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**Prevalence, symptoms and risk profiles of apathy at old age**  
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The background of the page is an abstract, textured composition of overlapping brushstrokes. The colors range from light, airy blues and whites to deep, dark blues and blacks, creating a sense of depth and movement. The strokes vary in thickness and direction, some being straight and others curved, giving the overall appearance that of a dynamic, expressive painting.

# Chapter 1

General introduction and outline of the thesis

## Introduction

### Case report

“Doctor, my husband just sits on the couch”.

Mr. A, a 73-year-old man, was admitted to the acute ward of our psychiatric hospital for older persons, because of a (first) depressive episode and suicidal ideation, after his brother-in-law had deceased. In the past months he had become much quieter, felt increasingly sad, lost interest in fishing (which he normally did four times a week), and slept poorly waking up at least 10 times during the night. He also lost about 10 pounds in weight and was becoming increasingly anxious, being convinced that he was suffering from a fatal disease. The last few weeks before hospital admittance, he thought about killing himself.

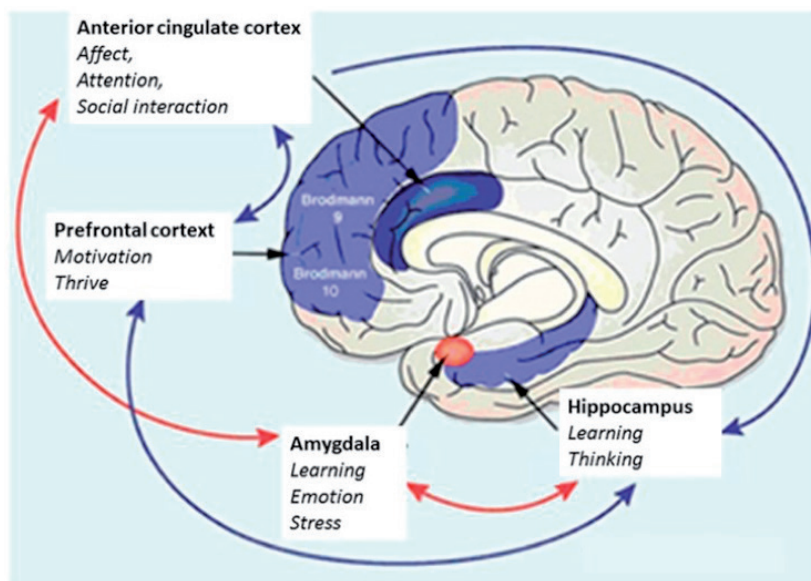
He was diagnosed with a first depressive episode with mood congruent psychotic symptoms. He was treated with nortriptyline 50 mg per day, with an adequate serum concentration, and olanzapine up to 20 mg per day. Recovery was slow and only after addition of lithium carbonate (400 mg per day) did his depression improve and the depressive symptoms disappear. Olanzapine was discontinued due to motor side-effects. After 3 months of hospitalization he was discharged and continued treatment in the psychiatry outpatient clinic. However, on one of the outpatient clinic appointments, his wife expressed her concern about the wellbeing of her husband, although he himself had no complaints. She mentioned that her husband had almost ceased to talk, lacked all initiative, and sat on the couch all day doing nothing. She was very worried because he seemed to be a different person: he had always been a very socially engaged and active person. According to the patient himself and his wife, he was no longer depressed; this, was also reflected in the score of 3 on the Geriatric Depression Scale.

This older man, showing lack of initiative, inactivity, lack of spontaneous speech, and the necessity for stimulation after remission of his depression, appears to suffer from apathy as a behavioral syndrome in its own right, especially since a sad mood and suicidal ideations are now absent.

The word ‘apathy’ has its origin in the old Greek ‘ἀπάθεια’ (apatheia), meaning ‘absence of feeling’. In the 3rd century before Christ, the Stoics believed that a human being could achieve true happiness when a condition free from ‘pathe’ in other words, free from emotions and passions was reached.<sup>1</sup> They thought that extreme emotions (such as fear, desire and pleasure) prevented humans from clear thinking and led them towards irrational behavior. The meaning of apathy changed in the early 20<sup>th</sup> century to that of a ‘state of non-reactivity’, both psychologically and physically.<sup>2</sup> Marin (1991) was the first to conceptualize apathy in its currently accepted significance.<sup>2</sup> He described apathy as a lack of motivation that was not attributable to a diminished level

of consciousness, intellectual deficit or emotional distress. He also developed diagnostic criteria for apathy that included a lack of motivation as the cardinal symptom with concomitant diminished goal-directed behavior (lack of effort, initiative, perseverance, and productivity), diminished goal-directed cognition (lack of interest, concern and awareness about one's personal, health, or financial problems), and diminished emotions (unchanging affect, lack of emotional responsivity to positive or negative events, and absence of excitement). Starkstein et al (2008) modified these diagnostic criteria into a more standardized set by adding i) the time period of 4 weeks in which, most of the time, symptoms should be present; ii) the necessity of experiencing functional impairment in different areas of daily living; and iii) by omitting the criterion that there should be an absence of a depressive disorder or cognitive decline.<sup>3</sup>

Apathy may be part of the symptomatology of many different neuropsychiatric disorders including cognitive decline and dementia, Parkinson's disease, Huntington's disease and, major depression, and may follow stroke. Several neuroanatomical and neurofunctional clinical studies have shown an association between the presence of apathy and pathology of the fronto-subcortical neuronal network and anterior cingulate cortex (ACC) in the brain (figure 1), such as reduced grey matter volume and decreased metabolic activity of the ACC.<sup>4-6</sup> Although apathy most often occurs as one of the symptoms of the abovementioned neuropsychiatric disorders, it is also found as a distinct behavioral syndrome, with its own cluster of symptoms, co-occurring with these disorders, but having a more prominent position.<sup>7-13</sup> However, apathy is sometimes present even in the absence of these morbidities.



**Figure 1.** Anterior cingulate cortex as part of the corticolimbic system

Cross-sectional studies found that a higher age,<sup>7,10</sup> having no partner and/or living alone,<sup>8,14</sup> male gender,<sup>7,15</sup> cognitive impairment,<sup>8</sup> and cardiovascular diseases<sup>16</sup> were risk factors for the presence of apathy. In longitudinal studies on apathy in old age a higher age,<sup>13,17</sup> male gender,<sup>13</sup> cognitive impairment,<sup>13,15,17,18</sup> the presence of depressive symptoms<sup>8,9</sup> and the presence of cardiovascular disease including stroke and/or risk factors for cardiovascular disease appeared to be predictive of future apathy.<sup>9,17</sup> Apathy is associated with decreased daily functioning,<sup>17,19</sup> a subjectively decreased quality of life as well as adverse health outcomes including a higher mortality and less likelihood to benefit from rehabilitation services and treatment.<sup>13,19-24</sup>

### **Assessment of apathy**

Marin was the first to develop an instrument to assess apathy, i.e. the Apathy Evaluation Scale (AES). The AES consists of three versions; a patient-rated version, a clinician-rated version, and a caregivers-rated version.<sup>25</sup> However, no conclusive threshold values of the AES for clinically relevant apathy are established.<sup>26</sup> Starkstein abbreviated the Apathy Evaluation Scale into the Apathy Scale (appendix), with proposed cut-offs for clinically relevant apathy based on research in a clinical population with Parkinson's disease.<sup>27</sup> Apart from these two scales, several other instruments have been developed to specifically assess apathy such as the Dementia and Apathy Interview Rating scale; the Apathy Inventory; and the Lille Apathy Rating Scale.<sup>28-30</sup> In addition, several (more general) assessment tools include items to screen for symptoms of apathy such as the Neuropsychiatric Inventory, the Brief Psychiatric Rating Scale, and the Frontal Systems Behavior Scale.<sup>26</sup> It is possible that different combinations of apathy symptoms indicate different apathy subtypes that are related to specific characteristics and, therefore, require distinct treatment approaches.<sup>31,32</sup> However, no studies have empirically examined possible subtypes of apathy in relation to specific patient and clinical characteristics. With data-driven techniques such as Latent Class Analyses (LCA) that cluster persons based on a given clinical outcome, an empirically based classification of apathy may be obtained that enables the identification of distinct subtypes of apathy.

### **Apathy and late-life depression**

Apathy is a well-known symptom of late-life depression. However, apathy can also occur as a distinct behavioral syndrome in depression, when playing a prominent role in its phenomenology. In older persons suffering from depression, apathy as a distinct behavioral syndrome was present in 38-96%.<sup>19,33,34</sup>

After an international consensus meeting the following definition and criteria were formulated (see table 1): Apathy as a clinically relevant syndrome consists of a cluster of clinical features including a (severe) loss of motivation and interest, and a significant decreased goal directed behavior, emotional responsivity and cognitive activity.<sup>2,3,35,36</sup> Differentiating between apathy and depression can be a challenge, since key symptoms

of both these disorders show considerable overlap. However, apathy is a motivational disorder, lacking mood-related symptoms, whereas depression is primarily a mood disorder.<sup>37-39</sup> It is unknown whether (or not) the presence and severity of apathy differs between early-life depression and late-life depression.

There is evidence that apathy and depression have different etiologies, risk factors, pathophysiology and outcomes. Immune activation, as indicated by higher C-reactive protein (CRP) concentrations, has been associated with more apathy symptoms but not with depression, although the results from different studies were inconclusive.<sup>9,12,16</sup> Moreover, longitudinal studies show that cardiovascular disease and cardiovascular risk factors predict the occurrence of apathy, but not of depressive symptoms.<sup>9,16</sup> Neuro-radiological research with MRI-scanning showed that both apathy and depression were associated with reduced gray matter volumes, but in different areas of the brain.<sup>40,41</sup> Also, fMRI-scans revealed that resting functional connectivity of the nucleus accumbens (NAcc) and the dorsal anterior cingulate (dACC) distinguished older depressed persons with apathy from older depressed persons without apathy and from healthy older persons.<sup>42</sup> In addition, treatment outcome of apathy differs from that of depression in that antidepressants effectively treat depression but not apathy,<sup>19,40,41</sup> and that in depressed older patients, apathy is a predictor of poor response to antidepressive therapy,<sup>20,40,43</sup> of chronicity of depression, and of more severe disability.<sup>19</sup>

### **Burden of apathy**

The presence of apathy can be extremely distressing for caregivers compromising their quality of life.<sup>8,44,45</sup> It is often suggested that caregivers of patients with apathy suffer more than the patients themselves, due to the frequent lack of awareness and insight in patients with apathy. However, to date, very few studies have investigated the quality of life in older persons suffering from apathy. In a study including a Japanese population-based older population, apathy was not associated with a diminished quality of life;<sup>46</sup> this is in contrast to findings in clinical populations suffering from dementia, in which apathy was associated with decreased subjectively perceived quality of life.<sup>47-49</sup>

### **Study cohorts used in this thesis**

#### *Netherlands Study of Depression in Older Persons (NESDO)*

NESDO is an ongoing prospective cohort study that aims to examine the determinants, long-time course and the consequences of depression in late life.<sup>50</sup> Between 2007 and 2010, 378 older persons with a depressive disorder in the previous 6 months before baseline assessment and diagnosed according to the DSM-IV criteria, and 132 non-depressed older persons, were included in the NESDO baseline sample (total sample n=510, aged 60-93 years). Participants were recruited from primary health care practices and mental health care institutes to create a sample that represents all stages of depression. Participating primary health-care practices were from the regions

**Table 1.** Diagnostic criteria for apathy

For a diagnosis of Apathy the patient should fulfil the criteria A, B, C and D

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

Amsterdam, Leiden and Groningen, and participating mental health-care institutes are the GGZ inGeest and the VUMC in Amsterdam, the LUMC and GGZ Rivierduinen and Parnassia in Leiden, the UMCG and Lentis in Groningen, the GGNet in Apeldoorn and Zutphen, and the RadboudUMC and GGZ Nijmegen in Nijmegen. Excluded were persons with a Mini-MentalState Examination score (MMSE) <18, a primary diagnosis of dementia, a psychotic disorder, obsessive-compulsive disorder or severe addiction disorder, or insufficient command of the Dutch language. During a 4-hour baseline assessment consisting of written questionnaires, interviews, a medical examination, a cognitive



computer task and collection of blood and saliva samples, a wide range of information was obtained with respect to health outcomes, demographic, psychosocial, clinical, biological and genetic characteristics. Data obtained from the baseline assessment are used in our cross-sectional studies. Every six months, severity of depressive symptoms was monitored with the Inventory of Depressive Symptomatology Self-Report (IDS-SR) that was sent to all participants. Between 2009 and 2012, a second extensive face-to-face assessment was performed. Because of attrition, only 285 of the 378 depressed older persons at baseline participated in the 2-year follow-up. Data obtained from the 2-year follow-up assessment are used in our longitudinal study.

#### *The Netherlands Study of Depression and Anxiety (NESDA)*

The Netherlands Study of Depression and Anxiety (NESDA) has almost the same study design as NESDO being a multi-site naturalistic 8-year longitudinal cohort study, among 2,981 participants aged 18 through 65 years.<sup>51</sup> Aims of this study were to: 1) describe the long-term course and consequences of depressive and anxiety disorders, and 2) integrate biological and psychosocial research paradigms within an epidemiological approach to examine (interaction between) predictors of the long-term course and consequences. The sample consists of 1,701 persons with a current (6 month recent) diagnosis of depression and/or anxiety disorder, 907 persons with life-time diagnoses, or at risk because of a family history or sub-threshold depressive or anxiety symptoms, and 373 healthy controls. Participants were recruited from general practices and mental healthcare organizations. During a 4-hour baseline assessment including written questionnaires, interviews, a medical examination, a cognitive computer task and collection of blood and saliva samples, extensive information was gathered about key (mental) health outcomes and demographic, psychosocial, clinical, biological and genetic determinants. Detailed assessments were repeated after 1, 2, 4 and 8-years follow-up. Wave 6 data (follow-up after 6 years, in which the Apathy Scale was assessed) are used in our study investigating apathy in late-life depression compared to early-life depressed persons.

#### *Proactive Management of Depression in the Elderly (PROMODE)*

The primary aim of the Proactive Management of Depression in the Elderly (PROMODE) study, a randomized controlled trial, was to investigate the (cost-) effectiveness of a combined screening and treatment program for older persons aged  $\geq 75$  years with depressive symptoms, in general practices in the Leiden region.<sup>52</sup> Therefore, 11,635 registered subjects aged  $\geq 75$  years, in 67 general practices in the Leiden region were invited for screening at home for depressive symptoms, from April 2007 until July 2008. Exclusion criteria were current treatment for depression, clinical diagnosis of dementia, or a Mini-Mental State Examination (MMSE) score  $< 19$  points, loss of a partner or child in the preceding 3 months, life expectancy  $\leq 3$  months, and not

speaking Dutch. Screening yielded 264 screen-positive persons according to a  $\geq 5$ -point score on an interviewer-administered 15-item version of the Geriatric Depression Scale (GDS-15). Of those, 2,393 persons gave written informed consent to participate in the randomized trial. By means of interviews and written questionnaires information was collected on sociodemographic, clinical and quality-of-life determinants. Data from 1,118 persons were used in our study on apathy and quality of life. Further, data from 120 persons suffering from clinically relevant apathy were used in our study examining the occurrence of relevant subtypes of apathy.

### **Background and aims of this study**

The aim of the work described in this thesis is to investigate different aspects of apathy - as a distinct clinical syndrome - in older persons with and without concurrent depression. The primary objectives are to assess prevalence, incidence, course, correlates and predictors of apathy, particularly in depressed older persons. Secondary objectives are to determine relevant subtypes of apathy and their associating correlates using Latent Class Analyses, the presence and associating factors of clinically relevant apathy in older depressed persons compared to younger depressed persons, and the impact of clinically relevant apathy on quality of life.

In this thesis the following research questions are addressed:

1. *Is it possible to distinguish clinically relevant subtypes of apathy in persons with apathy according to the Apathy Scale using specific data-driven Latent Class Analyses?*
2. *What is the prevalence, severity and clinical profile of apathy in depressed and non-depressed older persons and does apathy relate to severity of depression or other variables?*
3. *Which characteristics predict the incidence and course of apathy in depressed older persons over a 2-years period?*
4. *Is apathy - as a distinct clinical syndrome - also present in depressed younger adults and what are the associating factors in comparison to those in depressed older persons?*
5. *Is apathy associated with diminished quality of life among community-dwelling older persons, irrespective of depression and/or impaired cognition?*

### **Outline of this thesis**

In **Chapter 2**, the aim is to determine clinically relevant subtypes of apathy according to the Apathy Scale in older persons who were included in the PROMODE study using data-driven Latent Class Analysis (LCA), and to investigate specific characteristics across the classes identified by LCA. Then, in **Chapter 3**, the prevalence, severity and clinical profile of apathy in depressed and non-depressed older persons, in relation to various possible determinants, is assessed in the NESDO participants. **Chapter 4** examines which characteristics predict the incidence and course of apathy as a distinct

behavioral syndrome, in older persons in the NESDO study who were depressed at baseline, over a 2-year period. Then, using data of the NESDO and NESDA, **Chapter 5** explores whether apathy more frequently occurs in late-life depression compared to early-life depression. In addition, various determinants of clinically relevant apathy in older compared to younger depressed persons are assessed. **Chapter 6** investigates in the PROMODE study whether the presence of apathy among community-dwelling older persons is associated with a diminished quality of life. Finally, **Chapter 7** places our findings in a current perspective, discusses clinical implications, and makes some recommendations for future research.

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