness

[b]Schizophrenia spectrum = Schizophrenia, schizophreniform and schizoaffective disorders

Early clinical or demographic predictors of apathy development in FEP

In line with our hypothesis and evidence from more broadly defined negative symptoms [54], we found that a long DUP in FEP predicted higher levels of apathy throughout the follow-up period. This finding expand on previous research from our group that identified statistically significant associations between a long DUP and high apathy scores at 1-year follow-up in a sample partly overlapping with the current [21]. The TIPS study found statistically significant associations between a long DUP and high negative symptoms in the short term. DUP did, however, not predict the level of apathy at 10 years [30], possibly because the short median DUP in the TIPS study reduced statistical power. We do not know by which mechanisms, DUP contributes to a poor outcome [55–57]. However, findings from the TIPS study indicate that shortening DUP will lead to lower levels of negative symptoms and improved functioning from treatment start through long-term follow-ups [58–61]. In our sample, patients from Innlandet had a longer DUP than Oslo. This may partly explain why Innlandet also had higher apathy scores at BL (mean AES-S Innlandet = 31.6 (7.5), mean AES-S Oslo = 27.7 (7.5), $t = -3.2$, $p = 0.002$) and at 10YFU (mean AES-S Innlandet = 27.5 (7.2); mean AES-S Oslo = 22.9 (6.4), $t = -3.0$, $p = 0.004$) [54].

The associations between BL depression and the development of apathy is intriguing. Depression is common also in non-affective psychotic disorders, especially in FEP [62, 63]. Although the phenomenology of depressive symptoms resembles those of negative symptoms [64], the different symptoms do not cluster together in factor analyses and show modest or inconsistent overlap in both cross-sectional- and longitudinal studies [65]. Research suggests that low mood and suicidal ideation are more linked to depressive symptoms and alogia/blunted affect more linked to negative symptoms, while reduced motivation (i.e. apathy) and anhedonia are common to both [66]. The association of apathy-anhedonia to both depression and negative symptoms indicates similarities in underlying CNS functions [67].

We found that the effect of BL depression on apathy trajectories decreased over time, while the cross-sectional association between concurrent depressive symptoms and apathy was stable. The results are in line with findings from a 13-year follow-up study of early psychosis, describing three trajectories for negative symptoms, where the high-and-increasing trajectory was predicted by BL depression, cognitive dysfunction and reduced premorbid functioning [68]. Another study of the longitudinal development of anhedonia/apathy and depressive symptoms in FEP found that the symptom domains levelled off after 2-to-5 years, while the associations between concurrent levels of apathy and depression increased in strength in the female participants over time [51]. Due to sample size and participant attrition, our findings should be interpreted with caution. They nevertheless serve as an argument for

Table 3 Linear mixed model analysis. Early predictors of apathy (AES-S) development in first-episode psychosis during 10-year follow-up

Parameter	Estimate	SE	*t*	*p* value	95% CI for *t*	
					Lower	Upper
Intercept	22.17	1.19	18.61	< 0.001	19.82	24.51
Time	− 2.78	0.77	− 3.63	< 0.001	− 4.29	− 1.27
Time*time	0.27	0.07	3.64	< 0.001	0.12	0.42
DUP [a]	1.47	0.59	2.47	0.014	0.29	2.64
CDSS	0.59	0.10	6.07	< 0.001	0.40	0.78
CDSS*time	− 0.05	0.01	− 3.36	0.001	− 0.08	− 0.02

Estimate, SE, *t*, *p* and 95% CI refer to the numbers in the final model, adjusted for Inclusion site

Inclusion Site additionally showed a significant association with apathy development. Participants recruited at Innlandet had an increased likelihood of higher apathy levels during the follow-up (Est. = 2.15, $p = 0.048$)

SE standard error, *CI* confidence interval, time time in years from baseline to 10 years, *DUP* duration of untreated psychosis, *CDSS* calgary depression scale for schizophrenia

[a]DUP was log 10-transformed due to a severely skewed distribution

Table 4 Multiple hierarchical regression analyses at 10-year follow-up in first-episode psychosis, GAF-F[a] is the dependent variable

	10Y follow-up variable	*b*	*Std. β*	*t*	95% CI for *β*	R^2 change	R^{2b}	*p* value
	Constant	101.38	–	17.53	(89.85, 112.92)	–	–	< 0.001
1st block	Schizophrenia spectrum	− 7.01	− 0.18	− 2.22	(−13.30, − 0.72)	0.126	0.126	0.030
2nd block	PANSS positive	− 1.33	− 0.33	− 3.61	(− 2.06, − 0.59)	–	–	0.001
	PANSS disorganized	− 1.90	− 0.25	− 2.73	(− 3.29, − 0.51)	0.346	0.472	0.008
3rd block	CDSS	− 0.41	− 0.08	− 0.78	(− 1.47, 0.65)	0.053	0.525	0.440
4th block	AES-S	− 0.67	− 0.29	− 2.85	(− 1.14, − 0.20)	0.050	0.575	0.006

10Y ten-year, *Schizophrenia spectrum* schizophrenia, schizoaffective and schizophreniform disorders, *PANSS* positive and negative syndrome scale, *CDSS* calgary depression scale for schizophrenia, *AES-S* Apathy Evaluation Scale—Self-report version

[a]Global Assessment of Function Scale, split version-functioning subscale

[b]Neither age, gender, alcohol use (AUDIT), drug use (DUDIT) nor the amount of antipsychotic medication (Sum AP) contributed significantly to the model. Adjusted R^2 for the total model = 0.545

careful assessment- and active treatment of depression in FEP [69–71].

Finally, we expected that participants with poor premorbid adjustment as measured by the PAS and/or an earlier AAO had higher levels of apathy as a correlate of a more severe, neurodevelopmentally based illness. We did, however, not find any significant associations between PAS, AAO and apathy development in the multivariate analyses. We also hypothesized that a high BL Sum AP was associated with higher levels of apathy, since AP side effects may mimic negative symptoms [67]. Again, there were no significant associations between BL Sum AP and levels of apathy.

Prevalence of clinically significant apathy at 10 years and associations to global functioning

In line with previous long-term studies in FEP [30], the prevalence of clinically significant apathy was substantial. Apathy also had an independent negative association with global functioning at 10 years. While the cross-sectional design for this particular research question precludes causal inference, our findings corroborate previous cross-sectional findings at BL and 1YFU in overlapping samples to the current sample [19, 21] and the TIPS study [30], and thus add to the suggested burden of apathy in psychosis [17].

Strengths and limitations

The main strengths of this study include a richly phenotyped FEP sample and a prospective study design with a long follow-up period and a healthy control group. We also used validated psychometric tools, including a specialized tool for the assessment of apathy that was applied at BL and all follow-up assessments. Study participants were recruited through the Norwegian mental health care system, which is available to all citizens independent of socioeconomic status and thus increases the representativity of the study sample.

Finally, we used robust statistical methods to handle dependencies in the data set.

There are also some limitations: First, we were not able to fully match FEP-participants with HC due to sample size. Second, our study may be subject to bias if reduced insight into illness impairs the ability to self-report apathy or the CDSS and AES-S do not adequately distinguish depression from apathy. However, recent research suggests that people with schizophrenia are aware of and report negative symptoms in a similar manner to external observers [22, 72], in contrast to findings from older studies [73, 74]. The AES-S shows a high concordance with the clinician-rated AES-C in FEP [43], and the PANSS insight item was not significantly associated with AES-S at BL or 10YFU. Additionally, the CDSS was designed to reduce confounding from negative symptoms [45].

Third, due to state-effects, depressed participants may evaluate themselves as more apathetic than others perceive them. Fourth, apathy was not assessed between years one and ten, and further variability in the trajectory may thus go unobserved.

Fifth, our sample size was limited, with subsequent attrition of participants. Our long-term attrition rate (59%) is at the same level as naturalistic FEP studies [75–77] but higher than in the TIPS (38%) [30] and OPUS cohorts (39%) [6], where retention can be boosted by the intervention designs or more frequent follow-ups. Attrition analyses revealed that being male, having non-European ethnicity or a lower BL PANSS general symptom score was associated with an increased likelihood of study dropout at 10YFU. We did, however, not find any differences in other variables of interest, including DUP, BL AES-S, BL CDSS or BL GAF-F scores in follow-up analyses (Table 5). Follow-up analyses of BL symptoms, demographics and BL functioning across genders and ethnicity (data not shown), found no statistically significant differences in most variables of interest, including DUP, AES-S, the five PANSS factors and the GAF-F. Men were more likely to be single, have lower premorbid academic

Table 5 Comparisons of baseline characteristics between completers and non-completers at 10-year follow-up

Baseline variable	Completers	Non-completers	Statistic (X^2, t, U)	p value
N	77	121		
Gender (male)	33.3%	66.7%	$X^2 = 4.50$	0.034
Age (median)	23.0	25.0	$U = 4239.5$	0.286
Single	38.4%	61.6%	$X^2 = 0.07$	0.797
Non-European ethnicity	20.9%	79.1%	$X^2 = 7.45$	0.006
Working	40.8%	59.2%	$X^2 = 0.18$	0.673
Educational years	12.1	12.0	$t = -0.17$	0.863
IQ	101.2	99.9	$t = -0.61$	0.545
PAS social childh. (median)	1.3	1.0	$U = 3950.0$	0.246
PAS acad. childh. (median)	1.5	1.5	$U = 4270.5$	0.867
AAO psychosis	22.3	23.9	$t = 1.31$	0.190
DUP[a]	1.8	1.7	$t = -0.91$	0.362
Schizophrenia spectrum[b]	41.8%	58.2%	$X^2 = 1.47$	0.225
PANSS positive	16.7	15.9	$t = -1.21$	0.229
PANSS negative (median)	15.0	14.0	$U = 4611.0$	0.901
PANSS general	35.5	33.0	$t = -2.10$	0.037
AES-S	28.9	28.6	$t = -0.22$	0.825
AES-S ≥ 27	40.7%	59.3%	$X^2 = 0.39$	0.531
CDSS	7.1	6.6	$t = -0.69$	0.490
AUDIT (median)	6.0	5.0	$U = 3784.5$	0.142
DUDIT (median)	0.0	0.0	$U = 4150.5$	0.328
Sum AP (median)	0.7	1.0	$U = 3683.0$	0.377
GAF-F	42.2	42.8	$t = 0.346$	0.730

IQ intelligence quotient, *PAS* premorbid assessment scale, *AAO psychosis* age at onset of first psychotic episode, *DUP* duration of untreated psychosis, *PANSS* positive and negative syndrome scale, *AES-S* apathy evaluation scale-self-report version, *CDSS* calgary depression scale for schizophrenia, *AUDIT* alcohol use disorder identification test, *DUDIT* drug use disorder identification test, *Sum AP* weighted sum of antipsychotic medication, *GAF-F* global assessment of functioning scale, split version, Functioning subscale

[a]DUP was log10-transformed due to skewness

[b]Schizophrenia spectrum = Schizophrenia, Schizoaffective and Schizophreniform disorders

functioning, lower BL levels of depression and use more drugs. Europeans were more likely to use alcohol and have poorer premorbid social functioning, but higher IQ scores. We were not able to find a systematic trend of attrition that could affect our results and linear mixed models analysis is a recommended and robust statistical method when data are missing. Baseline predictors of attrition are regularly used to evaluate the likelihood of selection bias in longitudinal studies. The estimates of associations between variables are, however, not necessarily affected by attrition in long-term longitudinal studies, even in the presence of differences in the mean scores of BL variables between completers and non-completers [78]. We thus assume that the follow-up sample at 10YFU was likely to be representative for the general distribution of symptoms and functioning in our full FEP sample.

Sixth, to ensure that also initially acutely psychotic participants were able to give informed, written consent, FEP patients were eligible to enter the study up to 52 weeks after the start of the first adequate treatment, which could introduce more heterogeneity in BL symptom scores. Both positive- and depressive symptoms are causes of secondary negative symptoms and are higher at the start of the first adequate treatment. The observed decline from BL to 1YFU in levels of apathy may thus have been higher if the whole sample had entered the study at the start of the first adequate treatment.

Conclusion and clinical implications

The current study supports the notion that the early treated- and untreated phases of the first psychotic episode is a critical period for the development of apathy. Based on the long-term effects of DUP, we can hypothesize that detecting and treating psychosis adequately at an early stage could reduce long-term apathy levels. The effect of BL depression on early apathy levels supports the idea of more active treatment of depression in FEP [69–71]. Considering the lack of evidence-based treatments for negative symptoms, efforts to reduce DUP and to treat co-occurring depressive symptoms could help to prevent high levels of apathy in the long term and thus improve functional outcome.

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Author contributions IM, AF and SHL took part in study conception and design. ESG, MJE, CS, AF and SHL contributed to collecting data from first-episode psychosis participants, while BH collected data from healthy controls. SHL undertook the statistical analyses with contributions from authors ESG, KWR and HMI. SHL wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved of the final manuscript.

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Conflicts of interest All authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments. The Regional Ethics Committee for Medical Research (#2014/2345) and the Norwegian Data Inspectorate approved of the study.

Informed consent Informed, written consent was obtained from all individual participants included in the study.

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