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Chapter 7

Summary and general discussion
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Background
The main objective of the work presented in this thesis was to investigate different aspects of apathy, as a distinct clinical syndrome, in older persons with and without concurrent depression. Although the concept of apathy has existed for centuries, its meaning has changed over time. Nowadays, apathy as a distinct clinical syndrome indicates an important loss of motivation that interferes with daily functioning and is manifested by diminished goal-directed behavior, goal-directed cognition and reduced emotional display. Apathy as a distinct clinical syndrome interferes with quality of life and is associated with diverse negative health outcomes, including higher mortality and less benefit derived from rehabilitation and treatment of depression.

In late-life depression, apathy may be very prominent; nevertheless, knowledge on apathy as a distinct, clinically relevant behavioral syndrome in depressed older persons is scarce. In this thesis, apathy in both depressed and non-depressed older persons was broadly investigated: the main results are summarized and discussed below in the context of previous research. Then, methodological issues related to the study of apathy in old age are addressed, clinical implications are discussed, and some recommendations are made for future research.

Summary of the results
Subtypes of apathy
According to the diagnostic criteria, apathy as a disorder of motivation is characterized by symptoms in three different life domains: behavioral, cognitive, and emotional. Distinct symptom profiles of apathy may indicate different apathy subtypes that are related to specific characteristics and, therefore, require distinct treatment approaches. Such subtypes of apathy cannot be identified using (total) scale scores of a measurement scale. Therefore, we used the data-driven technique Latent Class Analysis (LCA) to identify groups of persons (Classes) based on distinct symptom profiles in the general population-based PROMODE cohort of 122 older persons with apathy (Chapter 2). Using LCA, we were able to identify three classes. Further exploration of the characteristics across these three classes showed that persons in Class 2 had more serious apathy and depression, higher alcohol consumption, and more often lived alone, compared to Class 1 and Class 3. On the other hand, Class 3 showed the lowest level of education, the lowest Mini-Mental State Examination (MMSE) score, and the highest quality of life, compared to the other two Classes. However, no distinct apathy subtypes could be identified, since only the level of education and severity of apathy were independent predictors for Class membership.
Apathy in late life

Although apathy often co-occurs with depression, there is increasing evidence that apathy may be a distinct, clinically relevant behavioral syndrome, independent of depression and, possibly, with a different etiology from depression. In Chapter 3 we describe the results of the baseline cross-sectional study among depressed and non-depressed older persons in the NESDO study; we showed that clinically relevant apathy was present in 75% of the depressed and in 25% of the non-depressed older persons. Depressed and non-depressed older persons with apathy differed from each other, since severity of depressive symptoms was associated with apathy in depressed persons, whereas higher levels of C-reactive protein (CRP) were associated with apathy in non-depressed older persons. Male gender and having had less education were independently associated with the presence of clinically relevant apathy in both depressed and non-depressed older persons.

To further study the presence and impact of apathy in depressed older persons, Chapter 4 investigates the incidence, course and several predictive factors of apathy at 2-year follow-up among depressed older persons in the NESDO study. Baseline severity of apathy, but not of depression, predicted the severity and persistence of apathy, as well as poor recovery of depression at follow-up. Furthermore, we found that worse global cognitive functioning at baseline, but not severity of depression, predicted the 2-year incidence of apathy in depressed older persons.

Although depression in younger adults is also often accompanied by apathy, studies show that depression in older persons may differ in its phenomenology from depression in younger persons. This may especially be the case for the presence of (clinically relevant) apathy, which is more prevalent in late-life depression. Therefore, in Chapter 5 we examined the presence and comorbidities of clinically relevant apathy in older compared to younger depressed persons. It was shown that, of the 363 older depressed persons, 269 (74%) had clinically relevant apathy compared to 116 (54%) of the 217 younger depressed persons. Although older depressed persons more often showed apathy, the same associated risk factors were largely found in both age groups; the exception was for smoking, which was specifically associated with apathy in older depressed persons. In the total group of both younger and older depressed persons, apathy was independently associated with higher age, male gender, and the presence of more severe depression.

Burden of apathy

Apathy is associated with poor functional outcome, chronicity, and increased overall mortality. Although apathy also gives rise to increased distress for the caregivers, it is largely unknown to what extent apathy places a burden on the patients themselves.
Chapter 6 presents the results of our study examining perceived quality of life in relation to clinically relevant apathy in 1118 community-dwelling older persons in the PROMODE study. Apathy was found in 122 (11%) of these community-dwelling older persons. In 73 of these older persons with apathy, without depressive symptoms and cognitive impairment, apathy was associated with a diminished quality of life in various aspects of daily life. Moreover, older persons with both apathy and cognitive impairment experienced decreased subjective health quality compared to those without apathy. In depressed persons, apathy had no additional negative effect on the already low quality of life.

General Discussion
Concept of apathy
The concept ‘Apathy’ is not yet fully clarified. For a long time, apathy was considered to be merely a symptom of diverse neuropsychiatric disorders. Only in the last 30 years has apathy been increasingly acknowledged and investigated as a distinct, clinically relevant syndrome. However, controversy remains as to whether apathy should primarily be seen as a symptom of a neuropsychiatric disorder, including late-life depression, or also as a syndrome in its own right. At the same time, when apathy is very prominent and shows a cluster of different (motivational) symptoms (as described e.g. by Marin), it seems appropriate to consider apathy as a distinct clinical syndrome.22 Another problem is that, due to the lack of formal diagnostic criteria for apathy, clinicians and researchers fail to consistently use the same terminology; e.g. terms such as “flattened affect,” “amotivation,” or “avolition” are sometimes used when they may possibly refer to apathy. Another important area of debate focuses on the differentiation between apathy and depression. Literature shows that in different clinical populations apathy can be present in the absence of depression, but then lacking mood-related symptoms.7,23-25 Supporting evidence for the existence of apathy as a distinct syndrome includes different pathophysiology, etiologies and risk factors for apathy compared with depression. Neuropathologic and neuroimaging studies link apathy to abnormalities in specific regions of the frontal lobe, anterior cingulate gyrus and basal ganglia, whereas depression is particularly associated with abnormalities in the frontal-striatal and subcortical limbic circuits.26,27 Neurochemically, apathy reflects a dysfunction of fronto-subcortical projection systems, including monoaminergic, cholinergic, glutamatergic, and GABAergic pathways, whereas depression is supposed to reflect serotonergic deficits or a dopamine and norepinephrine imbalance.27,28

Diagnosis of apathy
Marin was the first to conceptualise apathy as a distinct behavioral syndrome consisting of diminished or absence of motivation and drive, as the core feature that was noticeably expressed in decreased goal-directed behavior, cognition and/or emotion.22,29 He
stated that the lack of motivation should not be attributed to emotional distress, intellectual impairment, or diminished level of consciousness. In 2001, Starkstein et al. modified the diagnostic criteria formulated by Marin, by omitting the necessity of an absence of emotional distress and intellectual impairment. On the other hand, they included the following requirements: “The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning” and “The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication)”. A few years later they additionally stated “…the symptoms should be present for at least 4 weeks during most of the day”. Following Starkstein et al., a task force consisting of international experts from Europe, America and Australia formulated consensus criteria for apathy. In these consensus criteria the necessity to have at least one symptom present in each of the three domains (behavior, cognition, emotion) was changed to at least one symptom in at least two of the three domains. Additionally, the symptoms should not exclusively be explained by or due to physical or motor disabilities. Although these consensus criteria for apathy were validated in different clinical populations (Alzheimer disease, Parkinson disease, major depression, schizophrenia, etc.), until now they have not been formally acknowledged. In addition, apathy as a distinct clinical syndrome has hardly been described in textbooks and is not included in the DSM-5. Apathy is mentioned in the DSM-5 only under clinically relevant behavioral disturbances as a specifier of several neurocognitive disorders.

Assessment of apathy

In order to assess symptoms and severity of apathy, Marin et al. (1991) developed the Apathy Evaluation Scale (AES). Although the inter-rater and test-retest reliability, as well as its ability to discern apathy from depression are good, no consistent threshold values for the AES are known to determine clinically relevant apathy. Subsequently, in a number of clinical populations with Parkinson disease, Alzheimer disease, stroke, and major depressive disorders, other measurement scales including the Dementia and Apathy Interview Rating scale, the Apathy Inventory, and the Lille Apathy Rating Scale were developed to assess, characterize and quantify apathy as a distinct syndrome. Only for the Apathy Scale (derived from the AES) was a threshold score determined for the presence of clinically relevant apathy (in patients with Parkinson disease). To date, the Apathy Scale has been used in clinical studies among older persons with Parkinson disease, Alzheimer disease, post-stroke patients, Huntington disease, major depression, and chronic low back pain, as well as in community-based studies. Other instruments such as the Neuropsychiatric Inventory (NPI), the Brief Psychiatric Rating Scale, and the Frontal Systems Behavior Scale, include only a single item for the assessment of apathy, which makes it impossible to decide whether apathy is a clinically important behavioral syndrome. The Apathy Evaluation Scale, the Apathy Scale, the Apathy Inventory and the Lille
Apathy Rating Scale\textsuperscript{36} were all recommended by the Task Force for assessment of apathy, showing adequate psychometric properties. However, all these instruments lack proper validation against external criteria, which also applies to the Apathy Scale.\textsuperscript{27,34} Also, this diversity of instruments does not allow proper comparisons of different studies on apathy.

With this dilemma in mind, we sought the best possible way to answer our research questions. We found that the Apathy Scale was the most appropriate measure to assess apathy, giving the fact that it was recommended by the international Task Force, showed fairly good psychometric properties in different clinical populations and, importantly, has a known threshold score $\geq 14$ for apathy as a distinct, clinically relevant behavioral syndrome.\textsuperscript{29,38,39,45}

**Subtypes of apathy**

Decreased motivation, interests, action initiation and emotional reactivity are all dimensions of apathy, in which the lack of motivation is the core feature, which may relate to internal (self-conducted behavior) or external stimulation.\textsuperscript{9} Moreover, because multiple different prefrontal-basal ganglia circuits may underlie these various dimensions, apathy may differ in its clinical expression. In addition, neurochemically, apathy reflects dysfunction of different fronto-subcortical projection systems (including monoaminergic, cholinergic, glutamatergic, and GABAergic pathways). Also, different treatment approaches may then be needed, as was found in studies among various clinical populations.\textsuperscript{27} Thus, apathy is probably best regarded as a heterogeneous disorder with (possibly) numerous subtypes.\textsuperscript{27,46} Until now, however, no studies have focused on the identification of clinical subtypes of apathy. Our study in an older community-based sample with apathy (from the PROMODE study) did not reveal any subtype of apathy using the Apathy scale. Although 3 classes emerged using LCA, no associated differences were found between these classes, indicating that the Apathy scale measures a rather homogeneous concept. However, older persons with more severe depression and serious cognitive impairment (thus suffering from more severe apathy) were excluded from this study, which may have resulted in insufficient heterogeneity to detect distinct subtypes of apathy.

**Apathy in late life**

In 25\% of the non-depressed older persons apathy was present, which is in line with other studies among healthy community-dwelling older persons that reported an occurrence of 1-27\%.\textsuperscript{3,14,47-49} In addition, apathy occurred in 75\% of the depressed older persons, which is within the wide range of prevalence (38-96\%) reported in the literature. These differences in prevalence rates are probably due to different criteria and measurement instruments used to assess apathy.\textsuperscript{2,3,14,15,48-51} The three studies that reported prevalence rates of apathy of 70-96\% comprised older persons
suffering from more severe depression, whereas apathy was mostly assessed with measurement instruments specifically designed to quantify apathy. One study excluded depressive persons who did not use antidepressants, another study included only inpatients who were admitted to an acute psychiatric ward and the third study used high scores on the Hamilton Rating Scale for Depression (HAM-D) and the AES to determine the presence of apathy. The studies that reported apathy prevalence rates in the lower range (i.e. 38-55%) in persons with depressive symptoms used more general screening instruments (e.g. the NPI and the GDS). Further, these studies were performed in community-based populations and populations with Alzheimer’s disease; and apathy was also assessed in persons with comorbid depressive disorders according to the DSM-IV. Another study in older persons with major depression showed an apathy prevalence rate of 38%. However, this relatively low prevalence rate might be explained by the selection of older persons with less severe depression and less comorbidity, because persons with psychotic depression, those with comorbid severe medical and neurologic disorders, and those who used certain medications and drugs were excluded. Since our study population consisted of both inpatients and outpatients, mostly suffering from a major depression, and because apathy was assessed using a well-validated measurement instrument, and the prevalence rate of 75% for apathy is in line with the higher prevalence rates mentioned above, we believe that our prevalence rates are reliable and representative for a depressed sample of older adults.

Apathy may be associated with different risk factors in non-depressed compared to depressed older persons, which suggests a different etiology for apathy in both populations. In our study we found that male gender and level of education were independent correlates of apathy in both depressed and non-depressed older persons, whereas higher CRP levels were particularly associated with apathy in non-depressed persons. Higher CRP levels are associated with more severe apathy, also in community-dwelling older persons without a history of cardiovascular disease. At old age, these higher CRP levels may reflect low-grade inflammation that, like apathy, is associated with (subclinical) underlying cardiovascular disease. As hypothesized by Dantzer et al., this low-grade inflammation may result in a cluster of symptoms including somnolence, loss of energy, malaise, and diminished interest in activities, that resemble symptoms of apathy, and may be associated with underlying atherosclerosis that leads to future vascular events. Indeed, it was shown that symptoms of apathy, but not of depression, were a risk factor for cardiovascular disease in community-based older persons.

Cognitive decline is also associated with apathy in older persons, in that apathy is more often present when cognition decreases. Apathy predicts cognitive decline in the future, whereas, at the same time, cognitive decline may predict the occurrence
of apathy. This was shown by our finding that worse global cognitive functioning at baseline (and not severity of depression) predicted the 2-year incidence of apathy, but only in depressed older persons. The question remains whether apathy is a consequence, or a predictor, or both, of cognitive decline.\textsuperscript{3} It is essential to understand the direction of this relationship, since this can have important implications for the management and treatment of both apathy and cognitive decline.

Apathy is also a well-known symptom of depression in younger depressed persons,\textsuperscript{18-20} and we have shown that not only in older but also in younger depressed persons, apathy can be very prominent, presenting itself as a distinct behavioral syndrome. Although apathy was associated with different risk factors in late life, compared to early life, both in younger and older depressed persons clinically relevant apathy was only associated with depression severity, indicating more severe depression.

It is suggested that older persons with apathy suffer less than their caregivers do; this may be due to lack of insight into their illness (anosognosia) whereby they may not experience a diminished quality of life.\textsuperscript{59,60} However, several clinical studies have shown that this is not true and that older persons with apathy do indeed experience diminished quality of life,\textsuperscript{61-65} as we also found in our community-based study. It is possible that the absence of drive and motivation impedes these persons from expressing their experienced decline in quality of life.

Further, the presence of apathy appeared to have a negative effect on the recovery and prognosis of (underlying) depression, and was also associated with chronicity,\textsuperscript{4,16,50,66,67} and a more complicated course of depression, which leads to greater functional impairments, particularly at old age. This strengthens the need to distinguish between clinically relevant apathy and depression, and to pay appropriate attention to the treatment of both, thereby hopefully ameliorating both the course and prognosis.

**Methodological considerations**

**Study designs**

For the studies described in this thesis, data were used from two observational prospective cohort samples (the NESDO and NESDA studies) and from a randomized controlled trial sample (the PROMODE study). All participants from the PROMODE sample were recruited in a general healthcare setting, giving us the opportunity to investigate apathy in an older rather heterogeneous community-dwelling population. In NESDO, both older inpatients and outpatients were included from both general health care and mental health care, consisting of depressed and non-depressed older persons; this enabled us to examine apathy and its course in both a depressed and non-depressed older sample. This is unique since little is known about apathy in combination with depressive disorder at old age. Most studies until now examined apathy cross-sectionally and particularly in clinical populations suffering from dementia, stroke and...
Parkinson disease, with and without comorbid depressive symptoms. In addition, we had the opportunity to use data from the NESDA study that allowed us to examine possible differences in the presence and associating comorbidities of apathy between older depressed and younger depressed persons.

**General strengths and limitations**
The studies described in this thesis need to be interpreted in the light of certain strengths and limitations.
The use of a large community-dwelling population from the PROMODE study made it possible to examine quality of life in relation to the presence of apathy, which has only been examined within clinical populations, and to investigate possible subtypes of apathy. A major strength of the NESDO study was the follow-up of the older persons, which enabled us to investigate the incidence and course of apathy in older persons with depression. In addition, in our population, both depression and apathy were diagnosed using well-established validated measures.

An important limitation of the studies described in this thesis is that no formal diagnostic criteria exist for apathy as a distinct behavioral syndrome, which makes comparison with other studies difficult. Secondly, since symptoms of apathy and depression may overlap, especially with regard to motivational symptoms, underestimation and overestimation of apathy or depression may have occurred. However, the Apathy Scale has shown good discriminant validity between apathy and depression and the overlap of items in the Apathy Scale and the Inventory for Depressive Symptomatology (IDS) was low. Thirdly, most studies in this thesis have a cross-sectional design, which prevented us from drawing causal inferences. Fourthly, an important phenomenon in cohort studies, particularly among older persons, is the degree of attrition. In the NESDO study, almost 25% of the persons were lost after 2-year follow-up due to death, and refusal or inability to further participate, mainly among participants who at baseline already showed severe physical and/or neuropsychological morbidity. This may have led to an underestimation of the presence of apathy at follow-up, since those with apathy were most likely to drop out. However, compared to other studies among older persons, our attrition was not considered to be high. Fifthly, persons with more severe apathy might not have participated because of a lack of motivation, resulting in the inclusion of a less heterogeneous group of older persons with only mild to moderate apathy, missing associating factors with apathy and limiting generalizability to persons with more severe apathy.

**Clinical implications**
*Back to the case report*

Mr. A suffered from depression with comorbid apathy that persisted after adequate treatment of the depression. After admission to our hospital, the psychotic depression
Mr. A. suffered from was adequately treated with nortriptyline and lithium carbonate. However, he still showed hardly any spontaneous speech, almost never talked, lacked all initiative, sat on the couch all day doing nothing, was generally inactive, and showed no social engagement without being bothered by it. Our conclusion was that he (still) suffered from clinically relevant apathy. Although no evidence-based treatment is known for apathy, a possible treatment option is methylphenidate.\textsuperscript{27,70} Therefore, we treated the patient with low doses (5 mg) methylphenidate 2 times/day and, within 1 week, he showed an increase in motivational behavior (went cycling spontaneously) and was more responsive to his environment. The improvement continued and, after a year, the methylphenidate could be stopped without reoccurrence of the apathy. He was very happy about his improvement in daily functioning and stated that he had indeed been bothered by his inactivity.

It is known that caregivers of patients with apathy experience great distress, while patients themselves do not always seem to feel apathy as an important burden.\textsuperscript{49,71,72} However, this patient was bothered by being apathetic, even though he did not complain about it at that time, possibly due to lack of motivation and drive.

Thus, although Mr. A was adequately treated for his depression, the apathy remained and required a different treatment approach. There is no specific pharmacologic agent known to be effective in the treatment of apathy, the most frequently used pharmacologic agents in older persons with apathy include dopaminergic antiparkinson agents, acetylcholinesterase inhibitors for Alzheimer disease, and psychostimulants.\textsuperscript{27} However, there is insufficient evidence for any pharmacological treatment to improve apathy since randomized controlled studies with apathy as primary outcome are lacking.\textsuperscript{70}

**Directions for future studies**

The aim of the work described in this thesis was to investigate different aspects of apathy - as a distinct clinical syndrome - in older persons with and without co-occurring depression. Clear diagnostic criteria are needed to help clinicians recognize and diagnose the presence of clinically relevant apathy and to differentiate this syndrome from depression. Some researchers have hypothesized that apathy can be divided into different domains,\textsuperscript{36,73,74} thereby indicating disease-specific variations in the clinical presentation of apathy in certain populations; however, this line of investigation requires further research. Since apathy as a clinically relevant syndrome probably needs a different treatment approach, future studies should not only focus on (early) diagnosis and risk factors, but also on the treatment of apathy. Until now, no adequate pharmacotherapy has been approved for apathy and randomized controlled trials are needed to study the efficacy of pharmacotherapy and behavioral treatment programs for apathy in different clinical populations.
References


