Patterns of late-life depression: On the nature of depressive subtypes and the role of aging

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Contents

CHAPTER 1

General introduction

Prologue

In May 2013, during my last internship at a geronto-psychiatric hospital and two months away from taking Hippocrates' oath to become a medical doctor, patient A, a seventy-three-year-old male, was admitted to our ward. He has exhibited 'strange behaviour' for almost two years, and has had no medical record to date. His behaviour consisted of being passive to the point of being completely unable to take care of himself, and he showed no initiative towards washing or feeding himself. At home, he had passed his days by sitting at his kitchen table while tapping his feet and making nonsensical sounds. Further spontaneous movement was absent. At the ward, he felt depressed because he worried whether he would ever be able to go home again – a realistic worry considering his state. Extended physical examination, including blood analysis and imaging of the brain, did not show any abnormalities. Neurocognitive tests showed attention and memory deficits, which could be caused by either a depression or a neurocognitive disorder. Several antipsychotics and antidepressants were tried, to no avail.

A major depressive disorder was diagnosed, based on his depressed feelings, diminished enjoyment in his usual activities, and pessimistic thoughts. At the ward, both the repetitive movements and the lack of spontaneous movements were classified as symptoms of catatonia, which clouded his other depressive symptoms and complicated diagnosis. He was treated with electroconvulsive therapy (ECT). During the treatment, he began talking more frequently, telling the doctors he has felt completely emotionally empty during the past year and a half. After sixteen sessions of ECT, his depression was in full remission, and after a few more months he was discharged from the ward, to his own home. Neurocognitive tests showed no abnormalities anymore, in spite of the ECT course which often causes (transient) memory deficits as a side effect. At the same time my training ended and I started working elsewhere – but a few years later, I coincidentally met him at the shop where he used to volunteer before his depression took over. He told me he had resumed his volunteer work after being dismissed from our hospital; his depression had been in remission ever since.

During the same period, patient B, a sixty-nine-year-old female, was admitted to the ward for ECT. She was diagnosed with a major depressive disorder two years ago, but antidepressant treatment had been ineffective, despite trying numerous kinds of antidepressants. She felt depressed, although her mood improved a little when she was around other people. Her appetite has increased and she has gained weight over the course of her depression. She slept around twelve hours each day, and has a hard time getting out of bed. She had trouble concentrating, as well as pessimistic thoughts, and the lack of improvement, despite trying numerous antidepressants and psychotherapy, had left her increasingly hopeless about her future. She had recurrent suicidal thoughts, but still hoped ECT can improve her situation. Neurocognitive tests showed no abnormalities. She was treated in accordance with the Dutch ECT-protocol, and received six unilateral treatments. When she did not improve at all, treatment was switched to bilateral, again with no improvement. After twelve sessions with adequate seizures, the medical staff concluded that continuing was not useful, and in agreement with the patient and according to Dutch guidelines, the ECT was discontinued. A monoamine oxidase inhibitor

(MAOI) was then started, which was the one type of antidepressant she had not tried yet. After a few weeks, she felt remarkably better. She told me she felt less depressed, was making plans for the day, had adopted a healthier diet, and felt less tired all day. After another three weeks, her depression was in remission, and she was discharged from the ward.

These cases illustrate the heterogeneity in clinical presentations and treatment response of major depressive disorder in later life. Both patients had the same diagnosis of major depressive disorder, although their symptoms varied greatly. In fact, with the current criteria in the Diagnostic and Statistic Manual for Mental Disorders, fifth edition (DSM-5) (American Psychiatry Association, 2013), there are 227 possible ways to meet the symptom criteria for major depressive disorder (Zimmerman et al. 2015). Ultimately both of our patients had a very good response to treatment, but both also faced a great delay in finding effective treatment, with the time from onset of the index episode to remission being around a year and a half. Both were treated in accordance with the Dutch depression protocols, but these standard protocols do not take different symptoms patterns into account. Researchers have been trying to address this heterogeneity in treatment response for a long time now, but the currently used, DSM-based depression subtypes do not correlate with specific forms of treatment. However, improving our knowledge on late-life depression is of paramount importance, since late-life depression places a high burden on both the patient (Gallo et al. 2007), caregivers (Scazufca et al. 2002) and society (Hughes et al. 1997), and has a worse prognosis than depression in younger adults (Schaakxs et al. 2018).

Recognizing that depression is a heterogeneous concept, with different subtypes requiring different forms of treatment, is not new. For instance, the DSM-5 acknowledges 'melancholic depression' as a subtype, a concept which traces back to the early 1900's when Kraepelin coined a similar concept (Taylor and Fink 2006). The word itself is even older; in ancient Greece, μέλαινα χολή or *melaina cholè* means black bile, one of the four humours or bodily fluids and thought to be excessively present in persons with a melancholic temperament. According to Hippocrates, an abundance of black bile leads to an immense sadness, despair, and an inability to feel and to love (Hippocrates, 400 BC). Over the centuries, however, melancholy became less of a disease characterised by too much black bile and more of a Romantic, fashionable sense of suffering. It was thought a melancholic temperament increased sensitivity and fantasy, with artists pursuing this state as it would enable them to truly rise above themselves (Strong 1969). But in the late 19th century the German psychiatrist Emil Kraepelin, often referred to as the founding father of modern psychiatry, reframed melancholy as a severe mood disorder, which took psychotic and stuporous features into regard. Elaborating on the work of Kraepelin, Hopewell - Ash characterised melancholia in 1934 as a depressed state with depression of spirits, psychomotor retardation and general torpidity, with additional insomnia, constipation, morbid and restless anxiety, but at the same time a general slowing of the rhythm (Taylor and Fink 2006).

Currently, the DSM-5 recognizes melancholia as subtype of depression, among several other subtypes, including: 'with melancholic features', 'with atypical features', 'with psychotic symptoms', 'with catatonia', 'with a postpartum onset', and 'seasonally bound depression' (American Psychiatry Association 2013). These subtypes, however, are as heterogeneous as the original concept of depression itself. Melancholic and atypical depression says something about the quality or profile of a set of symptoms, while psychotic and catatonic symptoms are additional features that could well coexist with either a melancholic or atypical depression. The subtype 'with a postpartum onset' only describes the moment in life someone develops a first depressive episode, while seasonally bound depression has the cyclic nature of the depression as main distinguishing characteristic. These latter two subtypes do not provide information on the nature of the symptoms, either. Therefore, it could be possible that someone develops a first depressive episode postpartum, which goes on to have a season bound recurrence, with both melancholic and psychotic symptoms. Even more complicated, in later life depression is often thought to have a different presentation, with more somatic symptoms. Furthermore, atypical symptoms like weight gain could be nullified by muscle weight loss due to frailty and comorbidity. It is therefore not hard to imagine that this overlap between subtypes and symptoms makes it difficult for researchers to identify a subtype for research.

Part I: depressive subtypes and the NESDO study

Several studies have set out to improve the current subtypes, aiming to improve our understanding of depression and predictive value of subtypes on treatment and prognosis. The two main methods of subtyping that are used are either clinically based or data driven. With clinically defined subtypes, already existing criteria of subtypes, for instance DSM-derived atypical or melancholic subtypes, are used to characterize patients and examine their response to different treatments. Data-driven methods on the other hand, are trying to subtype patients without pre-existing hypotheses. These techniques cluster patients based on their congregate of different depressive symptoms.

In depressed younger adults, studies using latent class analysis (a specific data-driven method) have identified subtypes closely resembling (but not entirely matching) the DSM-based melancholic and atypical subtypes (Lamers et al. 2010; Alexandrino – Silva et al. 2013; Rodgers et al. 2013). This melancholic subtype was characterised by a decrease in appetite, weight and sleep, whereas the atypical subtype was driven by a gain in appetite, weight and sleep. Furthermore, the melancholic subtype had a higher prevalence of cortisol disturbances compared to non-melancholic subjects (Lamers et al. 2013; Penninx et al. 2013), while the atypical subtype showed higher serum inflammation parameters. Genetic examination also revealed a different genetic profile for the atypical subtype, with persons of the atypical subtype having a higher prevalence of genes linked to metabolic syndrome (Milaneschi et al. 2016). As could be predicted from aforementioned biological and genetic findings, the atypical subtype also proved to be the most stable over time, with a stability varying from 71 to 79% (Lamers et al. 2012; Rodgers et al. 2014).

In older depressed adults, latent class analyses have also been performed. However, since no study differentiated between increase and decrease in appetite, weight, and sleep, their resulting subtypes were not comparable to those found in the aforementioned studies in younger adults. Studies on inflammatory parameters and cortisol measures in older depressed adults often do not take subtypes of depression into account, and show inconsistent findings regarding both cortisol (Belvederi Murri et al. 2014) and inflammation (Martinez-Cengotitabengoa et al. 2016). Since studies in younger depressed adults show that these disturbances seem to be specifically tied to subtypes, we think that the lack of consistent outcomes on biological disturbances in late-life depression relied on the lack of taking the heterogeneity of depression into account.

A potentially very useful study to answer questions on the nature of late-life depression is the Netherlands Study on Depression in Old Age (NESDO) (Comijs et al. 2011). This study included 510 depressed and non-depressed persons sixty years or older, from 2007 until 2010. Patients were recruited from five cities throughout the Netherlands (Amsterdam, Apeldoorn/ Zutphen, Groningen, Leiden, and Nijmegen), from both mental health care institutes and general practices. Healthy controls were recruited through general practices. At baseline, depression was measured through items of the Composite International Diagnostic Interview (CIDI) and defined in line with the DSM-IV criteria (American Psychiatry Association 2000). Somatic and psychiatric comorbidity was measured through several questionnaires and interviews. Demographic, psychosocial, biological, cognitive and genetic determinants were collected. Participants underwent a medical examination, and blood and saliva samples were collected. The baseline NESDO sample consisted of 378 depressed persons and 132 non-depressed persons. Age ranged from 60-93 years old; for the depressed persons their mean age of depression onset was 49 years. Follow-up assessments were made every six months with written questionnaires, and face-to-face follow-up assessments occurred at two years and six years post baseline.

The aim of the first part of this thesis are to examine whether we can determine meaningful subtypes in late-life depression using data-driven approaches. We hypothesize that possible subtypes found will also have different demographics and clinical profiles, and that biological disturbances in late-life depression are subtype dependent.

For the study in **chapter 2**, 'Depressive subtypes in an elderly cohort identified using latent class analysis', we did a latent class analysis including the depressed persons with no missing data on baseline depressive symptoms (N=359). Although latent class analyses have been performed before on older depressed persons (Hybels et al. 2009; Lee et al. 2012; Mezuk and Kendler 2012), we divided the items appetite, weight change, sleep, and psychomotor symptoms in either gain or loss, an approach which differed to the aforementioned studies. Studies in younger adults have already showed the importance of this difference in determining subtypes; in our study, we wanted to examine whether this is the case for older adults, too.

Chapter 3, 'Inflammatory markers and cortisol parameters across depressive subtypes in an older cohort', examined differences in inflammation parameters and cortisol measures across our previously identified subtypes. Since in younger adults an increase in these biological parameters was tied to respective subtypes, we hypothesised that the lack of homogeneous results in the older population was due to the heterogeneity of late-life depression. Taking subtypes of depression into account would respect this heterogeneity, and could help determine the pathophysiological mechanisms of late-life depression in different subtypes.

Our **fourth chapter**, titled 'Stability and transition of depressive subtypes in older adults', examined whether our earlier detected subtypes are stable over time, thereby determining their clinical relevance. We did this by performing a latent transition analysis (LTA). This analysis consisted of two separate latent class analyses on the same cohort, on two different points in time (baseline (T0) and two year follow-up (T1)). The found classes are then compared, and the stability of classes is being examined.

Part II: Depression subtypes and ECT outcome. Findings from the MODECT study

In clinical practice, it is common knowledge that particularly melancholic depression benefits from ECT, although findings from clinical studies are inconsistent. A possible explanation is that a DSM diagnosis of melancholia does not require psychomotor disturbances (American Psychiatry Association 2013), even though psychomotor symptoms are thought to be a core characteristic of melancholic depression and have also been identified as predictor of response to ECT (Fink et al. 2007). ECT, among other effects, strongly enhances dopamine, the neurotransmitter mainly responsible for motor and psychomotor functioning (Nutt 2006). We hypothesized that a positive outcome of ECT on depression could be better predicted by focusing on psychomotor disturbances rather than the DSM diagnosis of melancholia. The CORE is a questionnaire measuring both psychomotor retardation and agitation, and in an earlier study in younger adults higher CORE scores predicted ECT response (Parker and Hadzi-Pavlovic 1996; Hickie et al. 1996). However, research on older adults is limited.

In addition to the efficacy of ECT on patients with specific symptoms, it is unknown whether all symptoms of depression benefit equally from ECT. Earlier studies on antidepressants found that not all depressive symptoms resolve with the same speed, and that remission often takes weeks to months (Bhar et al. 2008). On the other hand, ECT is known to rapidly ameliorate depressive symptoms, especially in older adults (Spaans et al. 2016), and especially psychomotor symptoms (Parker et al. 2010). However, further insight into the course trajectories of depressive symptoms within older persons treated with ECT is lacking.

In order to examine the efficacy of ECT on different symptoms of depression, data was derived from the Mood Disorders in Elderly treated with Electro Convulsive Therapy

(MODECT) study (Dols et al. 2017). This is a two-site naturalistic, longitudinal study including older in-patients (55 years or older) with severe unipolar depression according to DSM-IV-TR criteria (American Psychiatric Association (APA), 2013), referred for ECT (N=118). Patients were recruited from tertiary psychiatric hospitals (GGZ inGeest, Amsterdam, the Netherlands and University Psychiatric Center, KU Leuven, Belgium). Exclusion criteria were a DSM-IV-TR diagnoses of bipolar disorder and schizoaffective disorder and a history of major neurologic illness. The diagnoses were made by a psychiatrist and confirmed by the Mini International Neuropsychiatric Interview (Sheehan et al. 1998). Primary indication for ECT included pharmacotherapy resistance as assessed with the Antidepressant Treatment History Form (Prudic et al. 1996), life-threatening symptoms, elective, or other. Demographic and clinical variables were obtained by interview and double-checked by chart review. Physical comorbidity and medication use were assessed in a semistructured interview. During ECT, the Montgomery Asberg Depression Rating Scale (MADRS) (Folstein et al. 1975) was used to evaluate the depressive symptom severity during the treatment course. Cognitive functioning before, during and after the treatment course was measured by the Mini Mental State Exam (MMSE) (Hartong and Goedkoop, 1985).

The aims of the second part of this thesis are to examine whether ECT response could be predicted by the presence of psychomotor disturbances, with respect to both the number of patients reaching remission and the speed of their recovery. To test whether ECT improves all symptoms of depression, we examined the response of different depressive symptoms to ECT, as well as the speed of response.

In **chapter 5**, 'Differences in characteristics and ECT outcome between melancholic and non-melancholic depressed older patients', we examined whether psychomotor disturbances, as measured by the CORE, were a predictor of ECT outcome. We included patients from the MODECT study. Characteristics were compared across melancholic and non-melancholic patients. Furthermore the relation between psychomotor symptoms and remission/response, and their difference in time, was examined.

Chapter 6, 'Differences in speed of response of depressive symptom dimensions in older persons during Electro Convulsive Therapy', focuses on the question of whether ECT relieves all symptoms of depression, and whether each of the symptoms improve at the same speed. Both pharmacotherapy and psychotherapy do not relieve all depressive symptoms or symptom clusters, or not at the same speed. If all symptoms of depression will improve swiftly under ECT, this would be another argument to consider ECT as one of the first treatment options in late-life depression. Exploratory factor analysis was used to identify symptom dimensions, using the ten depression items of the MADRS. Thereafter, differences in course trajectories of symptom dimensions during two weeks were examined by multilevel analyses.

Chapter 7 of this thesis summarizes and discusses its main findings. This chapter provides a critical appraisal of subtypes of late-life depression, their stability over time and their response to treatment. Furthermore, methodological considerations will be given and strengths and limitations will be discussed. Finally, some clinical implications and future directions for clinical research will be described.

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CHAPTER 2

Depressive subtypes in an elderly cohort identified using latent class analysis

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Background: Clinical findings indicate heterogeneity of depressive disorders, stressing the importance of subtyping depression for research and clinical care. Subtypes of the common late life depression are however seldom studied. Data-driven methods may help provide a more empirically-based classification of late-life depression.

Methods: Data were used from the Netherlands Study of Depression in Older People (NESDO) derived from 359 persons, aged 60 years or older, with a current diagnosis of major depressive disorder. Latent class analysis (LCA) was used to identify subtypes of depression, using ten CIDI-based depression items. Classes were then characterized using various sociodemographic and clinical characteristics.

Results: The most prevalent class, as identified by LCA, was a moderate-severe class (prevalence 46.5%), followed by a severe melancholic class (prevalence 38.4%), and a severe atypical class (prevalence 15.0%). The strongest distinguishing features between the three classes were appetite and weight and, to a lesser extent, psychomotor symptoms and loss of interest. Compared with the melancholic class, the severe atypical class had the highest prevalence of females, the lowest mean age, the highest BMI, and highest prevalence of both cardiovascular disease, and metabolic syndrome.

Limitations: The strongest distinguishing symptoms, appetite and weight, could be correlated. Further, only longitudinal studies could demonstrate whether the identified classes are stable on the long term.

Discussion: In older persons with depressive disorders, three distinct subtypes were identified, similar to subtypes found in younger adults. The strongest distinguishing features were appetite and weight; moreover, classes differed strongly on prevalence of metabolic syndrome and cardiovascular disease. These findings suggest differences in the involvement of metabolic pathways across classes, which should be considered when investigating the pathogenesis and (eventually) treatment of depression in older persons.

Key words: latent class analysis, depression subtypes, atypical depression, melancholic depression, metabolic syndrome

Abstract

Background

Late-life depression is a very common disorder. In older persons living in different settings (e.g. from private households to institutions) prevalence rates of major depressive disorder (MDD) are estimated at 1-16% (Djernes 2006). In addition, depressive disorders among older persons are frequently of a chronic nature, with a high burden for both patients (Gallo et al., 2007) and their caregivers (Scazufca et al., 2002) and with high societal costs (Hughes et al., 1997; Unützer et al., 2009). Insight into the pathogenesis and possible treatment options is therefore of paramount importance. However, research on the aetiology and pathogenesis is impeded by the heterogeneity of depression and differences in biological underpinnings across subtypes, as demonstrated in younger adults (Marijnissen et al., 2011; Lamers et al., 2013; Liu et al., 2014; Vogelzangs et al., 2014; Mansur et al., 2015; Milaneschi et al., 2016).

Data-driven techniques are a fruitful way to investigate heterogeneity in depressive disorders (Lubke and Muthén 2005). These techniques cluster patients based on their congregate of different depressive symptoms, without a pre-conceived hypothesis. Studies using latent class analysis (LCA) in depressed, younger adult populations (Kendler et al., 1996; Sullivan et al., 1998; Lamers et al., 2010; Li et al., 2014) identified an 'atypical' class, characterized by increased appetite and increased sleep, and a 'typical' (often named 'melancholic') class, characterized by loss of appetite and weight, and by the presence of psychomotor symptoms. Subsequently, these empirically-derived classes could be linked to distinct biological correlates (Lamers et al., 2010, 2013; Milaneschi et al., 2015) as well as different genetic profiles (Milaneschi et al., 2016).

To what extent similar subtypes can be identified in late-life major depression needs to be established. Some studies have implemented LCA in late-life depression (Hybels et al., 2009, 2011, 2013; Lee et al., 2012; Mezuk and Kendler 2012), finding subtypes based mainly on severity. However, most of these studies also included non-depressed persons (Hybels et al., 2009, 2013; Mezuk and Kendler 2012), or persons with at least one depressive symptom (Lee et al., 2012), without a formal diagnosis of major depression. Whereas inclusion of subthreshold depressive disorders may generate insight into the heterogeneity of depression, it impedes examination of the assumed heterogeneity of particularly major depressive disorder (MDD). Furthermore, in populations with depression of varying severity, data-driven techniques are at risk to detect classes that are mainly driven by different levels of severity. Furthermore, because most studies included persons from community samples, no insight was provided into clinical (outpatient) populations (Lee et al., 2012; Mezuk and Kendler 2012; Hybels et al., 2013). Lastly, previously demonstrated in younger depressed adults, a differentiation between increased or decreased appetite, weight and/or sleep served as a core feature for differentiation between atypical and melancholic subtypes (Kendler et al., 1996; Sullivan et al., 1998; Lamers et al., 2010; Li et al., 2014). However, few studies among older, depressed persons distinguished between increased and decreased appetite, weight and sleep (Hybels et al., 2009, 2013; Lee et al., 2012), and the majority of data-driven studies in the older population identified subtypes primarily based on depression severity only (Hybels et al., 2009, 2011; Mezuk and Kendler 2012).

Therefore, this study aimed to gain more insight into the assumed heterogeneity of MDD in older persons by performing LCA, based on depressive symptoms. If distinct classes are identified, these are examined to establish whether they differ with respect to demographic and clinical characteristics, as well as other risk factors and comorbidity patterns.

Methods

Sample

Data were derived from the baseline measurements of the Netherlands Study of Depression in Older persons (NESDO), a longitudinal multi-site naturalistic cohort study, examining the course and consequences of depression in older people. The NESDO cohort (n=510) consists of persons aged 60-93 years, including 378 persons with a depressive disorder in the previous 6 months, and 132 non-depressed controls. Depressed older persons were recruited from both mental health care institutes and general practitioners in five regions in the Netherlands, in order to include persons with current late-life depression in various developmental and severity stages. Depression included a 6-month diagnosis of Major Depressive Disorder (MDD) (95%) and/or 6-month Dysthymic Disorder (26.5%), or minor depression (two to four depressive symptoms lasting at least two weeks, 5.0%) according to DSM-IV-R criteria. Age-of-onset of depression did not serve as an selection criterion. Non-depressed older persons were recruited from general practices and were included when no lifetime diagnosis of depression was present. Exclusion criteria are (suspected) dementia, and insufficient command of the Dutch language. The study design of NESDO is described in detail elsewhere (Comijs et al., 2011).

For the current study, we selected all persons with a 6-month DSM-IV diagnosis of major depression, as assessed with the Dutch version of the Composite International Diagnostic Interview (CIDI) lifetime version 2.1 (World Health Organization 1997; Andrews and Peters 1998). The CIDI was conducted by specially trained clinical research staff. Persons with a diagnosis of minor depression (n=13) or dysthymia only (n=6) were excluded. In addition, individuals with incomplete data on CIDI items for depressive disorder were excluded (n=10), thus retaining a data set of 359 persons. Attrition was non-differential with respect to age and gender but, compared to included persons, individuals with missing data had more years of education (OR 1.55; 95% CI 1.06-2.17) and lower severity of depression, as measured by the Inventory of Depression Symptomatology (IDS) (OR 0.21; 95% CI 0.13-0.36).

Method

Assessment of indicator variables for LCA items

Ten depressive symptoms (Table 1) were used as indicator variables in the LCA analyses, including the depression key symptoms of the DSM-IV as assessed with the CIDI (World Health Organization 1997; Andrews and Peters 1998). The items were coded as 'not present' or 'present', except for the four items regarding change in appetite, weight, sleep

and psychomotor disturbance. For these latter items, four categories were created and coded as 'no change', 'decrease', 'increase' or 'both increase and decrease'.

Finally, in order to check the assumption of local independence, required for LCA, we examined the magnitude of bivariate correlation using Spearman's rho. Correlations ranging from <0.001 to 0.29 were found. Since these correlations are only small to moderate, we assume that the assumption of local independence for LCA was sufficiently met.

Subject characteristics

Classes were characterized using sociodemographic and clinical characteristics. Sociodemographic variables included age, gender and years of education. Clinical characteristics included age-of-onset of the depressive disorder, presence of a 6-month comorbid anxiety disorder, severity of depressive symptoms as assessed with the 30-item Inventory of Depressive Symptomatology (IDS) (Rush et al., 1996), and apathy as assessed with the Apathy Scale (Starkstein et al., 1992). Psychosocial variables included overall functioning, personality measures, childhood adversity, and life events, all as continuous measurements. Overall functioning was measured with the World Health Organization Disability Assessment Schedule II (WHODAS) (Chwastiak and Von Korff 2003; Buist-Bouwman et al., 2008). Personality measures included levels of neuroticism and extraversion, assessed using the Neo Five-Factor Inventory (NEO-FFI) (Costa and McCrae 1995; Hoekstra et al., 1996). Childhood adversity/trauma was assessed using a structured inventory derived from a Dutch longitudinal cohort study (NEMESIS) (De Graaf 2002). An index (range 0-4) was constructed incorporating the occurrence and frequency of 4 types of abuse before age 16 years (emotional neglect, psychological abuse, physical abuse, and sexual abuse). The number of negative life events in the last year was assessed by the Brugha questionnaire (Brugha 1985). Physical health indicators included current smoking status (current versus not smoking), pain, body mass index (BMI), metabolic syndrome, presence of cardiovascular disease, and ankle brachial pressure index. Pain was measured using the number of pain locations (range 0-7) listed in the Chronic Graded Pain scale (Von Korff 1992). Height and weight were measured and BMI was calculated as kilograms divided by meter squared. In addition, both the presence of metabolic syndrome (yes/no) and its individual components were measured, including waist circumference, plasma triglycerides, plasma high-density lipoprotein cholesterol (HDL-cholesterol), blood pressure and fasting plasma glucose. Cut-off values for metabolic syndrome were based on the adjusted Adult Treatment Panel (ATP III) criteria (Expert panel 2001), including waist circumference ≥ 88 cm, triglycerides ≥ 150 mg/dl, HDL-cholesterol < 50 mg/dl, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or use of antihypertensive drugs, fasting blood glucose ≥ 100 mg/dl or use of a hypoglycemic drug. Persons scoring positive on ≥ 3 criteria were considered to have a metabolic syndrome. Diabetes was defined as fasting plasma glucose level ≥ 7.0 mmol/l. The presence of cardiovascular disease was determined as assessed by self-report of coronary disease, angina pectoris, heart failure or a history of stroke, supported by appropriate medication use or being currently under treatment by a physician (see Vogelzangs et al., 2010 for details). Ankle brachial pressure index was used as an indicator of possible peripheral vascular disease.

Statistical analysis

LCA was performed, using Mplus version 5 (Muthén and Muthén 2007). Free from any a priori assumptions, data-driven techniques such as LCA cluster persons based on a given outcome. LCA, often described as a 'categorical equivalent' of factor analysis, assumes that an unobserved, latent categorical variable explains the association among a set of observed symptoms, like depressive symptoms. Data-driven calculations start with one class, suggesting one classification fitting for all persons. The persons are then successively allocated to an ascending number of classes, here up to 5 classes. To determine the number of classes best fitting the data, we examined the Bayesian Information Criterion (BIC), sample size adjusted BIC (ssaBIC), entropy, the Lo-Mendell-Rubin likelihood ratio test (LMR), the bootstrapped likelihood ratio test (BLRT), the proportion of respondents in each computed class, and the interpretability and clinical relevance of the latent classes.

Of the traditionally used 'information criteria', the BIC performs best (Nylund et al., 2007). Lower BIC and ssaBIC values indicate better model fit. The Lo-Mendell-Rubin test (LMR) provides a p-value, which indicates whether the k-1 class model is rejected in favor of the k class model. Entropy, as a measure of the quality of classification, is presented for models with more than one class. Values for entropy can range from 0 to 1, with values closer to 1 indicating greater classification accuracy. In order to identify clinically relevant classes, we aimed to identify classes greater than 5% of the sample. Currently there is no consensus as to which criterion best identifies the best fitting number of classes, although reasons exist to regard the BLRT as superior compared to other parameters of fit (Nylund et al., 2007).

After identification of the classes and assignment of participants to their most likely class, the probability of occurrence of each depressive symptom per class was examined using Cramer's V as a measurement of a symptom's distinguishing power. Next, the distribution of the aforementioned characteristics across the identified classes was examined, using two-tailed chi-square statistics for categorical variables, one-way-analysis of variance statistics (ANOVA) for continuous variables, and Kruskal-Wallis tests for nonparametric continuous variables. Additional comparisons were performed to test for differences between pairs of classes. Multinomial logistic regression analyses were conducted to examine multivariable determinants of identified classes. All models were first adjusted for sociodemographic items (age, gender, years of education), with additional adjustment for all variables being significantly associated in bivariate analyses. For this purpose, a p-value <0.10 was considered statistically significant. All comparisons were conducted using SPSS version 21.0 for Windows (51).

Results

The total sample consisted of 359 depressed older people, of whom 66.0% were females, with a mean age of 70.5 (± SD 7.4) years and a mean age of depression onset of 48.5 (± SD 20.3) years.

Considering the various parameters of fit (data available upon request), the best-fitting model was the three-class model, with the lowest ssaBIC (4593.2) and a significant BLRT (p<0.001). From the four-class model onwards, the BLRT was no longer significant, indicating that adding more classes to the model did not improve model fit. Although some parameters pointed at a two-class model (highest entropy = 0.87; lowest BIC 4724.1; and a significant LMRT; p=0.001), the superiority of the BLRT has been reported (Nylund et al., 2007). In addition, the two-class model lumped together the moderate and melancholic class and was, therefore, considered clinically less relevant.

Table 1 shows the probability of the occurrence of different depressive symptoms in the three identified latent classes. The first class (prevalence 15.0%) showed a symptom pattern with the highest occurrence of both weight gain and increased appetite. The second class (prevalence 38.4%) was characterized by the highest occurrence of weight loss, decreased appetite, less sleep, and psychomotor changes. The third class (prevalence 46.5%) had the lowest occurrence of all ten depressive symptoms; hereafter, these classes are labeled "atypical", "melancholic" class, and "moderate severe" class, respectively. Although these labels resemble specific DSM specifiers, we explicitly do not intend to refer to these DSM specifiers. These labels were chosen to facilitate comparisons with previous data-driven studies in younger adults, finding a comparable class that has been dubbed 'atypical' (Lamers et al., 2010; 2013; 2015; Rodgers et al. 2014; Alexandrino et al. 2015). Strong distinguishing symptoms between classes were weight (Cramer's V= 0.59) and appetite (Cramer's V=0.79) and, to a lesser extent, psychomotor changes (Cramer's V=0.26) and loss of interest (Cramer's V=0.25).

Table 2 shows the sociodemographic and clinical characteristics of the three identified latent classes. Within the severe atypical class, there was a preponderance of females, with a slightly lower mean age compared to both other classes (p=0.002). The moderate class had the lowest depression severity and the lowest number of current anxiety disorders, confirming the lower severity in this class. There were no significant group differences for the psychosocial variables. As for physical health characteristics, metabolic syndrome was most prevalent within the atypical class, and least prevalent within the melancholic class (p=0.003). BMI was significantly higher in the severe atypical class compared to both the severe melancholic and moderate class (p<0.001). Presence of heart disease was significantly lower in the melancholic class compared to both other classes.

To evaluate whether characteristics were independently associated with class membership, multinomial logistic regression analyses were performed, comparing the two severe classes with the moderate class, and the two severe classes with each other (**Table 3**). Analyses were first adjusted for sociodemographic items (gender, age, years of education) and for variables that differed across classes in bivariate analyses with a p-value

=< 0.10, including age-of-onset, depression severity, presence of 1-year anxiety diagnosis, presence of heart disease and BMI. To avoid multicollinearity, metabolic syndrome was not included as this was highly correlated to both BMI (rs=0.52, p<0.001) and cardiovascular disease (rs=0.12, p=0.03). Using post-hoc tests we explored whether the results would differ if BMI and cardiovascular disease were replaced by metabolic syndrome; however, the results were similar. In the fully adjusted models, female sex (OR=4.57; 95% CI=1.96-10.66), lower age (OR=0.57; 95% CI=0.38-0.88), and higher BMI (OR=1.66; 95% CI=1.17-2.36) were significantly associated with the atypical class as compared to the moderate class. Likewise, female sex (OR=2.93; 95% CI=1.22-7.05), lower age (OR=0.63, 95% CI=0.41-0.98), higher BMI (OR=2.38; 95% CI=1.63-3.48) and cardiovascular disease (OR=2.78; 95% CI=1.09-7.09) were significantly associated with the atypical class as compared to the severe melancholic class. On the other hand, higher depression severity (OR=1.33; 95% CI=1.03-1.73), a lower BMI (OR=0.70; 95% CI=0.52-0.93) and a lower number of cardiovascular disease (OR=0.41; 95% CI=0.20-0.83) were significantly associated with melancholic class, as compared to the moderate class.

Since both BMI and metabolic syndrome showed a significant difference between groups, and since atypical depression is thought to be associated with metabolic syndrome (Lamers et al., 2010; Vogelzangs et al., 2011; Mansur et al., 2015), in post-hoc analyses we further explored the association between the separate criteria of metabolic syndrome and class membership (**Table 4**). Multinomial logistic regression analyses were performed to compare both severe classes with the moderate class, and the severe classes with each other. The covariates used were similar to those used in Table 3, except for BMI. The prevalence of metabolic syndrome was significantly higher in the atypical class compared to both the melancholic class (OR=3.12; 95% CI=1.52-6.40) and the moderate class (OR=2.08; 95% CI=1.02-4.22). A higher waist circumference was significantly higher in the atypical class compared to both the melancholic class (OR=1.84; 95% CI=1.27-2.66) and the atypical class (OR=1.44; 95% CI=1.01-2.06). Higher systolic blood pressure (OR=1.44; 95% CI=1.01-2.05) was significantly associated with the atypical class, as compared to the melancholic class. A lower blood glucose was significantly associated with the melancholic class (OR=0.64; 95% CI=0.47-0.86) as compared to the moderate class.

Next, to examine whether weight gain was induced by antidepressant use, instead of being an indicator of a specific depression subtype, we performed post-hoc analyses to explore whether including current antidepressant in the multivariate analyses had any significant effect on the odds ratios. Antidepressants included were selective serotonin-reuptake inhibitors (ATC-code N06AB), non-selective monoamine reuptake inhibitors (ATC-code N06AA), non-selective monoamine oxidase inhibitors (ATC-code N06AF), or other antidepressants (ATC-code N06AX). Prevalence of current antidepressant use was 72.1% in the entire population, 63% in the atypical subtype, 81.9% in the melancholic subtype, and 67.1 in the moderate subtype ($\chi 2$(df)=11.88(4), p=0.02). After additional adjustment of regression analyses for antidepressant use, odds ratios remained largely similar (results available upon request). In contrast to the expectations, that antidepressant use may induce weight gain, and hence would be associated with atypical class, antidepressant use was only significantly associated with melancholic class (OR=2.12; 95%CI 1.18-3.85, as compared to the moderate class; and OR=2.50; 95% CI 1.12-5.60, as compared to atypical

class). Notably, antidepressant use entailed current use, whereas lifetime depression symptoms served as indicator variables for the LCA. Therefore, antidepressant use were only included in post-hoc analyses, and not in the main analyses in this study.

Discussion

This study aimed to empirically identify distinct depressive subtypes among depressed older persons, and to investigate whether these subtypes differ with respect to sociodemographic and clinical characteristics. The most prevalent class, as identified by LCA, was a moderate severe class (prevalence 46.5%), followed by a severe melancholic class (prevalence 38.4%) and a severe atypical class (prevalence 15.0%). The strongest distinguishing features between the three classes were appetite and weight and, to a lesser extent, psychomotor symptoms and loss of interest. The severe atypical class had the highest prevalence of females, the lowest mean age, the highest BMI and highest prevalence of both cardiovascular disease and metabolic syndrome, as compared to the melancholic class.

Our findings are in line with previous studies. To date, several data-driven studies have been performed and, although the number and symptom patterns of identified classes vary between studies (depending on their design/methods), there is increasing evidence that within the heterogeneity of depressive disorders, atypical and melancholic subtypes may constitute clinically relevant subtypes (Kendler et al., 1996; Sullivan et al., 1998; Alexandrino et al., 2014; Li et al., 2014; Rodgers et al., 2014; Lamers et al., 2015). Although our atypical group does not exactly matches the DSM definition of atypical depression, we found similar symptoms (increased weight and appetite), characteristics (higher prevalence of female, lower mean age, lower age-of-onset) and co-occurring pathophysiology (higher prevalence of metabolic syndrome). Furthermore, previous data-driven studies have found similar classes, labeling them atypical, with similar characteristics (Novick et al. 2005; Lamers et al. 2010; Li et al. 2014; Rodgers et al. 2014; Alexandrino et al. 2014) and biological disturbances(Lamers et al. 2013; Lasserre et al. 2016; Rethorst et al. 2016), that largely correspond with the DSM-based atypical depression. This underlines the idea both approaches distinguish the same atypical subtype.

However, whereas most data-driven studies were performed in younger adult persons, data on older persons are less abundant. To our knowledge, previous data-driven studies in older persons were mainly community based (Lee et al., 2012; Mezuk and Kendler 2012; Hybels et al., 2013). Further, these studies either used appetite and weight change as one aggregated item (Lee et al., 2012), did not distinguish 'increased appetite' (Hybels et al., 2011, 2012; Mezuk and Kendler 2012), did only use 'decreased appetite' and 'weight loss' (Hybels et al., 2009), or used none of these items except for 'decreased appetite' (Hybels et al., 2013). However, not including both increased and decreased appetite and weight may hamper identification of specific subtypes as found in adults, characterized by, e.g., an increase in appetite or weight (e.g. atypical subtype). Our findings extend previous findings by showing that in late-life depression (using disaggregated symptoms) an

atypical and a melancholic subtype can be distinguished, and a relation with metabolic disease was found. This is in line with previous findings in younger adults (Kendler et al., 1996; Sullivan et al., 1998; Lamers et al., 2010; Li et al., 2014).

Considering the distribution of the classes identified with LCA, our prevalence rates seem to differ from previous studies that also investigated disaggregated symptoms in LCA. Studies in younger adults demonstrated a relatively higher prevalence of atypical depression, with rates as high as 24.6% (Lamers et al., 2010, 2012; Rodgers et al., 2013). Since increased appetite and weight gain are prominent differentiating features to identify atypical depressive subtypes (Lamers et al., 2010, 2013; Li et al., 2014), frequently occurring frailty in older persons, being associated with weight loss (and the development of depression) (Andrew and Rockwood 2007; Hegeman et al., 2012; Collard et al., 2014, 2015a, 2015b), may impact on prevalence rates of atypical subtypes in this population. Second, the prevalence of moderate severe depression is about 1.5 times as high in our older sample (46.5%) compared to younger adult studies [prevalence rates: 29.1-34.2% (Lamers et al., 2012a; Rodgers et al., 2014, respectively)]. This is in line with previous findings indicating that depression may become less severe with age, although these latter findings are based on the DSM criteria (Judd et al., 2002; Fiske et al., 2009). Alternatively, depressive symptom endorsement may change across ages, resulting in lower depression severity on instruments validated for use in younger adults and, hence, the risk of underestimating depression severity in older persons. For example, a decline of DSM-IV symptoms (such as guilt and anhedonia) was shown in older persons as compared to younger adults (Caine et al., 1994; meta-analysis Hegeman et al., 2012). Since these items are at the core of commonly used instruments like the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HDRS), it is conceivable that this influences measurement of the level of severity in older persons. Finally, late-onset depression may be of a different nature than early-onset depression. Whereas early-onset depression may be characterized by a relatively higher percentage of atypical depression, the pathogenesis and phenomenology of late-onset depression may differ, therefore reducing the proportion of atypical depression within the depressed older population.

Earlier studies found a higher prevalence of psychomotor symptoms in depressed older persons compared to depressed younger persons, but only for agitation (Hegeman et al., 2012), whereas we found a higher prevalence for both retardation alone and co-occurring with agitation. In the present cohort of depressed older persons, psychomotor symptoms were more prevalent than in several younger adult studies, in which the prevalence of psychomotor changes ranged from 46.5-59.6% (Lamers et al., 2010; Rodgers et al., 2014), compared to 27.6% in our study. However, we found that psychomotor symptoms were only moderately distinguishing features between the classes (Cramer's V= 0.26). This is remarkable, since psychomotor symptoms are commonly seen as a feature of melancholic depression (Parker et al., 2010). An explanation for our finding might be that the MADRS and CIDI are unable to reliably measure psychomotor symptoms. Use of a measurement that focuses on psychomotor symptoms of depression, such as the CORE (Parker et al., 1994; Parker 2007; Rhebergen et al., 2011; Attu et al., 2012), may further differentiate depressive subtypes. Notably, apathy differed neither across classes, whereas loss of

interest and psychomotor symptoms were moderately strong distinguishing features between classes. In clinical practice apathy may mimic psychomotor retardation or loss of interest, whereas our results suggest that apathy (as measured with the Apathy Scale) measures different clinical features/phenomena.

In the present study, the differences in characteristics found between our melancholic and atypical classes are in line with other studies (Schotte et al., 1997; Lamers et al., 2010, 2012). Considering the preponderance of females in the atypical subtype, it has been suggested that, especially in women, obesity co-occurs with depression (Luppino et al., 2010; Marijnissen et al., 2011; Milaneschi et al., 2014), which could explain the higher prevalence of females in the atypical class. The lower use of antidepressants in the atypical class compared to both other classes further adds to the idea that increased weight and appetite are part of the symptom profile rather than a result of antidepressant use. In post-hoc analyses we found that additional adjustment for antidepressant use did not alter our findings. However, our database only includes current antidepressant use, while we used lifetime symptoms for the determining the classes. Furthermore, in a study with a naturalistic design like we used, no reliable statement can be made regarding the impact of antidepressant use. Lastly, we used a cross-sectional design, making it impossible to draw causal inferences. Although the lower age within the atypical group is also in accordance with others (Angst et al., 2002; Novick et al., 2005; Halbreich and Kahn. 2007; Lamers et al., 2010), an explanation for this is lacking.

Finally, notable findings are the low prevalence of cardiovascular disease within the melancholic class, and the high prevalence of metabolic syndrome within the atypical class. Studies including younger adults also found a higher prevalence of metabolic syndrome within atypical depression (Lamers et al., 2010, 2013; Vogelzangs et al., 2014), but did not find a higher number of cardiovascular diseases. It is possible that atypical depression, which more often co-occurs with metabolic syndrome at a younger age, constitutes a phenotype with a higher risk of cardiovascular disease at an older age. In younger adults, studies have found that treating components of metabolic syndrome might also benefit depressive symptoms: persons with atypical depression benefit the most from exercise (Rethorst et al. 2016), and addition of the anti-inflammatory drug celecoxib lowers IL-6 rates (Abbasi et al. 2012), which are elevated in atypical depression (Lamers et al. 2013). Our finding stresses the importance of preventive cardiovascular management in persons with atypical depression, as well as studies on the effect of treating metabolic syndrome components and inflammation in depressed older persons.

The results of this study should be interpreted in the context of various strengths and limitations. A strength is that this study is the first to demonstrate depression subtypes, both in severity and symptom profile, in an older population with major depression. In addition, a wide selection of characteristics were examined.

However, some limitations also need to be addressed. The strongest distinguishing symptoms between classes were weight (Cramer's V= 0.59) and appetite (Cramer's V=0.79). One could argue that (in theory) these constructs are highly correlated, as was also the case in a study using factor mixture modelling (an extension of LCA) in a general population

sample (Ten Have et al., 2016); however, the correlation coefficient was small (rs =0.293). Albeit this seems counterintuitive, we hypothesize that, in older persons, these putative correlating items may be less correlated than in younger adults, since weight loss is a common problem and is associated with a broad range of physiological and pathological factors in aging. Also, using weight and appetite as separate items in LCA allows comparison with a large body of literature on adult LCA (Kendler et al., 1996; Sullivan et al., 1998; Lamers et al., 2010; Hybels et al., 2012; Mezuk and Kendler 2012; Rodgers et al., 2013; Alexandrino et al., 2014). However, despite potential issues with violation of the local independence assumption in adult studies, atypical and melancholic subtypes found in these latter studies had differential biology (Mansur et al., 2011; Lamers et al., 2013; Liu et al., 2014; Vogelzangs et al., 2014) and genetic differences (Milaneschi et al., 2016), highlighting the relevance of the distinction by appetite and weight. Further, due to the cross-sectional design of the study, it remains unknown to what extent the identified classes are stable over time. In addition, the lack of a comparison group of persons in the same age cohort without current depression limits thorough examination to what extent current depression state or age may impact on the identified classes, based on lifetime symptoms. However, studies in younger adults demonstrated a high diagnostic stability of LCA-derived subtypes (Lamers et al., 2012b; Rodgers et al., 2013), with especially great stability of the atypical class ranging from 70-79%, thus suggesting etiologically distinct entities. Schaakxs et al. (2017) found stability of depression severity with aging, albeit with different symptom prominence. Symptoms more prominent in older age were early awakening and problems with sleeping during the night, while symptoms occurring more often in younger age were interpersonal sensitivity and sleeping too much. Future longitudinal studies should examine whether classes are stable over time in older adults, too.

In addition, persons with missing data had lower depression severity and a higher education level. Had they not been excluded, they would probably have been allocated to the moderate class; this would have had an impact on the distribution of classes. Regarding education, the attrition presumably does not impact our findings, as there was no significant difference in education across the classes.

To conclude, this study applied data-driven methods to identify classes of depressive disorder in a large cohort of older persons. In line with studies in younger adults, three classes were identified (i.e. an atypical, melancholic and moderate severe depression), with appetite and weight being the main distinguishing features. The increased prevalence of metabolic syndrome within the atypical class, and the decreased prevalence of cardiovascular disease within the melancholic subtype (the latter not previously found in younger adult populations) illustrates the importance of differentiating into depressive subtypes, particularly in the older population. Furthermore, differentiation into depressive subtypes in late-life depression may facilitate further research on the underlying etiology of depression, the role of metabolic abnormalities, and the predictive value of subtypes on treatment response.

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Conflict of interest
All authors declare that they have no conflict of interests.

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Table 1. Estimated symptom profile probabilities of endorsing depressive symptoms from LCA (n=359)

Class Description	Total sample	Class 1, Severe atypical	Class 2, Severe melancholic	Class 3, Moderate severity	Cramer V Statistic	P-value(df)
Prevalence	359 (100%)	54 (15.0%)	138 (38.4%)	167 (46.5%)		
DSM-IV criterion symptoms						
Depressed mood	0.97	0.94	1.00	0.95	0.14	0.028(2)
Loss of interest	0.92	0.96	0.99	0.86	0.25	<.001(2)
Weight					0.59	<.001(8)
No weight change	0.57	0.54	0.27	0.84		
Weight loss	0.34	0.00	0.71	0.14		
Weight gain	0.06	0.37	0.01	0.00		
Both gain and loss	0.03	0.09	0.01	0.02		
Appetite					0.79	<.001(8)
No change in appetite	0.30	0.04	0.02	0.61		
Decreased appetite	0.53	0.00	0.92	0.38		
Increased appetite	0.12	0.80	0.00	0.00		
Both increase and decrease	0.05	0.17	0.06	0.01		
Sleep					0.16	0.004(8)
No change in sleep	0.10	0.09	0.04	0.14		
Less sleep	0.60	0.48	0.66	0.59		
More sleep	0.08	0.06	0.09	0.08		
Both less and more sleep	0.22	0.37	0.22	0.17		
Psychomotor					0.26	<.001(8)
No psychomotor change	0.28	0.28	0.11	0.41		
Psychomotor retardation	0.30	0.24	0.33	0.30		
Psychomotor agitation	0.15	0.17	0.17	0.16		
Both agitation and retardation	0.26	0.32	0.39	0.13		
Fatigue/energy loss	0.91	0.94	0.98	0.84	0.22	<.001(2)
Guilt/worthlessness	0.79	0.85	0.87	0.71	0.19	0.002(2)
Concentration/ indecisiveness	0.96	1.00	0.98	0.94	0.12	0.063(2)
Suicidal ideation	0.69	0.70	0.79	0.59	0.20	0.001(2)

Table 2. Characteristics of latent classes (n=359)

	Total sample	Class 1, Severe atypical (n=54)	Class 2, Severe melancholic (n=138)	Class 3, Moderate severity (n=167)	X2, F, (df), overall P-value
Prevalence	359 (100%)	54 (15.0%)	138 (38.4%)	167 (46.5%)	
Sociodemographics					
Sex, female, %	66.0	83.3	68.8	58.1	12.39(2), 0.002[1]
Age, mean (SD), years	70.5(7.4)	68.3(6.7)	70.5(7.1)	71.5(7.7)	3.95(2), 0.02[2]
Education, mean (SD), years	10.4(3.4)	11.0(3.7)	10.1(3.2)	10.4(3.4)	1.21(2), 0.30[2]
Clinical characteristics					
Age onset, mean (SD) years	48.5(20.3)	41.7(20.7)	49.6(19.1)	49.9(20.8)	3.58(2), 0.04[2]
Severity (IDS), mean (SD)	30.5(13.0)	32.2(11.8)	32.6(14.2)	28.0(11.8)	5.20(2), 0.01[2]
Presence 1 year anxiety diagnosis, %	40.1	38.9	48.6	33.5	7.13(2), 0.03[1]
Apathy, mean (SD)	17.2(5.6)	17.2(5.9)	17.2(5.7)	17.3(5.5)	0.02(2), 0.98[2]
Psychosocial					
Functioning, mean (SD)	33.3(15.8)	34.7(16.4)	35.0(16.3)	31.4(15.2)	2.23(2), 0.12[2]
Neuroticism, mean (SD)	39.0(7.0)	40.3(7.2)	38.7(6.7)	38.8(7.3)	1.00(2), 0.37[2]
Extraversion, mean (SD)	33.7(6.5)	34.3(6.9)	34.2(6.8)	33.2(6.2)	0.79(2), 0.46[2]
Childhood trauma index, mean (SD)	1.0(1.2)	1.2(1.3)	1.1(1.2)	0.9(1.2)	1.75(2), 0.18[2]
No. negative life events, median (IQR)	0.0(1)	0.0(1)	1.0(1)	0.0(1)	3.94(2), 0.14[3]
Physical health					
Current smoking, %	27.0	31.5	26.5	26.5	0.64(2), 0.75[1]
Chronic pain grade, median (IQR)	2.00(2)	2.00(3)	2.00(2)	2.00(2)	4.90(2), 0.09[3]
Presence of metabolic syndrome, %	44.0	63.0	35.5	44.9	11.98(2), <0.01[1]
Body mass index, median (IQR)	26.3(4.4)	27.7 (5.9)	25.3 (5.65)	25.3 (5.32)	23.74(2), <0.01[3]
Cardiovascular disease, %	17.8	24.1	10.1	22.2	9.13(2), 0.01[1]
Diabetes, %	12.8	11.1	9.4	13.9	1.35(2), 0.48[1]
Ankle brachial index, median (IQR)	1.1(0.2)	1.1(0.4)	1.1(0.2)	1.1(0.2)	0.37(2), 0.83[3]

Tests used: [1]Chi-square ($\chi 2$); [2]Anova (F); [3]Kruskal-Wallis ($\chi 2$)

Table 3. Odds Ratios and 95% CIs for the Multivariable Comparison of the three Latent Classes (N=359)

	Comparison of severe classes to moderate class (=reference)		Severe Atypical vs Severe Melancholic (=ref) OR (95% CI)
	Severe Atypical, OR (95% CI)	Severe Melancholic, OR (95% CI)	
Sociodemographics			
Female	4.55(1.95-10.59)	1.60(0.94-2.71)	2.93(1.22-7.05)
Age	0.58(0.38-0.89)	0.90(0.69-1.19)	0.65(0.42-1.00)
Education in years	1.38(0.96-2.00)	1.02(0.79-1.33)	1.35(0.93-1.97)
Clinical characteristics			
Age of onset	0.81(0.56-1.18)	1.03(0.78-1.35)	0.79(0.54-1.16)
Presence 1-year anxiety diagnosis	0.87(0.42-1.82)	1.47(0.87-2.48)	0.55(0.26-1.15)
Severity	0.95(0.65-1.40)	1.33(1.03-1.73)	0.71(0.48-1.06)
Antidepressant use	1.17(0.49-2.58)	2.12(1.18-3.85)	2.50(1.12-5.60)
Physical health			
Chronic pain grade	1.20(0.82-1.76)	1.10(0.83-1.44)	1.09(0.74-1.62)
Body mass index	1.67(1.18-2.36)	0.68(0.51-0.91)	2.45(1.67-3.59)
Cardiovascular disease	1.13(0.49-2.58)	0.44(0.21-0.89)	2.58(1.00-6.64)

Corrected for every other item in the table: gender, age, years of education, age of onset, presence of 1-year anxiety diagnosis, severity, antidepressant use, chronic pain grade, body mass index, cardiovascular disease. Exp(B) and 95% CI for Exp(B)

Table 4. Odds Ratios and 95% CIs for Metabolic Syndrome and the Separate Criteria (N=359)

	Comparison of severe classes to moderate class (=reference)		Severe Atypical vs Severe Melancholic (=ref), OR (95% CI)
	Severe Atypical, OR (95% CI)	Severe Melancholic, OR (95% CI)	
Metabolic syndrome	2.08(1.02-4.22)	0.63(0.38-1.05)	3.32(1.60-6.88)
Waist circumference	1.44(1.01-2.06)	0.76(0.57-1.01)	1.89(1.30-2.76)
Triglycerides	1.08(0.77-1.52)	1.02(0.79-1.32)	1.06(0.75-1.49)
HDL cholesterol	0.89(0.62-1.28)	1.03(0.80-1.33)	0.85(0.59-1.22)
Systolic pressure	1.24(0.87-1.76)	0.85(0.66-1.10)	1.45(1.02-2.08)
Diastolic pressure	1.21(0.84-1.72)	0.88(0.68-1.14)	1.37(0.96-1.96)
Blood glucose	0.73(0.50-1.07)	0.64(0.48-0.87)	1.14(0.75-1.75)

Corrected for variables in Table 3 except BMI: gender, age, years of education, age of onset, presence of 1-year anxiety diagnosis, severity, antidepressant use, chronic pain grade and presence of cardiovascular disease

CHAPTER 3

Inflammatory markers and cortisol parameters across depressive subtypes in an older cohort

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Background: There is growing evidence that inflammatory and cortisol dysregulation are underlying pathophysiological mechanisms in the aetiology of major depressive disorder, particularly in younger adults. However, findings of biological disturbances in late-life depression have been divergent, probably due to the even greater heterogeneity of depression in older adults with aging processes influencing biological factors. Using empirically derived subtypes may enable the identification of biological disturbances underlying depression in older adults.

Methods: Data were used from the Netherlands Study of Depression in Older Persons (NESDO) of 359 persons aged 60 years or older, with a current diagnosis of major depressive disorder (MDD). Depressive subtypes (severe atypical, severe melancholic, and moderate severe subtype) that were previously identified through latent class analysis (LCA), were examined on differences in inflammatory markers including C-reactive protein (CRP), interleukin-6 (IL-6), and neutrophil gelatinase-associated lipocalin (NGAL), as well as cortisol parameters.

Results: No differences in measures for inflammation and cortisol across subtypes were observed in uncorrected or for putative confounders corrected models.

Limitations: Several subjects had missing cortisol and inflammatory data, decreasing the power. However, results did not change after imputation analysis.

Discussion: In this cohort of depressed older adults, no differences in inflammation and cortisol measures between depression subtypes were observed. This is probably due to the many (patho) physiological processes that are involved in aging, thereby clouding the results.

Key words: latent class analysis; depression subtypes; inflammation; cortisol; atypical depression; melancholic depression

Abstract

Background

Major depressive disorder is a common disease, with prevalence rates in the older population ranging from 1-16% (Djernes 2006). However, the aetiology and pathogenesis of major depressive disorder remain largely unknown. Studies have suggested that possible underlying biological mechanisms include disturbances in inflammation pathways and the hypothalamic-pituitary-adrenal (HPA)-axis, which could predict course and treatment response (Berk et al., 2013; Miller et al., 2015; Martinez et al., 2016; Zalli et al., 2016). However, to date findings are inconsistent.

Regarding inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6), studies in older depressed adults have found mainly higher inflammatory markers in depressed persons compared to healthy controls (Biggelaar et al., 2007; Bremmer et al., 2008; Martinez et al., 2016). A meta-analysis concluded that of several inflammation markers, only IL-6 had a consistent positive correlation with late-life depression (Martinez et al., 2016). Findings on cortisol measures in older depressed persons are inconsistent too, with some studies finding higher cortisol measures (Balardin et al., 2011; Kuo et al., 2011; Belvederi Murri et al., 2014; Rhebergen et al., 2015), whereas others reported a U-shaped association between cortisol and depression in older adults (Bremmer et al., 2007; Penninx et al., 2007).

There are indications that these inconsistent findings might be due to the considerable heterogeneity of depression in older adults, stressing the importance of subtyping depression when researching underlying pathophysiological mechanisms. Within younger adults, inflammatory and cortisol dysregulations have been linked to specific subtypes of depression (Gold and Chrousos 2002; Stetler and Miller 2011; Lamers et al., 2013; Penninx et al., 2013). A melancholic subtype, identified by data-driven techniques, was linked to higher cortisol measures compared to other subtypes and healthy controls. An atypical subtype, characterized by increased appetite and weight, was linked to increased inflammatory markers (Lamers et al., 2013), and seemed to have a differential genetic profile (Milaneschi et al., 2016). Within older people, there are indications as well that the degree and quality of biological dysregulation may be correlated with both the severity of depression (Viinamäki et al., 2009; Duivis et al., 2011; Kahl et al., 2012) and depression characteristics (Vogelzangs et al., 2014). Data-driven subtypes of depression in older adults have been identified previously (Hybels et al., 2009; Lee et al., 2012; Mezuk & Kendler 2012; Veltman et al., 2017), but research on biological disturbances within these subtypes is lacking.

Therefore, to gain more insight into the role of immunometabolism and functioning of the HPA-axis within depressed older adults, we examined inflammatory markers and cortisol parameters within different subtypes of depression, as determined previously in this cohort of older people by latent class analysis (LCA) (Veltman et al., 2017). We hypothesized that inflammatory markers are higher in the atypical subtype compared to the other subtypes, and that cortisol parameters are higher in the melancholic subtype of depression.

Methods

Sample

Data were derived from the baseline measurements of the Netherlands Study of Depression in Older persons (NESDO), a longitudinal multi-site naturalistic cohort study, examining predictors of the course and consequences of depression in older people. The NESDO cohort (n=510) consists of persons aged 60-93 years, including 378 persons with a depressive disorder in the previous 6 months, and 132 non-depressed controls. The study protocol of NESDO has been approved centrally by the Ethical Review Board of the VU University Medical Center, and subsequently by the local ethical review boards of all participating universities. Written informed consent was obtained from all participants at the start of the baseline assessment. The study design of NESDO is described in detail elsewhere (Comijs et al., 2011).

For the current study, we selected all persons with a 6-month DSM-IV diagnosis of major depression (n=359), as assessed with the Dutch version of the Composite International Diagnostic Interview (CIDI) lifetime version 2.1 (World Health Organization 1997; Andrews & Peters 1998). The CIDI was conducted by trained clinical research staff. None of the participants used corticosteroids. Seventy-seven persons had missing data on all cortisol measures and were excluded from the cortisol analyses. Ten persons had missing data on all inflammatory markers and were excluded from the inflammation analyses. Four persons had missing values on all inflammatory markers and cortisol measures, and were excluded from all analyses, thus retaining a final study population of 355 persons on baseline characteristics, 349 persons on inflammatory markers, and 282 persons on cortisol measures. Attrition was non-differential with respect to sex, age, education level, severity of depression, and subtype of depression.

Depressive subtypes

The subtypes previously identified in this cohort by LCA were used. For a detailed description we refer to Veltman et al., (2017). In short, ten depressive symptoms were used as indicator variables in the LCA analyses, including the depression key symptoms of the DSM-IV as assessed with the CIDI (World Health Organization 1997; Andrews & Peters 1998). Three subtypes were identified: a severe atypical subtype (prevalence 15.0%), characterized by increased appetite and weight; a severe melancholic subtype (prevalence 38.4%), characterized by decreased appetite and weight; and a moderate severe subtype (prevalence 46.5%), characterized by lower symptom severity on all items. The subtypes are labelled “severe atypical”, “severe melancholic”, and “moderate severe” subtype, respectively. Although these labels resemble specific DSM specifiers, we do not intend to refer to these DSM specifiers. These labels were chosen to facilitate comparisons with previous studies (e.g. Lamers et al., 2013).

Biological measures

Inflammatory measures
Inflammatory markers included C-reactive protein (CRP), interleukin-6 (IL-6), and neutrophil gelatinase-associated lipocalin (NGAL). Fasting blood samples were obtained in the morning between 8 and 9 am after an overnight fast and kept frozen at -80°C. High-sensitivity plasma levels of CRP were measured in duplicate by an immunoturbidimetric assay (Tina-quant CRPHS, Roche Diagnostics, Mannheim, Germany). Plasma IL-6 levels were measured in duplicate by a high sensitivity ELISA (PeliKine Compact™ ELISA, Sanquin, Amsterdam, The Netherlands). Intra- and inter-assay coefficients of variation were 2% and 2% for CRP, and 8% and 12% for IL-6, respectively. Plasma NGAL levels, an inflammatory marker earlier associated with late-life depression (Naudé et al., 2013) were quantified via a constructed sandwich ELISA, with the absorbance being determined at 492nm and 620nm using an ELISA reader (Asys UVM 340, Biochrom, Cambridge, UK). The inter- and intra-assay coefficients of variation were 2% and 5%, respectively. For a detailed explanation we refer to Naudé et al., (2013). Persons with a CRP value above ten (N=33) were excluded, as this indicates a current inflammatory process as part of a somatic disease, which may interfere with a putative biological mechanism associated with a certain depressive subtype.

Cortisol
Respondents were instructed to collect saliva samples at home on two consecutive days shortly after the interview at baseline. Instructions concerning saliva sampling prohibited eating, drinking tea or coffee or brushing teeth within 15 minutes before sampling. Furthermore, no dental work 24 hours prior to sampling was allowed. Saliva samples were obtained using Salivettes (Sarstedt, Germany) at six time points; at the time of awakening (T1), 30 minutes post-awakening (T2), 45 minutes post-awakening (T3), 60 minutes post-awakening (T4) and at 22:00 h (T5). The salivettes were restored in the tube labeled with date and time. After collecting all samples, the persons were asked to return the samples by post to the research center. After receipt, salivettes were centrifuged at 2000 g for ten minutes, aliquoted and stored at –80°C. Cortisol analysis was performed by competitive electrochemiluminescence immunoassay (E170 Roche, Switzerland). The functional detection limit was 2.5 nmol/l and the intra- and inter-assay variability coefficients in the measuring range were less than 10%. A random selection of 22 assays were repeated if cortisol measures were high (> 60 nmol/L); 19 high vales remained high after reassessment and the mean of the values was used. Three high values became lower after reassessment and were reassessed for a second time. All three remained low and the mean of the two low values was used.

Cortisol awakening response
From the four saliva samples taken within 1 h after awakening (T1 to T4), we calculated the area under the curve with respect to the increase (AUCi) and with respect to the ground (AUCg) using Pruessner's formulas (Pruessner et al., 2003). The AUCg is an estimate of the total cortisol secretion over the first hour after awakening, whereas the AUCi is a measure of the dynamics of the cortisol awakening response (CAR), more related to the sensitivity of the system, emphasizing changes over time after awakening (Edwards et al.,

2001; Fekedulegn et al., 2007; Schmidt-Reinwald et al., 1999). AUCi and AUCg could be calculated for all persons for whom all four morning samples were available (n=335). For those with 1 missing morning cortisol value (n=53) the missing value was imputed using linear regression analyses including information on the available three cortisol measures, sex, age, awakening time, and smoking status (see also Vreeburg et al., 2009a; Rhebergen et al., 2015). After imputation, AUCs could be calculated for 267 persons.

Diurnal slope
Diurnal slope was calculated by subtraction of the evening sample (T5) from the sample at awakening (T1) resulting in the decline in cortisol levels during the day. Due to missing samples at T1 or T5, diurnal slope could be calculated for 400 persons.

Covariates and descriptive variables
Subtypes were characterized using sociodemographic and clinical characteristics. Sociodemographic variables included age, gender and years of education. Clinical characteristics included age of onset of the depressive disorder, presence of 1-year comorbid anxiety disorder, both assessed by the CIDI, and severity of depressive symptoms as assessed with the 30-item Inventory of Depressive Symptomatology (IDS) (Rush et al., 1996). Cognitive functioning was measured with the Mini Mental State Examination (MMSE) (Folstein et al., 1975).

Physical health indicators included smoking status; pain using the number of pain locations (range 0-7) listed in the Chronic Graded Pain scale (Von Korff 1992); presence of metabolic syndrome as assessed according to the adjusted Adult Treatment Panel (ATP III) criteria (Expert panel, 2001); body mass index (BMI); presence of cardiovascular disease as assessed by self-report of coronary disease, angina pectoris, heart failure or a history of stroke, and supported by appropriate medication use or being currently under treatment by a physician; and the use of non-steroidal anti-inflammatory drugs (NSAIDs) (ATC-code N02BA01), non-selective monoamine reuptake inhibitors (N06AA), selective serotonin reuptake inhibitors (N06AB), non-selective monoamine oxidase inhibitors (N06AF), monoamine oxidase A inhibitors (N06AG), or other antidepressants (N06AX). Daily alcohol use was measured with the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993). Number of chronic diseases was measured by using the LASA Questionnaire (Kriegsman et al., 1996). Previous literature demonstrates that a great variety of characteristics may act as putative confounders in the association between biomarkers and depression subtypes. However, in our previous studies (Veltman et al., 2017; Rhebergen et al., 2015), we examined the association of a wide variety of psycho-social characteristics with depression subtypes and putative confounders of HPA-axis functioning, respectively, in the NESDO-cohort. Characteristics that previously did not cause the estimate for subtypes or cortisol measures in regression analyses to change more than 10% were not considered as putative confounders in the current paper.

Statistical analysis

All analyses were performed in SPSS, version 21.0. First, levels of inflammatory markers and cortisol parameters were compared across groups using analyses of variance. In case of non-normal distributions, biological measures were natural log-transformed. If non-normality prevailed despite transformation, Kruskal-Wallis tests were performed.

Next, multinomial regression analyses were conducted, with depression subtypes as outcome. Analyses were adjusted for putative confounders, determined through adding all putative confounders separately to the model. Putative confounders were added to the final model if they caused the estimate for subtypes in regression analyses to change more than 10%. Despite not reaching the 10% threshold, severity was added as a putative confounder too, in line with earlier research that found biology measures and severity of depression to be correlated (Vreeburg et al., 2009b; Knorr et al., 2010; Lamers et al., 2013; Rhebergen et al., 2015).

Results

Table 1 shows the sociodemographic and clinical characteristics of the different subtypes of depression, with differences in distribution of sex, age, depression severity and onset, and comorbid anxiety. In addition, metabolic syndrome and BMI were higher in atypical depression, whereas the presence of heart disease was lower in the melancholic subtype.

Inflammatory markers and cortisol parameters across depression subtypes did not differ significantly in univariate analyses (**Table 1**). In addition, in the and fully adjusted regression models, no significant associations were found between inflammatory markers or cortisol parameters and depression subtypes (see **table 2**). Post-hoc we explored whether results would differ if we included cases with a CRP level >10, but no subtype differences were found with this approach either. Since we had a considerate number of missing values, we did post-hoc analyses on an imputated data set, exploring whether the lack of significance could be explained by missingness. Multiple imputation was used for missings on both inflammation (CRP, NGAL, IL-6) and cortisol (AUCg, AUCi, diurnal slope), using all covariates and variables as used in the regression models, generating five data sets. However, this did not give different results (data available upon request).

Discussion

This study aimed to examine differences in inflammatory markers and cortisol parameters in empirically derived subtypes of depression in older adults. Bivariate and multivariate analyses did not yield differences between atypical, melancholic and moderate severe forms of depression, neither for inflammatory markers nor cortisol parameters.

Although several studies have examined inflammation parameters and cortisol measures in the older depressed population before (Belvederi Murri et al., 2014; Martinez et al., 2016), this has not been done using data-driven subtypes. In younger adults these parameters have been examined within subtypes before. The results of our study differ from several studies done in younger adults, demonstrating a correlation between subtypes of depression and both inflammatory markers (Rothermundt et al., 2001; Lamers et al., 2013) and cortisol parameters (Nelson and Davis 1997; Gold and Chrousos 2002; Stetler and Miller 2011; Lamers et al., 2013). Studies on biological parameters and depression subtypes in older persons are scant. One study found an overall immunometabolic downregulation in older depressed persons, except for DSM-defined atypical depression (Vogelzangs et al., 2014). Another study found that late-life depression is correlated with NGAL, but only in patients with visceral obesity (Marijnissen et al., 2014), or in patients with recurring MDD (Naudé et al., 2013). Within our study, the atypical subtype is characterised by a higher mean BMI, but no significant correlation between this subtype and NGAL was found, nor an overall immunometabolic downregulation in our melancholic and moderately severe subtypes. Hence, the scarce previous findings could not be replicated. Next, a meta-analysis found a positive correlation between cortisol measures and late-life depression, especially morning cortisol, but again effects were small, and information on cortisol levels in depression subtypes was lacking (Belvederi Murri et al., 2014). In contrast with our hypothesis, we could not demonstrate an association between cortisol levels and depression subtypes, but due to the lack of studies in older adults on depression subtypes and cortisol, comparisons with other studies are hampered.

Since depression is believed to be a heterogeneous disorder, with different pathophysiological processes leading to different symptom complexes, we expected that subtyping late-life depression would give more consistent results, similar to findings in younger adults (Lamers et al., 2013). However, while depression subtypes in older adults mimick subtypes in younger adults (Hybels et al., 2011; Veltman et al., 2017), our study failed to show a similar, consistent correlation between depressive subtypes and biological measurements. These findings suggest that the pathogenesis of depression in older adults may be more difficult to disentangle than that of depression in younger adults. Possibly both (patho)physiological processes involved in aging and/or the presence of somatic comorbidities and corresponding medication use may impact on biomarkers, and, hence, blur any association between depression subtypes and inflammatory and cortisol measures. Insight into depression in the older population is of paramount importance in order to improve diagnosis, treatment, and prediction of prognosis. However, we think that the current biological parameters, being involved in a vast array of processes in both aging and disease, are not specific enough and therefore insufficient to demonstrate the pathophysiological processes underlying depression in older age.

Limitations
A limitation of this study is the missing data of cortisol measures for several subjects, and to a lesser extent inflammatory measures, decreasing the cohort size and thereby the power. However, results did not become significant after imputation analysis either (data available upon request). Another limitation is the lack of information regarding the duration of the current depressive episode.

Conclusion

To conclude, this study is the first to examine putative underlying pathophysiological mechanisms of previously identified, data-driven subtypes of depression, in a large cohort of older adults. No significant differences in inflammation markers and cortisol parameters across subtypes were observed. To date, studies on biological disturbances in depressed older adults consistently report inconsistent results, suggesting that the currently used biological parameters may be involved in both aging and disease processes, muddling insight in the pathogenesis of late-life depression.

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Table 1. Characteristics of stable subgroups (n=359)

	Total sample	Group 1, Severe atypical	Group 2, Severe melancholic	Group 3, Moderate severity	Overall P-value(df)
Prevalence	359 (100%)	54 (15.0%)	138 (38.4%)	167 (46.5%)	
Sociodemographics					
Sex, female, %	66.0	83.3	68.8	58.1	0.002(2)
Age, mean (SD), years	70.5(7.4)	68.3(6.7)	70.5(7.1)	71.5(7.7)	0.02(2)
Education, mean (SD), years	10.4(3.4)	11.0(3.7)	10.1(3.2)	10.4(3.4)	0.30(2)
Clinical characteristics					
Age onset, mean (SD) years	48.5(20.3)	41.7(20.7)	49.6(19.1)	49.9(20.8)	0.04(2)
Presence 1 year anxiety diagnosis, %	40.1	38.9	48.6	33.5	0.03(2)
Severity (IDS), mean (SD)	30.5(13.0)	32.2(11.8)	32.6(14.2)	28.0(11.8)	0.01(2)
MMSE score, median (IQR)	28.0(2)	28.0(2)	28.0(3)	28.0(2)	0.16(2)
Physical health					
Current smoking, %	27.0	31.5	26.5	26.5	0.75(2)
Chronic pain grade, median (IQR)	2.00(2)	2.00(3)	2.00(2)	2.00(2)	0.09(2)
Metabolic syndrome, %	44.0	63.0	35.5	44.9	0.003(2)
Body mass index, median (IQR)	26.3(4.4)	27.7(5.9)	25.3(5.7)	25.3(5.3)	<0.001(2)
Cardiovascular disease, %	17.8	24.1	10.1	22.2	0.01(2)
NSAID use, %	23.7	29.6	18.1	26.3	0.24(2)
Antidepressant use, %	72.1	63.0	81.9	67.1	0.02(2)
Alcohol # daily, median (IQR)	0.06(1.2)	0.03(1.2)	0.03(0.5)	0.15(1.2)	0.26(2)
# chronic diseases, mean (SD)	2.12(1.5)	2.44(1.5)	2.06(1.5)	2.07(1.4)	0.21(2)
Inflammation markers					
NGAL, mean (SD)[a]	63.8(29.5)	57.5(20.6)	66.7(37.4)	63.6(24.0)	0.59(2)
IL-6, median (IQR)[b]	0.52(1.48)	0.65(1.80)	0.47(1.32)	0.52(1.7)	0.63(2)
CRP, mean(SD)	2.3(1.9)	2.7(2.1)	2.1(1.8)	2.3(1.9)	0.18(2)
Cortisol parameters					
AUCg, mean (SD)[a]	20.0(9.8)	21.2(10.6)	20.4(9.8)	19.3(9.5)	0.49(2)
AUCi, median (IQR)[b]	-0.2(8.3)	-0.1(11.8)	0.6(8.8)	-0.2(8.3)	0.94(2)
Diurnal slope T5/ T1, mean (SD)[a]	13.6(11.0)	14.9(10.4)	13.8(12.0)	13.0(10.5)	0.56(2)

[a] Normal distribution was reached after natural log transformation. Untransformed means are presented.
[b] Despite transformation, no normal distribution was reached

Table 2. Odds Ratios and 95% CIs for inflammation markers (n=351) and cortisol parameters (n=294) across subtypes of depression in older adults

	Comparison of severe subtypes to moderate subtype (=reference)		Severe Atypical vs Severe Melancholic (=ref), OR (95% CI)
	Severe Atypical, OR (95% CI)	Severe Melancholic, OR (95% CI)	
NGAL[a]	0.83(0.58-1.20)	0.92(0.72-1.18)	0.83(0.58-1.20)
IL-6[a]	1.06(0.80-1.42)	1.02(0.79-1.33)	1.04(0.80-1.34)
CRP[a]	1.17(0.85-1.62)	0.91(0.70-1.20)	1.29(0.92-1.80)
AUCg[b]	1.24(0.84-1.84)	1.13(0.85-1.51)	1.10(0.73-1.64)
AUCi[b]	0.88(0.60-1.31)	0.91(0.68-1.21)	0.97(0.65-1.46)
Diurnal slope[b]	1.30(0.92-2.08)	1.14(0.87-1.51)	1.21(0.80-1.83)

[a]Adjusted for gender, age, severity, use of antidepressants.
[b]Adjusted for gender, age, severity, smoking, amount of daylight, use of salicylacid derivate.

CHAPTER 4

Stability and transition of depressive subtypes in older adults

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Background: The heterogeneity of late-life depression hampers diagnosis and treatment. Data-driven methods have identified several subtypes of depression in older persons, but the longitudinal stability of these subtypes remains unknown.

Methods: In total 111 older persons with a major depressive disorder both at baseline and 2-year follow-up from the Netherlands Study of Depression in Older persons (NESDO) were included. Latent class analysis was performed to identify subtypes of depression at baseline and at 2-year follow-up, and latent transition analysis was used to examine the stability of these subtypes over time. Transition rates between subtypes and characteristics of groups were examined.

Results: Two subtypes were identified in both baseline (T0) and follow-up data (T1), including a 'melancholic' subtype (prevalence 80.2% (T0) and 62.2% (T1)), and an 'atypical' subtype (prevalence 19.8% (T0) and 37.8% (T1)). The melancholic subtype was characterized by decreased appetite and weight and had a stability of 0.86. The atypical subtype was characterized by increased appetite and weight and had a stability of 0.93, although the discriminating power of different symptoms had decreased at T1. Mean age and education differed significantly between stable and transitioning subgroups, other characteristics did not differ between subgroups.

Limitations: Limited sample size might have hampered the analyses.

Conclusions: Subtypes of late-life depression are relatively stable, but symptoms of depression (like weight loss) seem to blur with symptoms of (patho)physiological aging. This underlines the clinical relevance of depression subtyping, but also the importance of further research into subtypes and the influence of aging.

Keywords: latent transition analysis; late-life depression; depression subtypes; stability of depressive subtypes; atypical depression; melancholic depression

Abstract

Introduction

Late-life depression is a common disorder, with a prevalence ranging from 1-16% (Djernes, 2006). Especially late-life depression is associated with a poorer course (Schaakxs et al., 2018), and comes with a high disease burden for both patients (Gallo et al., 2007) and their caregivers (Scazufca et al., 2002). Better insight into the aetiology and treatment options is therefore of great importance. However, to date research is being hindered by the heterogeneity of depression (Lux and Kendler, 2010; Goldberg, 2011), since the diagnosis of major depressive disorder (MDD) does not reflect the wide array of possible depressive symptom combinations. A diagnosis of MDD is made if 5 out of 9 DSM criteria are met, and since several of these symptoms are opposites (e.g. weight gain or loss), two patients diagnosed with MDD could have zero symptoms overlapping. In addition, previous, longitudinal studies demonstrated low longitudinal stability of depression categories described in the Diagnostic and Statistical Manual of Mental Disorders (DSM) edition 5 (American Psychiatry Association, 2013) such as major depressive disorder, dysthymia, and subthreshold depression (Angst et al., 1997, 2000). Acknowledging this heterogeneity, the DSM 5 contains several specifiers such as depression with atypical or melancholic features, but these have not proved sufficient to predict prognosis and treatment response (Parker et al., 2010; Lojko and Rybakowski, 2017).

A different approach to examine the heterogeneity of depression is through data-driven methods (Lubke and Muthén, 2005), such as latent class analysis (LCA). These techniques cluster patients based on their congregate of different depressive symptoms, without a pre-conceived hypothesis. Studies in younger adults using LCA identified an 'atypical' subtype characterized by increased sleep and appetite, and a 'typical' or 'melancholic' subtype characterized by decreased sleep and appetite, and the presence of psychomotor symptoms (Kendler et al., 1996; Sullivan et al., 1998, 2002; Lamers et al., 2010; Rodgers et al., 2013; Li et al., 2014). In addition, these empirically-derived subtypes and their most distinguishing symptoms as appetite and weight have been linked to distinct biological and genetic correlates, and different neural activity on functional MRI (Lamers et al., 2013; Milaneschi et al., 2017; Simmons et al., 2018). In older adults, earlier data-driven studies have found subtypes mainly based on severity, probably due to inclusion of persons without a formal diagnosis of depression (Hybels et al., 2009, 2013; Lee et al., 2012; Mezuk and Kendler, 2012). Furthermore, not all of these studies distinguished between increase and decrease of sleep, appetite, weight and psychomotor symptoms, while these distinctions appeared to be crucial in identifying subtypes of depression in both younger (Lamers et al., 2010; Alexandrino et al., 2013; Rodgers et al., 2013). We have performed an LCA on older depressed adults taking this symptom distinction into account, and have found an atypical, melancholic, and moderately severe subtype (Veltman et al., 2017), similar to the aforementioned studies in younger adults. To further examine the validity and clinical usefulness of these subtypes, insight is needed into the stability and the potential transition rate of subjects across subtypes over time.

Latent transition analysis (LTA) is a data-driven method useful for examining the longitudinal stability and transition of subtypes of depression. In younger depressed adults, studies performing LTA have found a relatively high stability of subtypes (48-90%),

with the atypical subtype being the most stable (71-79%) (Lamers et al., 2012; Rodgers et al., 2014). In older depressed adults, so far one earlier LTA has been performed (Ni et al., 2017). Their sample consisted of outpatients aged 60 to 96 years, and they demonstrated moderate stability of subtypes during 2-year follow-up (46-61%), with the highest stability in the subtype characterized by a moderate severity and a lack of positive affect. However, they did not differentiate between increasing and decreasing sleep, appetite, weight, and psychomotor symptoms, and as shown before, these symptoms are important in differentiating between subtypes of depression.

The Netherlands Study on Depression in Older persons (NESDO) provides an excellent opportunity to examine the stability of late-life depression subtypes, with recognition of the importance of differentiation between increase and decrease in sleep, appetite and psychomotor symptoms. This paper is a follow-up of an earlier cross-sectional study that identified three subtypes of depression using latent class analysis, including an atypical, a melancholic, and a moderate subtype (Veltman et al., 2017). The atypical subtype was characterized by a high severity, and an increase in sleep, appetite and weight. The melancholic subtype was characterized by a high severity, but a decrease in sleep, appetite and weight. The moderate subtype was characterized by an overall lower prevalence of depressive symptoms. To examine the 2-year longitudinal stability of these subtypes, in this study we perform a latent transition analysis on persons derived from the NESDO-cohort with a major depressive disorder (MDD) both at baseline and at 2-year follow-up. This study population differs from the population in Veltman et al. (2017) in chronicity, since a diagnosis of MDD on both time points was needed for inclusion. Nevertheless, considering the three identified subtypes in our previous study (Veltman et al., 2017), as well as the findings from LTA studies on younger adults identifying similar subtypes (Lamers et al., 2012; Rodgers et al., 2014), we hypothesize to find three subtypes among older depressed people using LTA, including a melancholic, atypical, and moderate subtype, with considerable stability during 2-year follow-up.

Methods

Study population

Data were derived from the baseline and 2-year follow-up measurements of the Netherlands Study of Depression in Older persons (NESDO), a longitudinal multi-site naturalistic cohort study, examining course and consequences of depression in older persons. The NESDO cohort (n=510) consists of persons aged 60-93 years, including 378 persons with a depressive disorder in the previous 6 months at baseline, and 132 non-depressed controls. Depressed older persons were recruited from both mental health care institutes and general practitioners in five regions in the Netherlands, in order to include persons with current late-life depression in various developmental and severity stages. Depression included a 6-month diagnosis of Major Depressive Disorder (MDD) (95%) and/ or 6 month dysthymic disorder (26.5%), or minor depression (two to four depressive symptoms lasting at least two weeks, 5.0%) according to DSM-IV-R criteria. Non-depressed older persons were recruited from general practices and were included when no lifetime

diagnosis of depression was present. Exclusion criteria were (suspected) dementia, and insufficient command of the Dutch language. The study design of NESDO is described in detail elsewhere (Comijs et al., 2011).

For the present study, persons with a 6-month diagnosis of MDD at baseline (T0), and a 6-month diagnosis of MDD at 2-year follow-up (T1), were included. Persons with dysthymia or minor depression only were excluded. We chose to include only persons with a present diagnosis of MDD on both T0 and T1 because we specifically wanted to examine the longitudinal stability of depression subtypes.

Symptoms of depression

Ten depressive symptoms were used as indicator variables in the LCA analyses in order to identify depression subtypes. Nine depression key symptoms of the DSM-IV were based on the Dutch version of the Composite International Diagnostic Interview (CIDI) lifetime version 2.1, (World Health Organization, 1997; Andrews and Peters 1998) which were used to diagnose depressive and anxiety disorders according to DSM-IV criteria and conducted by specially trained clinical research staff. Changes in appetite and weight were used as two separate variables. All items were coded as 'not present' or 'present', except for the items regarding changes in appetite, weight, sleep and psychomotor disturbance. Here we created four categories, so for example for weight the categories were: absence of weight changes, weight loss, weight gain, and both gain and loss.

Covariates

Several socio-demographic, clinical, psychosocial, and physical health indicators were used to characterize subtypes, equal to the covariates used in our baseline paper (Veltman et al., 2017) and mostly overlapping with similar studies in younger adults (Lamers et al., 2012) to enable comparison.

Socio-demographic variables, including age, gender and years of education, were collected during the baseline interview. *Clinical characteristics* such as age of onset of the depressive disorder and comorbid anxiety disorders were assessed by the CIDI. Severity of depressive symptoms was assessed with the of the 30-item Inventory of Depressive Symptomatology (IDS) (Rush et al., 1996). Further, we assessed several *psychosocial variables*. Overall daily functioning was measured with the World Health Organization Disability Assessment Schedule II (WHODAS) (Chwastiak and Von Korff, 2003); Buist-Bouwman et al., 2008). Apathy was measured using the Apathy Scale (Starkstein et al., 1992), and cognitive functioning by the Mini Mental State Examination (MMSE) (Folstein et al., 1975). *Physical health indicators* were included. Respondents were asked whether they were currently smoking (yes/no). In addition, their alcohol intake was calculated as number of drinks per week. Pain was measured using a count of pain locations (range 0-7) listed in the Chronic Graded Pain scale (Von Korff et al., 1992). The presence of metabolic syndrome (yes/no) was measured. Cut-off values for metabolic syndrome were based on the adjusted Adult Treatment Panel (ATP III) criteria (Expert panel, 2001), including waist circumference ≥88 cm, triglycerides ≥150 mg/dl, HDL-cholesterol < 50mg/dl, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or use of anti-hypertensive drugs, fasting blood glucose ≥100 mg/dl or use of a hypoglycemic drug. Persons scoring positive on ≥3

criteria were considered to have a metabolic syndrome. Diabetes was defined as fasting plasma glucose level ≥ 7.0 mmol/l. Objective and standardized assessments of height and weight were performed. Body mass index (BMI) was calculated as kilograms divided by meter squared and categorized as underweight-normal (BMI<25), overweight (25≤BMI<30) and obese (BMI≥30). The number of chronic diseases, presence of cardiovascular disease (assessed by self-report supported by appropriate medication use (see Vogelzangs et al. (2010) for a detailed description), the presence of diabetes (based on fasting plasma glucose level ≥ 7.0 mmol/l or use of anti-diabetic medication [ATC-code A10] (WHO 2007)) was determined. Muscle weakness as an indicator of frailty was measured with a hand-held dynamometer. This was considered present if persons scored below the cut off score after their performance was stratified by gender and BMI, according to Fried et al. (2001).

Outline of analyses

First, latent class analyses, using 10 CIDI-items as indicator variables, were performed at T0 and T1 separately. The conditional probability of occurrence of each depressive symptom, given class membership was examined using Cramer's V. After identification of classes, latent transition analysis was performed, to examine the stability of the identified classes. Characteristics of all classes were examined. In univariate analyses, repeated measurement T-tests were used for normally distributed variables, McNemar tests for dichotomous variables, and Wilcoxon paired rank tests for non-parametric variables. In multivariable analyses, the two stable subtypes were compared, and analyses were corrected for variables that significantly changed the bivariate associations, when added separately (change odd's ratio >10%).

Latent Class Analyses

To determine and identify subtypes of depressive disorders, we performed Latent Class Analysis (LCA). Free from any a priori assumptions about the number and characterization of subtypes, data-driven techniques such as LCA cluster persons into unobserved ('latent') classes, based on their values on several observed variables. Analysis starts with one class, suggesting one class fitting for all persons. Then, iteratively, one class is added to the model, and the best fitting number of classes is determined on the basis of several statistical indicators and interpretability. The LCAs were conducted using M*plus* version 5 (Muthén and Muthén, 2007).

To determine which model best fitted the data, we examined the sample size adjusted BIC (ssaBIC), entropy (i.e., classification accuracy), the bootstrapped Lo-Mendell-Rubin likelihood ratio test (LMR) (number of bootstraps used = 1000), the bootstrapped likelihood ratio test (BLRT) and the proportion of respondents in each class. Lower ssaBIC values indicate better model fit (Nylund et al., 2007a). Entropy, as a measure of classification accuracy, is presented for models with more than one subtype. Values for entropy can range between 0 and 1 with values closer to 1 indicating greater accuracy. The Lo-Mendell-Rubin test (LMR) provides a p-value, which indicates whether the *k*-1 subtype model is rejected in favor of the *k* subtype model. Similar to the LMR test, a p-value below .05 for the bootstrapped likelihood ratio test (BLRT) indicates that the present model fits the data better than the model with one class less; a p-value exceeding .05 indicates that the model with one class less should be preferred (Nylund et al., 2007a). There is no

consensus yet as to which criterion best identifies the best fitting number of classes, but the BLRT seems to be superior to other model fit indices (Nylund et al., 2007a).Finally, we only accepted models in which all classes contained at least five percent of the sample.

Latent transition analysis

Latent transition analysis is a longitudinal mixture model that explores change in latent classes of individuals over time. Latent class analysis on two time points is used as a measurement model in LTA, from which individual-level change among these classes over time is defined by the transition analyses (Nylund, 2007b). Depending on the outcome of the two separate latent class analyses performed for T0 and T1, the latent transition analysis was modelled according to Nylund (2007b). In case of an equal number of subtypes for both latent classes analyses, these subtypes were compared in order to see to what extent they were similar. The latent transition model, calculating the movement of subjects between subtypes across time points, was modelled with respect to the comparability of subtypes found on T0 and T1. First, the degree of similarity between subtypes was compared through loglikelihood tests. For this purpose, we examined the extent of (in)variance of the subtypes in different models: a model where all conditional probabilities of variables were constrained to be equal across time, a model where all conditional probabilities were estimated freely across time, and models in which all conditional probabilities started out as variant, and were gradually coded as invariant (testing for partial invariance). The higher the number of conditional probabilities that were invariant across time, the higher the similarity of identified classes over time.

Results

The total sample consisted of 111 depressed older people, of whom 67% were females, with a mean age of 70.9 (SD ±7.7) years at baseline and a mean age of depression onset of 44.2 (SD ±20.1) years.

In **Table 1**, demographics of the total sample at baseline (T0) and 2-year follow-up (T1) are shown.

Severity significantly decreased over time ($p<0.01$), as did body mass index ($p=0.01$), while muscle weakness increased ($p=0.04$).

Table 2 shows the model fit indices for 1 to 4 classes on both T0 and T1. The best fitting model for the analysis on both baseline and 2-year follow-up was the 2-class model, with a significant Lo-Mendell-Rubin test (LMR) (T0 $p=0.01$; T1 $p<0.01$), a significant bootstrapped likelihood ratio test (BLRT) (T0 $p<0.01$; T1 $p=0.01$), lowest BIC and highest entropy. There is no consensus yet as to which criterion best identifies the best fitting number of classes, but the BLRT seems to be superior to other model fit indices (Nylund et al., 2007a). From the 3-class model onwards, the BLRT was no longer significant, indicating that adding more than two classes to the model did not improve model fit. Classification accuracy was

high, with average posterior probabilities for subgroups ranging between 0.825 – 1.000 (n=111, data not shown), further indicating a reasonable classification quality.

Table 3 shows the estimated symptom profile probabilities for the two-class model on both T0 and T1. Variables are dichotomous (present or not present), except for the variables appetite, weight, sleep, and psychomotor symptoms, which are nominally divided into four categories (increase, decrease, both, or no change). In both subtypes weight and appetite, and to a lesser extent sleep and psychomotor symptoms, are the main significantly differing symptoms between subtypes. The first subtype in both T0 and T1 shows an atypical symptom pattern, with the highest occurrence of both weight gain and increased appetite, and is therefore labeled 'atypical'. The second subtype in both T0 and T1 is characterized by a more typical or melancholic symptom pattern with symptoms such as weight loss and decreased appetite, and is therefore labeled 'melancholic'. Although especially the 'atypical' label resembles a specific DSM diagnosis, we explicitly do not intend to refer to this DSM diagnosis. Rather, the label is chosen to facilitate comparisons with our previous data-driven study on older depressed adults (Veltman et al., 2017), and with earlier latent class and latent transition analyses in younger depressed adults (Lamers et al., 2012; Rodgers et al., 2014).

We then performed a latent transition analysis to examine the stability of these subtypes between T0 and T1. The best fitting model included appetite as invariant symptom, and all other symptoms as variant. Both subtypes showed high stability (atypical subtype N=15, stability =0.93; melancholic subtype N=62, stability=0.87). The estimated transition probability of melancholic to atypical (N=27) was 0.14, and of atypical to melancholic (N=7) was 0.07.

Table 4 shows the characteristics of the stable subjects and transitioning subjects. The group transitioning from atypical to melancholic has the lowest mean age, followed by the stable atypical subtype. The stable melancholic subtype has the lowest years of education. Prevalence of diabetes was lowest in the stable atypical group and highest in the group transitioning from atypical to melancholic. Further group differences in demographic characteristics did not reach significance. Multivariable comparison of the stable atypical and the stable melancholic subgroup showed no significant differences (data not shown). Due to low numbers in the transitioning groups (melancholic to atypical, N=27, and atypical to melancholic, N=7), power limited multivariable analyses across all four groups. Next, multivariable comparison of the stable subjects, including both atypical and melancholic subtypes (N=77), versus the transitioning subjects, including persons transitioning from melancholic towards atypical and vice versa (N=32), did not yield significant findings.

Discussion

In this study, data-driven subtypes of old age depression and their stability over two-year follow-up were examined. Both at baseline and 2-year follow-up, two depression subtypes were identified. The first, melancholic subtype was mainly characterized by a decrease in appetite and weight. The second, atypical subtype was predominantly characterized by an increase in appetite and weight. Both subtypes had high temporal stability, with a slightly higher stability for the atypical subtype. Whereas transition rates between subtypes were low, subjects were more likely to shift from the melancholic subtype to the atypical subtype than vice versa. The stable atypical subtype had a lower mean age and a lower age of onset than the stable melancholic subtype, but this difference disappeared in multivariable analyses. Diabetes was lowest in the stable atypical group and highest in the group transitioning from atypical to melancholic. Other demographic variables were not significantly correlated to subtypes, neither in univariate, nor in multivariable regression analyses. No variables predicting transitioning, as compared to stable class membership, were discovered in multivariable analyses.

In contrast to our hypothesis and our previously published LCA (Veltman et al., 2017), based on data derived from the same cohort (N=359), we now identified two subtypes (atypical and melancholic) instead of three. The previously identified moderate subtype is now absent, which may be caused by a decline in study population and thereby a decrease in power. Since we specifically wanted to examine the longitudinal stability of depression subtypes, persons were only eligible for inclusion in the current study if they fulfilled DSM-criteria for MDD both at baseline and 2-year follow-up. Hence, a study population of chronic or recurrent MDD was selected, whereas in the former study (Veltman et al., 2017) persons with non-chronic MDD were also included. Since chronic depression has been associated with higher depression severity (Reisinger Walker and Druss, 2015), this selection procedure may have resulted in a study sample with higher mean depression severity, and hence, the absence of a moderately severe subtype. Severity scores of the different cohorts indeed reveal a higher severity in the current study towards, with an IDS sum score of 34.9 (SD ± 13.1) in the present study and of 30.5 (SD ± 13.0) in our previous LCA study. In post-hoc analyses, we further explored the characteristics of the subjects that were included in our earlier LCA (Veltman et al., 2017), but not in our current LTA. These were subjects with either missing data on T0, or with MDD on T0 but not on T1 (N=248). First, we found that participants in the current study were equally selected with respect to original subtypes (p=0.12); persons from all three LCA-derived classes were equally selected for inclusion in the current study. This suggests that the absence of a moderate severe subtype might be (partly) caused by a relatively small sample (N= 111), with less power for complex modelling. Furthermore, included subjects had a higher MDD severity on T0 (p=0.02) compared to excluded subjects. Of the 248 excluded subjects, 64.1% (N=159) did not reach the criteria for MDD, and 35.9% (N=89) had dropped out. Reasons for drop-out were dropout due to unknown reasons between T0 and T1 (8.0%, N=20), refusal to participate at T1 (5.2%, N=13), not eligible due to physical or mental reasons (16.5%, N=41), no contact could be made (2.0%, N=5), or passing away (4.0%, N=10).

Next, the symptom profiles of the identified atypical and melancholic subgroup in both T0 and T1, and their high temporal stabilities correspond to earlier studies on younger depressed adults (Lamers et al., 2012; Rodgers et al., 2014). In line with studies on younger adults, the atypical subtype was characterized by increased appetite and weight, and the melancholic subtype by decreased appetite and weight. In the current study however, the difference in appetite and weight symptoms between both subtypes was smaller at T1 as compared to T0. The reduced item discriminating power and very small number of invariable symptoms (1 out of 10) in the LTA model might imply that the nature of the atypical and melancholic subtypes is not completely stable over time. This might be because old age and aging are often associated with diminishing physical health (e.g. weight loss and muscle weakness) and somatic comorbidity, especially in depressed older persons (Holvast et al., 2017). These (patho)physiological processes might influence the presentation of late-life depression, and decrease the distinguishing power of symptoms such as appetite and weight over time. This hypothesis is supported by our finding that BMI and muscle strength significantly decreased during 2-year follow-up (see **Table 1**). This indicates the dwindling health of our subjects and may complicate the identification of depressive subtypes in an older population where depressive symptom presentation might be clouded by (patho)physiological aging.

Nevertheless, taking these possible (patho)physiological alterations in aging into account by freeing conditional probabilities across time, the stability of the identified subtypes was high, and several characteristics were in line with earlier studies on subtypes of depression. Age was significantly lower in the stable atypical subgroup and in the subgroup transitioning from atypical to melancholic, compared to the stable melancholic subgroup and the subgroup transitioning from melancholic to atypical. In earlier studies among younger adults identifying a similar atypical subtype, age and age of depression onset were also lowest in the atypical subtype (Lamers et al., 2010; Veltman et al., 2017). In contrast with previous studies, however, in our study prevalence of metabolic syndrome and cardiovascular disease did not differ between the atypical and melancholic subtype, and prevalence of diabetes was lowest in our stable atypical subtype. It was previously demonstrated that chronic depression, in particular in older age, is associated with a wide array of somatic illnesses (Hegeman et al., 2017; Holvast et al., 2017). Likewise, in non-depressed older persons, prevalence of somatic illnesses is higher in older age. Hence, competing pathways, other than pathways associated with depression subtype, may result in onset of diabetes and cardiovascular disease in older persons. To conclude, we hypothesize that in our chronically depressed cohort of older persons, the lack of significant difference in metabolic and cardiovascular disturbances may rather reflect pathophysiological disturbances associated with either chronicity of depression or aging processes that are not linearly correlated with depression subtypes in late-life. In addition to this, the limited sample size and 2-year follow-up period might have been insufficient to find the true diversity in depression subtypes and their underlying pathophysiological pathways. Future research on the longitudinal stability of late-life depression subtypes with larger sample sizes and longer follow-up is warranted.

Strengths and limitations

The results of this study should be interpreted in the light of various strengths and limitations. A strength of this study is that it is the first latent transition analysis on older depressed persons taking both increase and decrease of weight, appetite, sleep, and psychomotor changes into account. This differentiation of symptoms has been especially distinguishing in earlier found data-driven subtypes, and it enables comparison with several studies on both younger and older adults. Furthermore, a wide selection of characteristics was examined. The limited sample size is an important limitation of the current study. Due to both selection of patients with chronic or recurrent MDD and to dropout due to morbidity and mortality in this older population, only a small number of the original population in our earlier study was included. This may decrease the reliability of our LTA, and may hamper our univariate and multivariable analyses. Another limitation is the possible violation of the local independence assumption (correlation between variables in a class is accounted for by the latent variable). This could occur if separate variables are included that measure different expressions of the same underlying symptom.

Conclusion

To conclude, this is the first study that examined the temporal stability of data-driven subtypes of late-life depression taking into account both increase and decrease in sleep, appetite, weight, and psychomotor symptoms. An atypical and a melancholic subtype were found, both with a high stability over 2-year follow-up. Appetite and weight were main distinguishing symptoms, but their discriminating ability decreased over time. Since the overall cohort significantly declined in weight and physical health during 2-year follow-up, the process of (patho)physiological aging might blur the differentiation of depression subtypes in older age. These findings stress the importance of taking the pathophysiological tangle of aging into account when searching for a better approach to diagnosis, treatment and prevention of late-life depression.

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Table 1. Characteristics of total sample at baseline (T0) and 2-year follow-up (T1) (N=111)

	T0	T1	Overall p-value (df)
Socio-demographics			
Sex, female, %	66.7	*	*
Age, mean (SD), y	70.7(7.6)	*	*
Education, mean (SD), y	10.5(3.8)	*	*
Clinical characteristics			
Age of onset, mean (SD) y	43.8(19.7)	*	*
Severity (IDS), mean (SD)	34.9(13.1)	32.1(12.3)	0.01(110)[1]
Anxiety dx last year, %	46.8	37.8	0.13[2]
Psychosocial			
Functioning sx, mean (SD)	35.7(16.4)	37.4(16.1)	0.26(105)[1]
Apathy score, mean (SD)	18.3(5.1)	19.7(6.2)	0.09(108)[1]
MMSE score, median (IQR)	28.0(2.0)	28.0(2.0)	0.67[3]
Physical health			
Current smoking, %	27.0	#	#
# alcohol/ week, median (IQR)	0.3(4.9)	#	#
Chronic pain grade, mean (SD)	2.3(1.3)	2.2(1.1)	0.53(100)[1]
Body mass index, median (IQR)	26.6(5.4)	26.3(6.2)	0.01[3]
Cardiovascular disease, yes, %	26.1	27.0	1.00[2]
Diabetes, yes, %	17.1	19.1	0.32[1]
# chronic diseases, mean(SD)	2.9(1.9)	2.2(1.1)	0.80(109)[1]
Metabolic syndrome, yes, %			
Muscle weakness, %	21.6	27.9	0.04[2]

Tests used: 1=paired-samples t-test; 2=McNemar; 3=Wilcoxon paired rank test

** = no change over time/ no added value in mentioning*

 # = no data available on T1

\s

Table 2. Model fit indices for different classes at T0 and T1

Model fit indices for different classes, T0											
Classes	**Maximum likelihood**	**BIC**	**ssaBIC**	**Entropy**	**Lo-Mendell-Rubin**		**BLRT**	**Proportion per class**			
					2LL	p	p	1	2	3	4
1	-680.618	1446.007	1389.123	-	-	-	-	1.000			
2	-649.427	1473.107	1356.180	0.888	62.381	0.0100	0.00	0.198	0.802		
3	-633.110	1529.953	1352.982	0.814	32.635	0.0939	0.1750	0.243	0.568	0.189	
4	-620.831	1594.877	1357.862	0.803	30.650	1.000	0.0900	0.270	0.189	0.432	0.108

Model fit indices for different classes, T1											
Classes	**Maximum likelihood**	**BIC**	**ssaBIC**	**Entropy**	**Lo-Mendell-Rubin**		**BLRT**	**Proportion per class**			
					2LL	p	p	1	2	3	4
1	-683.285	1451.342	1394.458	-	-	-	-	1.000			
2	-660.989	1496.230	1379.303	0.764	44.593	0.0082	0.0130	0.378	0.622		
3	-648.750	1559.323	1382.352	0.780	26.338	0.9855	0.7130	0.423	0.252	0.324	
4	-643.177	1625.251	1388.237	0.864	26.549	0.8232	0.4140	0.360	0.243	0.297	0.099

Table 3. Estimated symptom profile probabilities of endorsing depressive symptoms from LCA T0 and T1 (n=111)

	T0					T1				
	Total sample	T0 Class 1 Atypical	T0 Class 2 Melancholic	Cramer's V	P-value T0(df)	Total sample	T1 Class 1 Atypical	T1 Class 2 Melancholic	Cramer's V	P-value T1(df)
Prevalence		**22 (19.8%)**	**89 (80.2%)**				**42 (37.8%)**	**69 (62.2%)**		
DSM-IV criterion symptoms		**Symptom probabilities**					**Symptom probabilities**			
Depressed mood	99.1	1.00	0.99	0.05	0.62(1)	95.5	1.00	0.93	<0.01	0.07(1)
Loss of interest	93.7	0.96	0.93	0.04	0.70(1)	91.0	1.00	0.86	<0.01	0.01(1)
Weight				0.78	<0.01(3)				0.43	<0.01(3)
No weight change	55.9	0.36	0.61			77.5	0.81	0.75		
Weight loss	31.5	0.00	0.39			16.2	0.05	0.23		
Weight gain	10.8	0.55	0.00			5.4	0.14	0.00		
Both gain and loss	1.8	0.09	0.00			0.9	0.00	0.01		
Appetite				0.80	<0.01(3)				0.47	<0.01(3)
No change in appetite	26.1	0.09	0.30			37.8	0.57	0.26		
Decreased appetite	55.0	0.14	0.65			43.2	0.00	0.70		
Increased appetite	15.3	0.73	0.01			16.2	0.43	0.00		
Both increase and decrease	3.6	0.05	0.03			2.7	0.00	0.04		
Sleep				0.28	0.03(3)				0.13	0.02(3)
No change in sleep	9.0	0.05	0.10			13.5	0.24	0.07		
Less sleep	65,8	0.59	0.67			64.0	0.60	0.67		
More sleep	8.1	0.00	0.10			11.7	0.14	0.10		
Both less and more sleep	17.1	0.36	0.12			10.8	0.08	0.16		
Psychomotor				0.25	0.07(3)				0.06	<0.01(3)
No psychomotor change	22.5	0.14	0.25			27.9	0.29	0.28		

	T0					T1				
	Total sample	T0 Class 1 Atypical	T0 Class 2 Melancholic	Cramer's V	P-value T0(df)	Total sample	T1 Class 1 Atypical	T1 Class 2 Melancholic	Cramer's V	P-value T1(df)
Prevalence		**22 (19.8%)**	**89 (80.2%)**				**42 (37.8%)**	**69 (62.2%)**		
DSM-IV criterion symptoms		**Symptom probabilities**					**Symptom probabilities**			
Psychomotor retardation	36.0	0.32	0.37			32.4	0.36	0.31		
Psychomotor agitation	20.7	0.14	0.23			22.5	0.05	0.34		
Both agitation and retardation	20.7	0.41	0.16			16.2	0.31	0.07		
Fatigue/energy loss	94.6	1.00	0.93	0.12	0.21(1)	98.2	1.00	0.97	0.07	0.27(1)
Guilt/worthlessness	83.8	1.00	0.80	0.22	0.02(1)	70.3	0.88	0.59	0.18	<0.01(1)
Concentration/ indecisiveness	95.5	1.00	0.94	0.11	0.26(1)	96.4	1.00	0.94	0.10	0.11(1)
Suicidal ideation	74.8	1.00	0.69	0.29	<0.01(1)	70.3	0.74	0.68	0.03	0.52(1)

The left half of the table shows the symptom probabilities of the entire cohort and of the two different subtypes at T0 (ranging from 0-1), and the p-value for the difference in probability. The right half of the table shows the symptom probabilities of the two subtypes at T1, again with their corresponding p-values. All symptoms are dichotomous, except for the symptoms weight, appetite, sleep and psychomotor symptoms. These are nominally divided into four categories: no change, increase, decrease, and both increase and decrease.

Table 4. Characteristics of stable and transitioning subtypes at baseline

	Stable atypical (N=15)	Stable melancholic (N=62)	Atypical » Melancholic (N=7)	Melancholic » Atypical (N=27)	Overall p-value (df)
Socio-demographics					
Sex, female, %	80.0	64.5	71.4	63.0	0.67(3)[1]
Age, mean (SD), y	67.6(6.7)	71.8(8.0)	65.7(5.0)	71.2(6.8)	0.04(3)[2]
Education, mean (SD), y	11.1(3.7)	9.6(3.7)	11.4(4.7)	11.8(3.6)	0.05(3)[2]
Clinical characteristics					
Age onset, mean (SD) y	35.1(21.4)	45.8(19.2)	44.3(15.1)	44.1(20.6)	0.28(3)[2]
Severity sx, mean (SD)	37.2(11.9)	33.3(14.4)	37.4(7.1)	36.8(11.8)	0.43(3)[2]
Anxiety dx last year, %	53.3	48.4	57.1	37.0	0.65(3)[1]
Psychosocial					
Functioning, mean (SD)	37.1(15.4)	36.6(16.1)	41.1(12.6)	31.1(18.3)	0.65(3)[2]
Apathy score, mean (SD)	19.6(4.1)	17.5(4.6)	16.7(5.8)	19.8(6.1)	0.17(3)[2]
MMSE score, mean (SD)	28.3(1.6)	27.5(1.9)	27.6(1.3)	27.9(2.2)	0.41(3)[2]
Physical health					
Current smoking, %	33.3	29.0	28.6%	18.5%	0.70(3)[1]
# alcohol/ week, median (IQR)	1.0(3.7)	0.4(3.7)	0.0(1.0)	0.2(8.2)	0.73(3)[3]
Chronic pain grade, mean (SD)	2.5(1.2)	2.2(1.3)	2.3(1.3)	2.2(1.4)	0.95(3)[2]
Presence of metabolic syndrome, %	73.3	50.0	57.1	37.0	0.16(3)[1]
Body mass index, median (IQR)	27.8(9.2)	26.6(6.2)	27.4(1.7)	25.5(5.3)	0.22(3)[3]
Cardiovascular disease, yes, %	33.3	22.6	57.1	22.2	0.21(3)[1]
Diabetes, %	0.0	22.6	42.9	3.7	0.01(3)[1]
# chronic diseases, mean (SD)	3.1(1.8)	2.8(1.9)	3.6(2.9)	2.7(1.7)	0.76(3)[2]
Muscle weakness, %	20.0	27.9	0.0	14.8	0.25(3)[1]

Estimated transition probabilities: atypical to atypical=0.928; atypical to melancholic=0.072; melancholic to atypical=0.135; melancholic to melancholic =0.865
Statistical tests used: 1) chi-square; 2) Anova; 3) Kruskal-Wallis

CHAPTER 5

5

Melancholia as predictor of electroconvulsive therapy outcome in later life

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Objectives: In clinical practice, particularly melancholic depression benefits from electroconvulsive therapy (ECT), albeit research using DSM-derived melancholia is not conclusive. We compared clinical characteristics and ECT-outcome of melancholic and non-melancholic depression, here defined by psychomotor symptoms.

Methods: 110 depressed older inpatients treated with ECT were included in the Mood Disorders in Elderly treated with ECT (MODECT) study. The CORE was used for the assessment of psychomotor symptoms, with a score of ≥ 8 defining melancholic depression. Depression severity was measured before, during and after ECT. Characteristics were compared across melancholic and non-melancholic patients. Regression analysis was used to assess the relation between psychomotor symptoms and remission/response, and survival analysis to examine the difference in time.

Results: Patients with melancholic depression had higher severity, lower cognitive and overall functioning and lower prevalence of cardiovascular disease. However, no significant relations were found between CORE scores and remission/response. Since psychotic symptoms are a positive predictor of ECT response and remission, we examined whether CORE score was a predictor of response in the non-psychotic group (N=49). In non-psychotic patients remission was 62%, and the association between CORE scores and remission almost reached significance (p=0.057).

Discussion: Although melancholically and non-melancholically depressed patients differed significantly on several clinical characteristics, ECT-outcome did not differ. Analyses may be hampered by a high prevalence of psychotic features. In non-psychotic patients CORE scores neared significance as predictor of remission, suggesting CORE scores might be a distinguishing characteristic of melancholia in non-psychotic patients, and a clinical useful predictor of ECT response.

Key words: late life depression; melancholic depression; psychomotor disturbances; predicting ECT response

Abstract

Introduction

Unipolar depressive disorders are among the most common psychiatric disorders in our society. Prevalence rates in older patients range from 1-16%, depending on setting (e.g. private households to institutions) and criteria used[1]. Electroconvulsive therapy (ECT) has been proven to be very effective in (older) patients with depression[2-4], especially with psychotic[5] or pronounced psychomotor disturbances, including catatonia[6] . Considering its distinct phenomenology and treatment response, it is suggested that depression characterised by profound psychomotor disturbances may delineate a distinct mood disorder called 'melancholic depression'[7].

The Diagnostic and Statistical Manual of Mental Disorder version IV Text Revision[8] and version 5[9] classifies melancholic depression as a depression subtype with psychomotor disturbances, decreased appetite and sleep, and diurnal symptomatology variation. In addition, it was recently demonstrated that patients with melancholic depression, either defined clinically[10] or data-driven[11,12] differed with respect to clinical characteristics and biological parameters from non-melancholic depression (e.g. higher mean age, higher age of onset, higher cortisol levels, and altered brain-connectivity in melancholic depression)[13-15] . However, previous studies using DSM-derived criteria for 'melancholic depression' failed to demonstrate favourable course trajectories during ECT[16] . A possible explanation is that a DSM diagnosis of melancholia does not require psychomotor disturbances, even though psychomotor symptoms are thought to be a core characteristic of melancholic depression and have also been identified as predictor of response to ECT [16]. Hence, the DSM criteria may lack content validity to identify melancholic depression[16] in depressed patients referred for ECT.

An observational instrument better suited for identifying melancholic depression by thorough assessment of psychomotor disturbances is the CORE[17]. Indeed, one study demonstrated that higher CORE scores predicted ECT response[18]. However, further CORE-based research is limited, especially in older adults, and a recent meta-analysis could not confirm the predictive value of psychomotor symptoms for ECT-outcome, since too few studies examined psychomotor disturbances[19,20]. To conclude, to date there is no consensus on the predictive value of presence of psychomotor disturbances on ECT outcome. Further insight into this predictive value could help clinicians to better identify patients who will probably benefit from ECT, facilitating personalised medicine.

In this study we examine differences in clinical characteristics and course trajectories during ECT across older depressed patients with and without psychomotor disturbances, defined by a cut-off CORE score of 8. We hypothesise that depressed patients with psychomotor disturbances (named 'melancholic') differ in several clinical characteristics from depressed patients without psychomotor disturbances (named non-melancholic), i.e. presence of psychotic symptoms, age, and depression severity[20], and cortisol measurements[21]. In addition, we hypothesise that melancholic depression is associated with a more favourable ECT-outcome compared to non-melancholic depression.

Methods

Data were derived from the Mood Disorders in Elderly treated with Electro Convulsive Therapy (MODECT) study, a two-site longitudinal study including older in-patients (55 years or older) with severe unipolar depression according to DSM-IV-TR criteria (American Psychiatric Association (APA), 2013), referred for ECT. Patients were recruited from tertiary psychiatric hospitals (GGZ inGeest, Amsterdam, the Netherlands and University Psychiatric Center, KU Leuven, Belgium). Patients with another major DSM-IV diagnosis or a major neurological illness (including Parkinson's disease, stroke and dementia) were excluded, thus retaining a data set of 110 patients. For a detailed description of the MODECT-study, we refer to Dols et al[5]. For the current study, patients with missing data on baseline CORE and/or MADRS scores were excluded (n=17). Attrition analysis showed that excluded patients more often started with bilateral treatment ($p = 0.002$), used alcohol more often ($p = 0.02$), and had more often missing baseline data of both MMSE ($p < 0.001$) and Apathy scale ($p = 0.03$). Attrition was non-differential with regard to sociodemographics (age, sex and education), presence of psychotic symptoms, ECT indication, response, remission, and physical comorbidities.

Melancholic depression

Psychomotor disturbances were assessed with the Dutch version of the CORE[17,22], an observational instrument proved to be reliable and valid in assessing psychomotor symptoms in depression[22-26]. The CORE consists of eighteen items, subdivided into three different subscales: retardation, agitation and non-interaction. Each item is scored from 0-3, with 0 defined as the 'absence or triviality' of a feature. In accordance with guidelines[17], a total CORE score of ≥ 8 served as the cut-off for melancholic depression. Hence, patients were divided into melancholic (CORE ≥ 8) and non-melancholic (CORE < 8) depressed patients.

Remission and response

The Dutch version of the MADRS was used to evaluate severity of depressive symptoms at baseline, weekly during ECT treatment, and the first week after treatment finished[27,28]. Remission was defined as a MADRS score ≤ 10 one week after ECT treatment finished. Response was defined as a decline in MADRS score of at least 50% one week after ECT treatment finished, compared to baseline MADRS score.

Characteristics

Sociodemographic, clinical and physical health characteristics as well as biological parameters were examined at baseline. Sociodemographics included sex, age, and education level (low, middle or high), and were obtained by interview. Clinical characteristics included age of onset of depression, severity of psychomotor symptoms, depression severity, psychotic features, cognitive functioning, apathy, daily functioning, treatment resistance, and ECT-characteristics. Age of onset of depression was dichotomized into early versus late onset of depression (age of first depressive episode < 55 years) and was obtained by interview. Severity of psychomotor disturbances was assessed by total CORE-scores. Depression severity was obtained by the MADRS[28]. Depression and the presence of psychotic features were based on the DSM-IVcriteria[8]. Cognitive functioning was

measured by the Mini Mental-State Examination (MMSE)[28]. Apathy was scored by the Apathy scale[30]. Daily functioning was assessed using the WHO Disability Assessment Schedule (WHO-DAS)[31,32]. The Antidepressant Treatment History Form (ATHF)[33] was used to assess previous antidepressant use for the current depressive episode, and treatment resistance. Through chart review we obtained use of psychotropic medication during ECT treatment (non-selective monoamine reuptake inhibitors (N06AA), selective serotonin reuptake inhibitors (N06AB), non-selective monoamine oxidase inhibitors (N06AF), monoamine oxidase A inhibitors (N06AG), other antidepressants (N06AX), lithium (N05AN01), haloperidol/ butyrophenone derivated antipsychotics (N05AD), atypical antipsychotics (N05AH) antiepileptics (N03A)), number of ECT treatments, percentage of patients receiving unilateral ECT, the amount of patients switching from unilateral to bilateral ECT, and ECT indication (medication resistance or urgent).

For cortisol measurements, salivary cortisol samples were obtained at several time points: at time of awakening, 30, 45 and 60 minutes after awakening and at 10 pm (e.g. T1; 07.00 am, T2; 07.30 am, T3; 07.45 am, T4; 08.00 am and T7; 22.00 pm). Patients received instructions concerning saliva sampling. Eating, drinking tea or coffee, and brushing teeth 15 minutes prior to sampling were not permitted. From the samples obtained within 2 hours after awakening (T1-T4), the area under the curve to the ground (AUCg) and to the increase (AUCi) was calculated, using Pruessner's formula[34]. For a more detailed description of the procedures, we refer to Suijk et al[35]. Finally, physical health characteristics included smoking status, alcohol use and physical comorbidity. Current versus former/ no smoking was obtained through interview. Alcohol use was obtained through the Alcohol Use Disorders Identification test (AUDIT)[36]. Physical comorbidity was assessed in a semi-structured interview, including the presence of chronic obstructive pulmonary disease/ asthma/ emphysema, cardiovascular disease, myocardial infarction, hypertension, diabetes, cerebrovascular disease, arthrosis, (rheumatoid) arthritis, malignant neoplasms, migraine, thyroid disease, consequences of an accident, permanent disability due to surgery, Parkinson disease, other disease of the central nervous system, or other diseases. Furthermore, we separately examined the prevalence of cardiovascular disease, hypertension and diabetes within groups.

ECT procedure

At least one week before starting ECT, patients were withdrawn from psychotropic medication, if clinical condition allowed. If this was deemed impossible, pharmacotherapy was kept stable 6 weeks before and during ECT. ECT therapy was administered twice weekly and conducted according to Dutch guidelines[37], starting right unilateral, unless there was an indication to start bilateral. All patients received brief-pulse ECT (0.5-1.0ms) with the Thymaton System IV, following dose titration protocol. A motor seizure of 20 seconds or more was considered adequate, otherwise the dose was raised according to Dutch guidelines. Switching to bilateral ECT occurred in case of clinical worsening or no clinical improvement after 6 unilateral sessions. Clinical worsening was defined as an increase in MADRS scores, increased suicidality, weight loss, dehydration or increase of psychotic features. See also Dols et al[5] for a more detailed description of ECT procedure.

Statistical analysis

Data were analysed using SPSS (Statistical Package of the Social Sciences, version 23, SPSS Inc., Chicago, IL). Statistical significance was defined as $p < 0.05$. Differences across groups for continuous variables were determined by independent t-tests for normally distributed data, and by Mann-Whitney tests for non-normally distributed data. Group differences for categorical variables were determined by chi-square tests.

Logistic regression analyses were conducted to analyse the association between melancholic depression and both remission and response as outcome measures, compared to non-melancholic depression, using total CORE scores and the retardation, agitation, and non-interaction subscales.

The analyses were adjusted for putative confounders, selected either on significant difference across melancholic and non-melancholic patients ($p < .05$), or based on previous findings[5,19].

Survival analyses (Cox regression) were performed in order to examine whether the melancholic and non-melancholic group differed in time (in days) to reach remission and response.

Results

Table 1 summarises demographic and clinical characteristics across melancholic and non-melancholic patients. The total population consisted of 89 patients, of whom 71 had melancholic depression. 66.7% were females, with a mean age of 73.0 years (SD=8.4). Sex and age did not differ significantly between groups. Patients with melancholic depression had higher baseline MADRS scores, lower MMSE scores, lower overall daily functioning, and lower prevalence of cardiovascular disease. No differences in cortisol measurements were found.

Next, the association between melancholic depression and ECT-outcome (remission and response) was examined (non-melancholic depression is reference) (see **table 2**: outcome defined as remission; and **table 3**: outcome defined as response). In model 1, the association between total CORE score and ECT-outcome was examined. In model 2, we additionally adjusted model 1 for demographics (age, sex and education). In model 3, analyses were further adjusted for psychotic symptoms, MMSE and cardiovascular diseases. Finally, in model 4, analyses were adjusted for all previous variables and MADRS scores. Note that there is considerable correlation between CORE and MADRS scores (Spearman's rho = 0.42, $p < 0.001$), reducing the reliability of model 4 due to possible multi-collinearity. Hence, these findings are presented in a separate model. In all models, melancholic depressionwas not associated with remission. Within melancholic patients, only psychotic symptoms were significantly associated with remission (model 4: OR: 3.61, CI: 1.02–12.71; **table 2**) and response (model 3: OR: 7.09, 95% CI: 1.41–35.73; model 4: OR: 6.16, CI: 1.21–31.29; **table 3**).

Subsequently, using logistic regression analyses the association between CORE subscales (respectively agitation, retardation and non-interaction) and ECT-outcome was examined. The results are shown in **table 4**. Again, scores on the three CORE subscales were not significantly associated with either remission or response; and within melancholic depression only psychotic symptoms were significantly associated with response.

Cox regression analysis was performed to examine potential differences in the time to achieve remission or response for the melancholic and non-melancholic patients. The survival distributions for two groups did not differ significantly (remission: OR(95%CI)=0.78(0.38-1.59), p=0.50, response: OR(95%CI)=0.95(0.51-1.77)).

With post-hoc sensitivity analyses, we examined whether characteristics and ECT outcome would differ if melancholic depression was defined as the median CORE score or higher (median CORE = 14.0). Using a higher threshold may exclude mild psychomotor disturbances due to other causes than melancholia, like medication or essential tremor. We also examined whether the outcome would differ when using the CORE as a continuous measure. However, both approaches did not change the results. (data available upon request). Furthermore, we examined whether there was an interaction effect between total CORE score and psychotic symptoms, which was not the case (p=0.80). Lastly, since psychotic symptoms are a positive predictor of ECT response and remission, we examined whether CORE score was a predictor of response in the non-psychotic group (N=49). 61% of non-psychotic subjects reached remission. For response, we found no significant difference (p=0.105), but the association between CORE score and remission nearly reached significance(p=0.057).

Discussion

In this study, we examined differences in clinical characteristics and course trajectories during ECT in older patients with melancholic depression compared to non-melancholic depression. Patients with melancholic depression, as defined by a cut-off CORE score of 8, had a higher depression severity, a lower MMSE score, lower overall daily functioning, and were less likely to have cardiovascular disease. Contrary to our hypothesis, response and remission rates did not differ between the two groups.

Previous findings suggested that melancholic depression has distinct characteristics[11,12,14] and a favourable ECT outcome[17], which is partly in line with the finding that our melancholic group showed several different characteristics compared to the non-melancholic group. Earlier studies defined a data-driven subtype of melancholia, and in line with our findings, this group was characterised by a higher severity, lower overall functioning, and a lower prevalence of cardiovascular disease[12,38]. However, we found no group differences for both number of patients and time to reach response or remission after ECT. Only psychotic features predicted a better ECT outcome. Using median CORE score (14.0) as cut-off did not alter results. However, since the ratio of melancholic versus

non-melancholic patients was rather askew (non-melancholic 19.4% (N=18)), the lack of a correlation with ECT outcome could be due to underpowering.

Previous studies suggested that people suffering from melancholic depression, have on average a higher age and age of onset of depression[39-41], although not all studies could replicate this[42]. We found limited differences in characteristics between melancholic and non-melancholic patients, with no difference in age, nor age of onset. Unfortunately, we could not examine the impact of age of onset on a continuous scale due to dichotomization of the data, with a cut-off of 55 years. The equal distribution of gender among groups is in line with earlier research[43], as is the significantly higher depression severity in the melancholic group[42,44,45], and the lower prevalence of cardiovascular disease in the melancholic group[12]. In our population, no significant difference in cortisol measures was found. This is in contrast with previous studies based on DSM-criteria reporting higher cortisol levels in melancholic versus non-melancholic depression[11,46], and with Parker et al[7] who argued that biological changes, such as hypercortisolemia, are distinct features of melancholic depression.

Next, we examined the impact of depression subtype on ECT outcome. In contrast to our hypothesis, response and remission did not differ significantly between both groups. Likewise, in multivariable regression analyses, melancholic depression was not associated with ECT-outcome, nor the CORE subscales, including agitation, retardation and non-interactiveness. An earlier study using the CORE demonstrated that higher CORE scores predict ECT response[18], as opposed to the non-predictive value of DSM-defined melancholia on ECT response[16]. These results have not been replicated yet as most studies to date did not use CORE measurement to define melancholic features, hampering comparisons. Psychotic features however did predict ECT outcome in our study within the melancholic group, in line with a recent meta-analysis, finding that psychotic features predict both response and remission in ECT treatment[20]. It is suggested that psychotic features are a symptom of a very severe (melancholic) depression rather than a distinct subtype[47]. In our study, post-hoc analyses showed a moderately high correlation between total CORE score and psychotic features (Spearman's rho = 0.42). This matches findings of Parker et al[7], who hypothesised that psychotic features within depression are a specific feature of melancholia, and therefore maybe even more distinguishing than psychomotor disturbances. In post-hoc analyses, we found the association between total CORE scores and remission within the non-psychotic group almost reached significance (p=0.057). This fits Parker's hypothesis, suggesting that CORE scores might be a distinguishing characteristic of melancholia, but that this effect has been 'overruled' in our study by the high prevalence of psychotic features in our sample.

To summarise, melancholic and non-melancholic depression only differed on a limited number of characteristics and were not associated with ECT-outcome. A possible explanation for our non-significant findings could be the high mean age of our cohort. CORE scores are found to increase with age[14,48,49], although the CORE is validated in the older population, too [50]. It is possible that higher CORE scores in older patients might be explained by various underlying pathophysiological pathways, such as neurodegenerative or vascular factors, and are therefore not clinically distinguishable from *true* melancholic

psychomotor disturbances. However, presence of psychotic features did predict ECT response, which may be indicative of a severe melancholic depression and thus a stronger predictor of response than the CORE.

The findings of this study should be interpreted in the context of the following strengths and limitations. Strengths of this study are the detailed observation of psychomotor disturbances, and the vast number of characteristics that were examined. However, selection bias may have hampered our findings. The number of non-melancholic patients was low (n = 18 (19.4%)), indicating a probable selection bias in ECT-referrals. Combined with a relatively small number of included participants (N=93) and a high response percentage, this study population may have been too homogenous to identify differences in outcome. In addition, it remains to be settled to what extent the CORE is a valid measure to assess psychomotor disturbances in older depressed patients. Psychomotor disturbances due to other clinical conditions, such as cerebral vascular damage, neurodegeneration, other somatic comorbidities or medication side effects , may artificially increase the CORE. Lastly, attrition differed with respect to type of ECT (more bilateral ECT), suggesting that attrition may differ with respect to severity and/or melancholic depression as well.

Conclusion

Patients with melancholic depression (defined as a CORE score ≥ 8) had higher depression severity, lower cognitive and overall daily functioning, and lower prevalence of cardiovascular disease than patients with non-melancholic depression. Total CORE score did not predict ECT outcome, but psychotic features did, and were moderately correlated to CORE scores. This suggests that psychotic features in combination with psychomotor disturbances may better characterize melancholic depression in older patients than psychomotor disturbances or psychotic features alone. Considering the significant correlation of CORE score with depression severity, our findings suggest that in this specific, rather homogeneous, sample of severely depressed in-patients, CORE-measurements may only have any additional value for prediction of treatment outcome in non-psychotic patients. However, replication studies are required to confirm our findings.

Conflict of interest
No conflict of interest is declared.

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Table 1. Baseline characteristics with melancholy defined as CORE >=8 (N=89)

	Total sample	Non-melancholic	Melancholic	X2, F, (df), overall P-value
Prevalence	89 (100%)	18(19.4%)	71(80.6%)	
Sociodemographics				
Sex, female, %	66.7	66.7	66.7	<.001(1), 1.00[1]
Age, mean (SD), years	73.0(8.4)	71.8(9.8)	73.3(8.1)	0.69(91), 0.49[2]
Education level, %				2.27(2), 0.32[1]
Low	15.9	11.8	16.9	
Middle	57.3	47.1	60.6	
High	26.8	41.2	23.1	
Clinical characteristics				
Age onset <55 years, %	54.8	50.0	56.0	0.21(2), 0.79[1]
CORE sumscore, median (IQR)	14.0(13.0)	5.0(3.0)	16.0(10.0)	<.001(-6.57), <.001[3]
MADRS sumscore, mean (SD)	33.7(8.7)	27.4(10.0)	35.2(7.7)	-3.62(91), <.001[2]
Psychotic features, %	47.3	50.0	46.7	0.07(1), 0.80[2]
MMSE sumscore, median (IQR)	26.0(6.0)	28.0(5.0)	25.0(7.0)	419.00(-2.03), 0.04[3]
Apathy, mean (SD)	24.8(7.2)	22.7(7.6)	25.3(7.1)	-1.31(75), 0.20[2]
WHO-DAS functioning, mean (SD)	43.6(15.0)	37.2(11.5)	45.6(15.4)	-2.01(65), 0.05[2]
No. antidepressant trials, median (IQR)	2.0(2.0)	2.0(1.0)	2.0(2.0)	3.26(5), 0.66[3]
Max. resistance score, median (IQR)	3.0(2.0)	2.5(3.0)	3.0(2.0)	5.32(4), 0.26[3]
Medication use during ECT, %	39.8	27.8	42.7	1.34(1), 0.25[1]
Electroconvulsive therapy				
No. ECT treatments, median (IQR)	11.0(7.0)	10.5(8.0)	12.0(7.0)	562(-1.10), 0.27[3]
Start unilateral, %	96.8	94.4	97.3	0.39(1), 0.53[1]
Switch unilateral to bilateral, %	31.2	38.9	29.3	11.98(2), <0.01[1]
ECT indication				0.97(1), 0.32[1]
Life threatening symptoms, %	25.8	16.7	28.0	
Pharmacotherapy resistance, %	62.4	66.7	61.3	
Other, %	11.8	15.7	10.7	
Response after ECT, %	77.4	72.2	78.7	0.35(1), 0.56[1]
Remission after ECT, %	68.8	55.6	72.0	1.83(1), 0.18[1]
Cortisol measurements				
AUCg, median (IQR)	6.9(4.6)	6.7(5.5)	7.4(5.2)	162(-1.69), 0.09[3]
AUCi, median (QR)	5.9(4.6)	5.7(4.9)	6.4(4.9)	163(-1.67), 0.09[3]
Evening cortisol, median (IQR)	3.2(2.2)	2.6(0.9)	3.5(2.2)	167.5(-1.76), 0.08[3]
Physical health				
Current smoking, %	25.6	29.4	24.6	1.16(2), 0.56[1]
Alcohol use, %	29.9	43.8	26.8	1.80(1), 0.18[1]
Alcohol units/ week, median (IQR)	0.0(1.0)	0.0(6.0)	0.0(1.0)	452.50(-1.57), 0.12[3]
No. physical comorbidities, median (IQR)	1.0(2.0)	2.0(2.0)	1.0(1.0)	6.54(5), 0.26[3]
Cardiovascular disease, %	23.7	50.0	17.3	8.58(1), 0.003[1]
Hypertension, %	30.1	27.8	30.7	0.06(1), 0.81[1]
Diabetes, %	7.5	0.0	9.33	1.62(1), 0.18[1]

Table 2. Logistic regression analysis of remission for total CORE score

Variable	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)
Total CORE score	1.04 (0.98–1.09)	1.02 (0.96–1.09)	1.05 (0.97–1.14)	1.07 (0.98–1.16)
Sex (female)	-	0.47 (0.14–1.57)	0.41 (0.11–1.56)	0.40 (0.11–1.54)
Age	-	1.02 (0.96–1.09)	1.04 (0.97–1.11)	1.04 (0.97–1.11)
Education, low (high=ref) Education, middle (high=ref)	-	1.38 (0.29–6.39) 3.01 (0.87–10.46)	2.37 (0.41–13.72) 4.05 (0.98–16.69)	2.45 (0.41–14.72) 3.77 (0.89–15.87)
Psychotic symptoms	-	-	3.16 (0.95–10.48)	3.61 (1.02–12.71)
MMSE	-	-	1.13 (0.98–1.31)	1.14 (0.98–1.32)
Cardiovascular disease	-	-	0.61 (0.17–2.19)	0.57 (0.16–2.07)
MADRS	-	-	-	0.97 (0.89–1.05)

* Model 2 adjusted for demographics. ** Model 3 adjusted for demographics, psychotic symptoms, MMSE and cardiovascular diseases. *** Model 4 adjusted for variables in model 3, as well as MADRS score.

Table 3. Logistic regression analysis of response for total CORE score

Variable	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)
Total CORE score	1.02 (0.96–1.08)	1.02 (0.95–1.09)	1.04 (0.95–1.13)	1.02 (0.93–1.12)
Sex (female)	-	0.70 (0.19–2.52)	0.67 (0.16–2.89)	0.69 (0.16–3.03)
Age	-	0.70 (0.19–2.52)	0.67 (0.16–2.89)	0.69 (0.16–3.03)
Education, low (high=ref) Education, middle (high=ref)	-	1.56 (0.28–8.78) 2.58 (0.68–9.73)	2.56 (0.36–18.39) 3.28 (0.69–15.53)	2.45 (0.34–17.67) 3.66 (0.75–17.80)
Psychotic symptoms	-	-	7.09 (1.41–35.73)	6.16 (1.21–31.29)
MMSE	-	-	1.14 (0.95–1.37)	1.13 (0.94–1.35)
Cardiovascular disease	-	-	0.63 (0.15–2.59)	0.70 (0.16–2.85)
MADRS	-	-	-	1.05 (0.96–1.13)

* Model 2 adjusted for demographics. ** Model 3 adjusted for demographics, psychotic symptoms, MMSE and cardiovascular diseases. *** Model 4 adjusted for variables in model 3, as well as MADRS score.

Table 4. Logistic regression analysis of remission and response with CORE subscales

Variable	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)
		Outcome defined as remission		
CORE agitation	1.09 (0.91–1.29)	1.13 (0.92–1.39)	1.11 (0.89–1.39)	1.13 (0.89–1.42)
CORE retardation	1.05 (0.94–1.17)	1.01 (0.89–1.14)	1.04 (0.91–1.20)	1.06 (0.91–1.23)
CORE non-interaction	1.08 (0.96–1.21)	1.06 (0.93–1.21)	1.14 (0.96–1.35)	1.16 (0.97–1.39)
		Outcome defined as response		
CORE agitation	1.03 (0.86–1.24)	1.05 (0.84–1.31)	1.01 (0.80–1.28)	0.98 (0.77–1.25)
CORE retardation	1.03 (0.91–1.16)	1.01 (0.89–1.16)	1.06 (0.91–1.24)	1.03 (0.86–1.21)
CORE non-interaction	1.06 (0.94–1.21)	1.06 (0.91–1.23)	1.10 (0.91–1.34)	1.07 (0.88–1.31)

* Model 2 adjusted for demographics. ** Model 3 adjusted for demographics, psychotic symptoms, MMSE and cardiovascular diseases. *** Model 4 adjusted for variables in model 3, as well as MADRS score.

CHAPTER 6

6

Differences in speed of response of depressive symptom dimensions in older persons during Electro Convulsive Therapy

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Introduction: Electro Convulsive Therapy (ECT) is an important and effective treatment for depression. However, research on course trajectories of depressive symptoms during ECT is limited. Insight into putative differences in speed of response of depressive symptom dimensions may enable clinicians to optimally inform patients and their relatives. Therefore, we aim to examine course trajectories of depressive symptom dimensions in depressed older persons during ECT.

Methods: Data were derived from the Mood Disorders in Elderly treated with Electro Convulsive Therapy (MODECT) study, including 110 persons, aged 55 years or older, with a current diagnosis of major depressive disorder and referred for ECT. Exploratory factor analysis was used to identify symptom dimensions, using the ten depression items of the Montgomery-Asberg Depression Rating Scale (MADRS). Differences in course trajectories of symptom dimension during two weeks were examined by multilevel analyses.

Results: Three symptom dimensions were identified: a 'mood', 'melancholic' and 'suicidal' dimension. 'Mood' showed a significantly greater severity decline as compared to 'melancholic' and 'suicidal' at one-week follow-up. At two–week follow-up, both 'mood' and 'melancholic' demonstrated a significantly greater decline as compared to 'suicidal'. However, since scores on the suicidality item of the MADRS were already lower at baseline compared to the other items, a floor effect cannot be ruled out.

Discussion: All symptom dimensions of depression showed a rapid response to ECT. Our findings did not support the general assumption that suicidal symptoms may be the first to improve. However, a floor effect on the suicidality item cannot be ruled out.

Key words: course trajectories; factor analysis; major depressive disorder; late-life depression

Abstract

Introduction

Depressive disorders among older persons are highly common and frequently of a chronic nature. They cause a high burden for both patients [1] and their caregivers [2], with high societal costs [3,4]. Considering this great personal and societal impact, adequate treatment is of paramount importance. In addition to pharmacotherapy, electroconvulsive therapy (ECT) is an important treatment option for severe depressive disorders in older persons. It was demonstrated that older age is a positive predictor for ECT outcome [5,6], with remission rates from 73-90% in patients over 65 years of age [7,8]. In addition, the speed of remission is high [9,10], and significantly higher for ECT compared to pharmacotherapy [11].

When treating depression, not all symptoms resolve at the same pace or to the same magnitude [12-14]. Both pharmacotherapy and psychotherapy are known to ameliorate not all symptoms to the same extent [15,16], and, on average, remission occurs after several weeks to months. On the other hand, studies on ECT in both depressed older and younger adults have found that depressive symptoms show a very rapid response to ECT [9,10], and within younger adults response has been found especially rapid for psychomotor symptoms, such as inhibition, agitation, or inner tension [17-19]. In a recent study on early remission in ECT, the early remitters [requiring four or less ECT sessions, accounting for 14% of the study population] had a significantly higher age than the other subjects [20]. However, insight into response trajectories of different symptom dimension within depressed older persons is lacking.

In order to gain a better insight into dimensions of depressive symptoms and their course trajectories during ECT in depressed older persons, we explored the speed of response of different depressive symptom dimensions in an elderly cohort receiving ECT.

Materials and Methods

Study population

Data were derived from the Mood Disorders in Elderly treated with Electro Convulsive Therapy (MODECT) study, a two-site longitudinal study including older in-patients (55 years or older) with severe unipolar depression according to criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, Text Revision (DSM-IV-TR) [21], referred for ECT. Patients were recruited from tertiary psychiatric hospitals (GGZ inGeest, Amsterdam, the Netherlands and University Psychiatric Center, KU Leuven, Belgium). Patients with another major DSM-IV diagnosis or major neurological illness (including Parkinson's disease, stroke and dementia) were excluded, thus retaining a data set of 110 persons. Diagnosis was made at admittance to the ward by a psychiatrist and confirmed by the Mini International Neuropsychiatric **Interview** (MINI) 5.0.0, Dutch version [22]. The study protocol of MODECT has been approved centrally by the Ethical Review Board of the VU University Medical Center, Amsterdam, the Netherlands and subsequently by the ethical review board of the Leuven University, Leuven, Belgium. Before participating

in the study, all patients were provided with oral and written information. Written informed consent was obtained from all patients or - in case of inability consent- a legal representative. For a detailed description of the MODECT-study, we refer to Dols et al. [23].

Depressive symptoms

Depressive symptoms were measured by the Dutch version of the 10-item MADRS (Montgomery Åsberg Depression Rating Scale [24,25], a validated questionnaire for investigating ten symptoms of major depressive disorder (MDD), including apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, anhedonia, pessimistic thoughts and suicidal thoughts. For each item, a minimum of 0 points and a maximum of 6 points can be scored, according to symptom intensity. The cumulative score of the MADRS can be used as an indicator for the severity of a depression. In MODECT, MADRS was assessed at baseline (prior to ECT), and weekly during ECT by raters trained to administer the MADRS. For the current study baseline measurements and MADRS-scores during the first two weeks were used, since significant improvement to complete remission is often seen within two weeks already [11,20]. Patients were excluded if baseline MADRS, one-week follow-up, or two-week follow-up MADRS were missing (n=21).

Attrition analysis showed that persons with missing MADRS-scores did not differ with respect to total MADRS score for baseline, week 1 and week 2, sex, age, and education from persons included in the study.

Characteristics

To characterize the study population and to enable comparison to other, similar studies, socio-demographics and clinical variables were examined. For a detailed description of measurement of characteristics and clinical variables, we refer to Dols et al. [23]. In short, socio-demographics included sex, age, and years of education. Clinical variables included early-onset of depression (<55 years) versus late-onset, assessed by interview. Number of prior depressive episodes and prevalence of psychotic features was assessed at baseline by the MINI and clinical interview. Current medication use was assessed by interview and double-checked by chart review. Previous antidepressant treatment and treatment resistance was scored with the Antidepressant Treatment History Form (ATHF) [26,27]. Depression severity was defined as the Montgomery-Åsberg Depression Rating Scale (MADRS) total score [24]. Number of somatic disorders was assessed in a semi-structured interview (see also Dols et al. [23]). Prevalence of cardiovascular disease was being defined as presence of hypertension or a history of myocardial infarct or stroke, and obtained through semi-structured interview. Current smoking was assessed by semi-structured interview. Alcohol use was measured by two questions based on the Alcohol Use Disorders Identification Test (AUDIT) [28] on frequency and amount of alcohol consumption.

ECT-procedures

A course of twice weekly ECT along Dutch standards was given to all patients [29,30]. A course started with right unilateral stimuli. For ECT the Thymatron System IV (Somatics, LLC, Lake Bluff, IL, USA) (maximum energy 200%, 1008 mCoulomb) was used, according to a titration dosing protocol. All patients were treated with brief-pulse ECT (0.5-1.0 ms) twice a week. The stimulus intensity was determined by empirical dose titration at the first treatment, for right unilateral ECT six times the initial seizure threshold, and for bilateral ECT 1.5 times the initial seizure threshold. A motor seizure of less than 20 seconds or a seizure on electro-encephalogram (EEG)-recordings of less than 25 seconds was considered inadequate, upon which the dose was raised according to Dutch guidelines [29,30]. If the clinical condition worsened or if no clinical improvement was seen after six unilateral treatments, a switch to bilateral ECT was applied. ECT was continued until the patient reached a MADRS score of less than 10 at two consecutive ratings with a week interval. Additionally, if no further improvement was seen for two weeks, after a minimum of six unilateral and six bilateral sessions, ECT was stopped. Psychotropics such as benzodiazepines, antidepressants, and mood stabilizers were tapered off within two weeks before starting ECT, if clinically possible. Antipsychotics were allowed if clinically indicated.

Statistical Analyses

Since the MADRS consists of 10 items, examination of course trajectories of all items within depressed persons during 2-week follow-up would entail multiple comparisons, prone to type I error. Therefore, a factor analysis on baseline data incorporating the 10 items of the MADRS was conducted in order to reduce the number of items into a limited number of dimensions. Previously, several studies have addressed factor analysis of the MADRS, with factor structures ranging from two to four dimensions [31]. However, since the number of dimensions across studies differed, and since earlier studies used populations ranging from younger to older persons, we decided to perform an exploratory factor analysis (EFA) instead of a confirmatory factor analysis. Oblique rotation (promax) was used because the final dimensions were expected to be inter-correlated. Dimensions were extracted, based on preferential loading on one dimension, differences between loadings of at least 0.20, and eigenvalues (>1.0) [32], observation of the scree plot, and interpretability of the dimensions. Next, course trajectories of the identified dimensions within depressed persons during one-week follow-up and two-week follow-up were compared using multivariate, multilevel analyses (multivariate with respect to both the different groups, and follow-up in time). For that purpose, depression dimensions were standardized over the entire measurement period, and multilevel analyses were performed on three levels. The dimensions were clustered within time points, and time points were clustered within patients. In multilevel analyses, time, different dimensions (both represented by two dummy variables), and the interaction between time and dimension were added to the model. The EFA was performed with SPSS version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) and the multilevel analyses were performed with MLwiN version 2.31 (Multilevel Modelling for Windows, Centre for Multilevel Modelling, University of Bristol).

Results

The total sample consisted of 89 depressed older people, of whom 66.4% were females, with age ranging from 55 to 92 years and a mean age of 73.1 years (SD ± 8.3). Almost half of the sample (46.4%) had psychotic symptoms, and the mean number of prior depressive episodes was 3.7 (SD ± 3.3). MADRS scores at baseline ranged from 20 to 49, with a mean score of 32.6 (SD ± 7.6) and 78.7% had physical comorbidity, with a prevalence of cardiovascular disease of 43.8% (see also **table 1**).

Exploratory factor analysis identified three symptom dimensions (**table 2**), including a dimension consisting of apparent and reported sadness, concentration difficulties and anhedonia (MADRS items 1,2,6,8), henceforth called 'mood' dimension; a second dimension consisting of inner tension, reduced sleep, reduced appetite, lassitude, and pessimistic thoughts (MADRS items 3,4,5,7,9), henceforth called 'melancholic' dimension; and a third, separate dimension consisting of suicidality only (MADRS item 10), henceforth called 'suicidality' dimension. Factor loadings are presented in **table 2**.

Next, the course trajectories of the three symptom dimensions during the first two weeks of ECT were compared. Figure 1 shows the observed development over time in the three depression symptom dimensions. Within depressed persons, all symptom dimensions rapidly declined in severity after the start of ECT. **Table 3** shows the results of the multivariate multilevel analyses. The mood dimension showed a significantly greater decline than the melancholic and suicidal dimension during the first week of ECT (i.e. the mood dimension decreased with 0.31 standard deviation units more than the melancholic dimension between baseline and follow-up). However, during two-week follow-up, the speed of response in the mood dimension did not differ significantly from the melancholic symptom dimension. Notably, although the decline of the suicidality dimension after one week was comparable to the decline of the melancholy dimension, after two weeks the suicidal dimension declined significantly less than the other two dimensions (i.e. the mood dimension decreased with 0.76 standard deviation units more than the suicidal dimension). Post-hoc analyses revealed that the median baseline score on the suicidality item was 2 (IQR=3), which was significantly lower than scores on most other MADRS items, and decreased to 1 (IQR=3) after one week (**table 4**).

Post-hoc, we also performed analyses of the decline over time for each individual MADRS item, to see whether this would generate new insights (supplement 1). All items (apart from lassitude and suicidality) declined significantly each week. In addition, the individual 'mood' items showed greater coefficients of decline in week 1 as compared to week 2, except for reported sadness (coefficient= 0.88 in week 1 versus 0.89 in week 2); and all individual 'melancholic' items showed greater coefficients of decline in week 2 as compared to week 1 (results available upon request).This is in line with findings on speed of response of the aggregated domains, in which the 'mood' dimension shows a significantly higher speed of improvement as compared to 'melancholic' dimension in week 1. Improvement of lassitude seemed to lag behind, since there was only significant improvement in week 2. Suicidality only showed significant improvement in week 1 (as compared to baseline). To conclude, findings are largely in line with findings on aggregated items.

Discussion

The aim of our study was to identify dimensions of depressive symptoms within an older population, and to examine differences in speed of response of symptom dimensions within depressed older persons during the first two weeks of ECT. Three depressive symptom dimensions were identified, including a 'mood', 'melancholic' and 'suicidal' dimension. All dimensions showed rapid and significant improvement during the follow-up, but the mood dimension demonstrated the highest speed of improvement during the first week of ECT, as compared to the 'melancholic' and 'suicidal' dimension. Likewise, both 'mood' and 'melancholic' dimensions improved at a significantly faster speed than the 'suicidal' dimension during two-week follow-up.

Through EFA three dimensions were identified, similar to an earlier study by Parker et al. [33]. This study used MADRS-items in a population of 225 in- and outpatients aged 59 years and older with major depressive disorder. They identified three distinct dimensions: a 'dysphoric apathy/ retardation' dimension, similar to our mood dimension, a 'psychic anxiety' dimension, and a dimension with vegetative symptoms. Our melancholic dimension corresponds to their psychic anxiety and vegetative dimension combined. However, whereas our EFA supports a separate suicidal dimension, Parker et al. [33] included suicidal symptoms in the vegetative dimension. Our finding of a distinct suicidal dimension can be explained by the fact that our study sample contains solely inpatients, while Parker et al. [33] used a mixture of in- and outpatients. Severely suicidal depressed older persons are more likely to be admitted and treated with ECT, which means that suicidality is probably a more prominent symptom in our inpatient sample compared to other studies including outpatients too, even though our population had a moderately high score on suicidality. Unfortunately, the study of Parker et al. [30] does not provide mean MADRS scores on the suicidal item, thereby hampering comparison. Other studies analyzing the factor structure of the MADRS also identified three dimensions, but great differences between theirs and our study population hampers comparisons with our study findings [34].

Our main study aim was to examine differences in course trajectories of the identified dimensions. All dimension improved significantly during the first two weeks, an advantage of ECT over other antidepressant treatments, since the latter usually requires several weeks to reach improvement [11], with studies also finding lagging on different symptoms or symptom dimensions [12-16]. We found that the suicidal dimension significantly lagged behind the mood dimension after the first week of ECT, but a floor effect causing that delay could not be ruled out. In post-hoc analyses, we examined the decline of each individual MADRS item in week 1 compared to baseline, and week 2 to week 1. We found that all items, apart from lassitude and suicidality, decline significantly each week, with a greater improvement of 'mood' items as compared to 'melancholic' items in week 1. To conclude, findings are largely in line with findings on aggregated items. Since the suicidal dimension was comprised of only one item, the responsiveness of this domain may be limited and a floor effect may be present.

Since ECT is known to strongly enhance dopamine [35], the fast improvement of the mood dimension may be caused by the inclusion of anhedonia in this dimension, a symptom linked to disturbances in the dopamine pathways [36-38].

The findings of our study should be interpreted in the context of the following strengths and limitations. The design of this study provided the opportunity to examine course trajectories of depressive symptoms in detail, with weekly assessment of the MADRS. The MADRS however does not fully correspond to the DSM-IV-TR criteria for major depressive disorder [21]. The MADRS only addresses loss of sleep and weight/ appetite, whereas the DSM-IV-TR includes change of sleep and both gain and loss in weight/ appetite. Likewise the DSM-IV-TR criterion of psychomotor changes (both agitation and retardation) is not properly addressed by the MADRS. This may be of particular importance to our study, since psychomotor symptoms are considered to be a predictor of ECT response [19]. Earlier studies found a correlation between the MADRS item 'inner tension' and total CORE score (an instrument to assess psychomotor symptoms in depression), but being a single item measure, this item may not be sufficiently valid to measure the full construct of psychomotor disturbances [39].

Next, our results show that, although suicidality improved rapidly, the speed of response significantly lagged behind the mood dimension in week one, and behind both dimension in week two. Post-hoc analyses revealed that the median baseline score on the suicidality item was 2 (IQR=3), which was significantly lower than scores on most other MADRS items (**table 4**), and decreased to 1 (IQR=3) after one week. These findings suggest that a floor effect probably hampered any further decrease after week one, since the median baseline value was, of all items, closest to zero.

To conclude, our findings show that ECT induces a rapid decline of all symptom dimensions in depressed older persons, with primacy of the mood dimension. Since anhedonia was included in this dimension, these findings suggest that ECT may rapidly restore dopamine-related symptomatology. To what extent the (relatively) lagging behind of suicidal symptoms is related to clinometric properties of the MADRS (e.g. a floor effect) needs to be settled. Above all, since all depressive symptom dimensions already improved during the first week after ECT, this study underlines the potency of ECT to rapidly ameliorate depressive symptoms; a great benefit for clinical practice.

Conflict of interest

No conflict of interest is declared. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1. Characteristics of study population (N=89)

Sociodemographics	
Sex, female, %	66.7
Age, mean (SD)	73.4(9.8)
Education level (in years), mean (SD)	6.4(2.7)
Clinical characteristics	
Age onset, early, %	42.9
# prior depressive episodes, median (IQR)	3(2)
Psychotic features, %	46.4
Current medication use, %	39.8
ATHF (resistance sum score), mean(SD)	6.3(4.9)
MADRS, mean (SD)	32.6(7.6)
Physical health	
Physical comorbidity, present, %	78.7
Cardiovascular disease, %	43.8
Smoking, %	18.2
Alcohol # daily, mean (SD)	2.2(0.7)

Table 2. Factor loadings of MADRS items after oblique rotation (N=89)

	Dimension		
	Mood	**Melancholic**	**Suicidality**
MADRS items			
Apparent sadness	**.275**	-.047	.007
Reported sadness	**.212**	.143	.070
Inner tension	.161	**.197**	-.145
Reduced sleep	-.093	**.497**	-.071
Reduced appetite	.094	**.165**	.147
Concentration difficulties	**.274**	.022	-.208
Lassitude	.030	**.403**	-.213
Anhedonia	**.290**	-.156	.203
Pessimistic thoughts	-.036	**.217**	.198
Suicidality	.008	-.014	**.781**

Grey marked cells indicate highest factor loading

Table 3. Comparison of course of three symptom dimensions

	Mood vs melancholic, Score difference, p (95% CI)	Mood vs suicidal, score difference, p (95% CI)	Melancholic vs suicidal, score difference, p (95%CI)
Baseline – 1 week follow up	**0.31, p=0.03(0.42-0.96)**	**0.35, p=0.01 (0.38-0.92)**	0.05, p=0.73 (0.91-1.24)
Baseline – 2 week follow up	0.18, p=0.23(0.53-1.11)	**0.76, p<0.01 (0.54-0.96)**	**0.55, p<0.01 (0.16-0.74)**

Bold = significant

Table 4. Scores on separate MADRS items (N=89) (mean (SD); median (IQR))

	Baseline	After 1 week	After 2 weeks
1. Apparent sadness	4.2(1.2); 4.0(1)	3.1(1.5); 3.0(2)	2.5(1.4); 3.0(1)
2. Reported sadness	4.4(1.4); 5.0(1)	3.5(1.4); 4.0(1)	2.7(1.5); 3.0(3)
3. Inner tension	3.7(1.2); 4.0(1)	3.0(1.3); 3.0(2)	2.3(1.3); 3.0(2)
4. Reduced sleep	2.7(1.6); 3.0(2)	2.3(1.7); 2.0(3)	1.6(1.5); 2.0(3)
5. Reduced appetite	2.8(1.8); 3.0(3)	2.5(1.8);2.5(3)	1.9(1.6); 2.0(3)
6. Concentration difficulties	3.8(1.3); 4.0(2)	3.2(1.4); 4.0(2)	2.7(1.4); 3.0(2)
7. Lassitude	3.3(1.6); 4.0(3)	3.0(1.6); 3.0(2)	2.3(1.6); 2.0(3)
8. Inability to feel	3.8(1.4); 4.0(2)	2.8(1.3); 3.0(2)	2.3(1.5); 2.0(2)
9. Pessimistic thoughts	3.1(1.7); 3.0(2)	2.8(1.4); 3.0(2)	2.1(1.6); 2.0(2)
10. Suicidal thoughts	1.8(1.6); 2.0(3)	1.4(1.4); 1.0(3)	1.1(1.2); 1.0(2)

Figure 1. Speed of response of symptom dimensions within depressed persons during first 2-weeks of ECT (1=baseline, 2=after one week, 3=after two weeks)

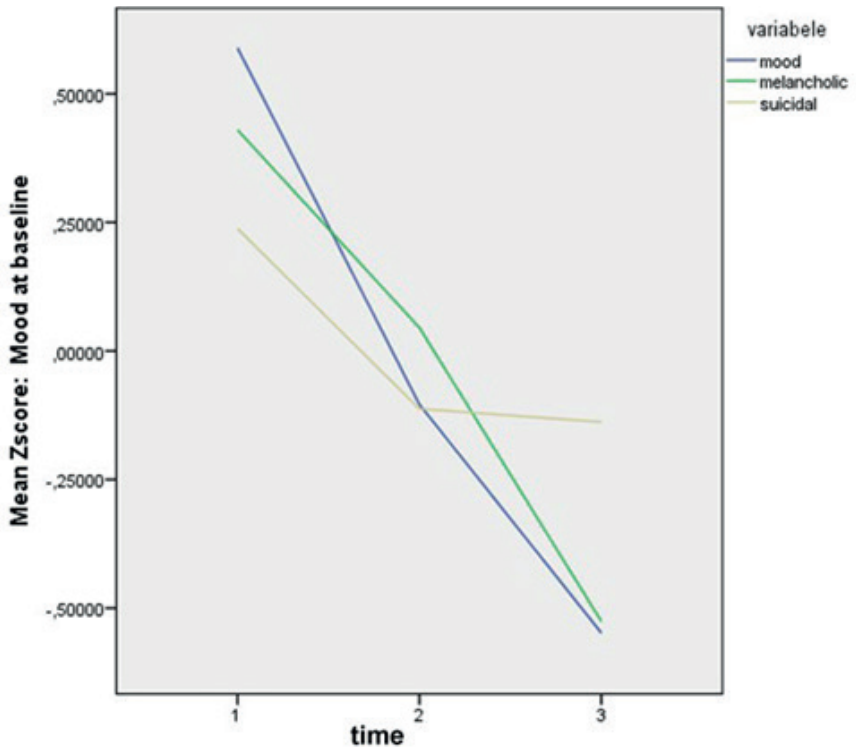

Figure legend: Speed of response of mood (blue line), melancholic (green line), and suicidal (yellow line) cluster, measured at baseline, one, and two weeks. Note that while all symptoms improve rapidly, the decline of the yellow line stalls after one week. This might be due to a floor effect, since baseline scores on the suicidal cluster were lower than both other clusters.

Supplement 1. Coefficients and 95% CIs for separate MADRS items comparing scores at baseline, week 1 and week 2

	Comparison of week 1 and week 2 to baseline (=reference)		Comparison of week 2 to week 1 (=reference)
MADRS items	**Week 1, coef (95%CI)**	**Week 2, coef (95%CI)**	**coef (95%CI)**
1. Apparent sadness	-1.07 (-1.35 – -0.80)	-1.71 (-2.00 – -1.43)	-0.64 (-0.93 – -0.36)
2. Reported sadness	-0.88 (-1.18 – -0.58)	-1.77 (-2.08 – -1.47)	-0.89 (-1.20 – -0.58)
3. Inner tension	-0.59 (-0.87 – -0.31)	-1.32 (-1.61 – -1.04)	-0.73 (-1.02 – -0.45)
4. Reduced sleep	-0.45 (-0.77 – -0.14)	-1.16 (-1.48 – -0.84)	-0.71 (-1.03 – -0.38)
5. Reduced appetite	-0.34 (-0.67 – -0.02)	-0.85 (-1.18 – -0.52)	-0.51 (-0.84 – -0.17)
6. Concentration difficulties	-0.61 (-0.88 – -0.34)	-1.14 (-1.14 – -0.86)	-0.53 (-0.81 – -0.25)
7. Lassitude	-0.30 (-0.61 – 0.01)	-1.09 (-1.40 – -0.77)	-0.78 (-1.10 – -0.46)
8. Anhedonia	-0.94 (-1.21 – -0.66)	-1.50 (-1.78 – -1.22)	-0.56 (-0.85 – -0.27)
9. Pessimistic thoughts	-0.34 (-0.64 – -0.04)	-1.08 (-1.39 – -0.78)	-0.74 (-1.05 – -0.43)
10. Suicidality	-0.46 (-0.72 – -0.20)	-0.71 (-0.97 – -0.45)	-0.25 (-0.51 – 0.02)

Non-significant findings are underlined

CHAPTER 7

7

Summary and general discussion

Summary

Late-life depression is a disease with a high burden on patients, their relatives and society (Gallo et al. 2007; Unützer et al. 2009). Improving our understanding of treatment and prognosis of this disease is of paramount importance. However, late-life depression is also a heterogeneous concept with many different forms of expression, hindering research and clinical practice. The DSM-5 distinguishes several subtypes (American Psychiatry Association 2013), such as depression with atypical features such as an increase in sleep and appetite, and with melancholic features such as a decrease in sleep and appetite, and psychomotor disturbances. However, research on underlying pathophysiology, and prognosis and treatment regarding different subtypes, remains inconclusive. Therefore, in this thesis we have tried to disentangle the heterogeneous concept of late-life depression, with a focus on melancholic depression and using data-driven techniques in order to identify putative subtypes of late-life depression. We further examined differences in clinical course and biological underpinnings of the identified subtypes. To determine clinical relevance of subtypes of depression, we investigated to what extent melancholic subtype, as characterized by psychomotor disturbances, would predict the outcome of electroconvulsive therapy (ECT). We also studied whether symptom clusters, as identified by factor analysis, show a differential speed of response to ECT. This may facilitate the identification of depression subtypes that may particularly benefit from ECT.

Subtypes of depression and their stability over time

In **Chapter 2**, a latent class analysis (LCA) was performed on 359 older persons with major depressive disorder, with data derived from the Netherlands Study of Depression in Older People (NESDO). Ten CIDI-based depression items were used to identify subtypes. Subtypes were then characterized using various sociodemographic and clinical characteristics. Three classes were identified: a moderate-severe class (prevalence 46.5%), a severe melancholic class (prevalence 38.4%), and a severe atypical class (prevalence 15.0%). The strongest distinguishing features between the three classes were appetite and weight and, to a lesser extent, psychomotor symptoms and loss of interest. Compared with the melancholic class, the severe atypical class had the highest prevalence of females, the lowest mean age, the highest Body Mass Index (BMI), and the highest prevalence of both cardiovascular disease and metabolic syndrome.

In **Chapter 3**, we examined to what extent these LCA-identified classes differ with respect to biological underpinnings. Previous studies have suggested that depression subtypes may differ in inflammation markers and hypothalamic-pituitary-adrenal axis functioning (Gold and Chrousos 2002; Stetler and Miller 2012; Lamers et al. 2013; Penninx et al. 2013), suggesting differences in underlying pathophysiological mechanisms. We examined differences in inflammatory markers including C-reactive protein (CRP), interleukin-6 (IL-6), and neutrophil gelatinase-associated lipocalin (NGAL), as well as cortisol parameters. No differences in measures for inflammation and cortisol across subtypes were observed in uncorrected models, nor in models corrected for putative confounders.

In order to examine their clinical relevance, in **Chapter 4**, data-driven subtypes were examined with respect to their temporal stability over a follow-up period of two years.

Again, data from the NESDO study was used, this time including all subjects with a diagnosis of major depressive disorder for the past six months on both baseline and two-year follow-up (n=111). Latent class analysis of depressive symptoms was performed at both time points, followed by a latent transition analysis to examine the stability of identified classes over time. Stability and transition rates between subtypes and characteristics of groups were then examined. Two subtypes were identified in both baseline (T0) and follow-up data (T1), including an atypical subtype (prevalence 19.8 (at T0) and 37.8% (at T1)) and a melancholic subtype with typical depressive symptoms (prevalence 80.2 (at T0) and 62.2% (at T1)). The atypical subtype had a stability of 0.93, and the melancholic subtype had a stability of 0.86, suggesting high temporal stability. No moderately severe subtype could be identified, in contrast to our study in **Chapter 2** where a third subtype was identified, characterized by moderate depression severity.

Melancholic depression and electroconvulsive therapy

In **Chapter 5**, we examined whether melancholic features in late-life depression, characterized by profound psychomotor disturbances as measured by the CORE (Parker et al. 1995), had predictive value for ECT outcome. We included patients (n= 110) from the Mood Disorders in Elderly treated with ECT (MODECT) study. Characteristics were compared across melancholic and non-melancholic patients (i.e. a CORE score of respectively ≥ 8 or < 8). Furthermore the relation between psychomotor symptoms and remission/response, and the relation between psychomotor symptoms and time to remission/response, was examined. Patients with melancholic depression had higher severity, lower cognitive and overall functioning, and lower prevalence of cardiovascular disease. Notably, the latter characteristic was also found in the data-driven melancholic subtype in **Chapter 2**. However, no significant relations were found between CORE scores and remission/response. Since psychotic symptoms are a positive predictor of ECT response and remission (Van Diermen et al. 2018), and hence may subsequently overrule psychomotor symptoms as predictor of ECT-outcome, we examined whether CORE scores were predictive for response in the non-psychotic group (N=49). In non-psychotic patients, remission rate was 62%, and the association between CORE scores and remission almost reached significance (p=0.057).

Finally, in **Chapter 6**, we examined whether ECT would ameliorate all depressive symptoms at the same speed. Differential speed of response of depressive symptoms may inform us on putative working mechanisms of ECT, and could facilitate the identification of depression subtypes that may particularly benefit from ECT. Hence, in Chapter 6, we examined whether different symptoms of depression improved at the same speed during the first two weeks of ECT. In order to avoid multiple comparisons, exploratory factor analysis was used to identify symptom dimensions, using the ten depression items of the Montgomery-Asberg Depression Rating Scale (MADRS). Differences in course trajectories of symptom dimensions during two weeks were examined by multilevel analyses. Three symptom dimensions were identified: a 'mood', 'melancholic' and 'suicidal' dimension. 'Mood' showed a significantly greater decline in severity as compared to 'melancholic' and 'suicidal' at one-week follow-up. At the two-week follow-up, both 'mood' and 'melancholic' demonstrated a significantly greater decline as compared to 'suicidal', but all dimensions showed a rapid and large decline of symptoms over the course of two weeks.

General discussion

In clinical practice, late-life depression has many different manifestations. This complicates diagnosing, treating, and predicting course for those suffering from depression. Treatment protocols for depression do not take this heterogeneity into account, because subtypes of depression, as currently specified in the DSM-5, are not yet so well-defined that specific treatment can be based on them. This may lead to a large delay in finding the right treatment, and to the risk that patients have to endure potentially harmful side effects from trying several kinds of medication. A first step in disentangling late-life depression is identifying meaningful subtypes, and we aimed to find these using latent class analysis.

Although we identified three subtypes of late-life depression (**Chapter 2-3**) , including a severe atypical subtype, a severe melancholic subtype, and a moderately severe subtype, these did not correlate with distinctive biological disturbances, contrary to our hypothesis and to results in younger depressed people (Lamers et al. 2013). We think that associations between depression subtypes and biological markers, if present, may be obscured since currently used biological parameters such as CRP, IL-6 and NGAL, may also be involved in aging processes, other (somatic) disease processes, and polypharmacy. Nevertheless, the subtypes identified in **Chapter 2** may be of value in disentangling depression, since they have a distinct symptom and characteristics profile. Especially in our study, the atypical subtype may represent a distinct subtype, characterized by a relatively young age and early onset of depression, a high prevalence of females, and a high prevalence of metabolic syndrome. This is in line with the results of latent class analyses on younger adults (Lamers et al. 2010; Rodgers et al. 2013), and with a study by Schaakxs et al. (2017), the latter studying a population of depressed persons aged 18-93 and finding that depression in younger persons was correlated with BMI. Notably, the atypical subtype was also identified in our latent transition analysis (**Chapter 4**), showing a high temporal stability. This suggests that atypical depression constitutes a specific depression subtype across the life-span. Further supporting this is the overlapping phenomenology of atypical depression in younger (Lamers et al. 2010; Rodgers et al. 2014; Li et al. 2014) and older adults (**Chapter 3**), the high temporal stability of the atypical subtype, which is in line with previous studies in younger adults (Lamers et al. 2012; Rodgers et al. 2014), and the findings on a genetic overlap with metabolic disturbances (Milaneschi et al. 2015).

Likewise, in addition to an atypical depression subtype, we also identified a melancholic depression subtype (**Chapter 2**), as was previously found in studies on younger adults (Lamers et al. 2010; Alexandrino et al. 2013; Rodgers et al. 2014). Symptom profiles of the melancholic subtype in these different studies are largely similar, characterized by a decrease in appetite, weight and sleep, together with psychomotor disturbances and a high symptom severity, as well as similar characteristics such as a high prevalence of males and a low prevalence of metabolic syndrome.

However, contrary to research in younger adults (Gold and Chrousos 2002; Stetler and Miller 2011; Lamers et al. 2013), the melancholic subtype in older adults was not associated with alterations in cortisol measures, as compared to the non-melancholic subtypes. Earlier (**Chapter 2**), we found that the melancholic subtype had a higher age

and higher age of depression onset, compared to the two other subtypes in our older population. In younger adults, however, melancholic subtype is not characterized by a higher age or age of onset (Lamers et al. 2010; Alexandrino et al. 2014). Considering these studies on younger adults and our findings, we hypothesize that this melancholic type of depression can develop during (early) adulthood, but seems to have a renewed influx of older patients in late life, causing the higher mean age of the melancholic subtype in late-life depression (**Chapter 2**). To what extent there is indeed a bimodal distribution of melancholic depression subtype, and to what extent these subtypes actually represent different etiological and pathophysiological pathways needs to be established.

Both the older people with a melancholic depression described in **Chapter 2**, and those in **Chapter 5**, who were not defined by data-driven subtyping but by a CORE score ≥ 8, had a very low prevalence of cardiovascular disease compared to the non-melancholic depressed persons. This is remarkable since cardiovascular disease is often more prevalent in old age (Khan et al. 2017), and because one would expect a higher prevalence considering the worse overall health of depressed older persons (Grover et al. 2017). Although cardiovascular disease and inflammation are intertwined with aging and therefore hard to tell apart, these findings show that it is important to examine the role of cardiovascular disease in two ways; both higher and lower prevalence may be associated with specific subtypes in depression. A possible explanation for this finding is that our relatively old groups with melancholic disease (mean age melancholic depression in NESDO 70.5 years ±7.1; mean age melancholic depression in MODECT 73.3 years ± 8.1) simply are survivors, and that persons with atypical depression may die younger because of comorbid cardiovascular diseases.

To summarize, whereas our findings are largely in line with findings in younger adults, the lack of associations between depression subtypes and various biomarkers in our older population is remarkable. This raises the question as to what extent other mechanisms in older age are involved, which may blur any underlying pathophysiological mechanism and affect the clinical picture. Ageing is a process that is associated with many homeostatic, metabolic and hormonal changes and disturbances (Aalami et al. 2003; Khan et al. 2017). It is extremely difficult to define where normal aging ends, and pathophysiology begins. One of the common processes present in aging is the elevation of blood inflammatory measures, for which the phrase 'inflammageing' has been coined (Ferrucci and Fabbri, 2018) and which has been linked to an array of predisposing factors, ranging from genetic susceptibility to changes in the microbiome and central obesity (Monteiro et al. 2010). On the other hand, low-grade inflammation in aging can also lead to frailty (Soysal et al. 2016; Marcos – Pérez et al. 2018), a concept describing a state in which the physical condition of (older) patients has decreased to a critical minimum, and in which a relatively small disturbance of these systems can lead to the development of severe mental and physical problems (Collard and Oude Voshaar 2012). Further complicating matters is that frailty may also largely overlap with phenomenology of depression in older persons. These various endpoints (e.g. either obesity or frailty) of a common pathophysiological pathway, illustrate that the process of ageing is a complicated tangle of possible physiological disturbances. This could especially be true for our depressed population. Late-life depression is known to have a high prevalence of physical comorbidity and polypharmacy, even beyond the

increased rates of comorbid somatic diseases (Holvast et al. 2017), further complicating its pathophysiology and making it impossible to link biological disturbances to co-occurring psychopathology. For instance, elevated cortisol levels are both linked to depression in older persons (Belvederi Murri et al. 2014) and to aging itself (Larsson et al. 2009), making it increasingly difficult to determine the role of cortisol in late-life depression. However, understanding pathophysiology and risk factors of late-life depression are important for a better treatment and prevention, and ideas on how to approach this pathophysiological tangle are addressed below in 'Future Directions for Clinical Research'.

Subtypes and treatment response

Another way of trying to differentiate between types of depression is to examine differences in treatment response across subtypes. Psychomotor disturbances (PMD) might be a main feature of melancholic depression (Parker et al. 2010) and is thought to react especially well to ECT, which targets the dopaminergic networks (Nutt et al. 2006, 2008) likely underlying PMD and psychotic symptoms (Van Diermen et al. 2018; Heijnen et al. 2019). The CORE (Parker et al. 1995) is a clinical instrument that measures PMD in depression, and could help identify the melancholic subtype, defined by PMD, of depression (Parker et al. 2010). In **Chapter 5**, we have examined whether higher CORE scores may identify subtypes of depression with favourable ECT-outcome. However, CORE scores did not predict ECT outcome, whereas the presence of psychotic symptoms predicted a positive ECT outcome. Our cohort included a large number of persons with psychotic features (47.3%). Since we think that psychotic features are an even stronger predictor of ECT response, the possible predictive effect of PMD may have been overshadowed.

Although one would expect that ECT mainly relieves symptoms specifically related to dopaminergic networks, in **Chapter 6**, we show that all depressive symptoms quickly improve with ECT, also those that are commonly related to disturbances in serotonergic and noradrenergic networks (Nutt et al. 2008). This underlines the necessity of further studies to distinguish those patients who will have a good response to ECT.

This thesis has tried from various angles to better understand late-life depression and to relate (pathophysiological) subtypes of depression with clinical implications. We think our studies have contributed to the understanding of late-life depression and its different appearances, but we have also shown the difficulties in understanding its pathophysiology, and how research in older adults demands a different approach from research in younger adults. It is generally accepted that in older people, little physiological changes can have an important and enduring impact. The key to understanding depression in late life might therefore not be studying changes in different physiological systems separately, but rather in a complex network of physiological systems. This could also be a reason for why the prognosis of late-life depression is generally poor (Comijs et al. 2015; Schaakxs et al. 2018). If a complex system changes, a new equilibrium will be the result of many little shifts and will probably be worse than before, especially in frail older persons in whom reserve capacity was already low. Viewing (patho)physiology as a complex network has implications for the research methods that should be used, and this will be further addressed below in 'Future Directions for Clinical Research'.

Methodological considerations

The findings of this thesis should be considered regarding various strengths and limitations. A major overall strength of this thesis is that we used different methods and different study populations of depressed older persons to gain more insight into the heterogeneity of late-life depression. The large study population and the longitudinal design of the NESDO study enabled us to apply data-driven methods and test the stability of subtypes over time, and to include several covariates. Furthermore, the design of the study being similar to the Netherlands Study on Depression and Anxiety (NESDA) (Penninx et al. 2008) in younger adults enabled us, to a certain extent, to compare results. The MODECT study allowed us to gain better insight into the course trajectories of ECT response, because of the thorough and frequent data collection with measurements on depressive symptoms every week during ECT.

Of course, the studies presented in this thesis also have methodological limitations. The NESDO cohort existed mainly of outpatients, and therefore our results might not be generalizable to the group of severe (hospitalized) patients. Furthermore, the results from **Chapter 4** are only applicable to a specific subset of chronically depressed older persons, and it is unclear whether the persons included in **Chapter 2**, but not in **Chapter 4**, were either excluded due to remission of depression, the development of comorbid disorders like dementia which was also an exclusion criterion, or even due to a high mortality between baseline and two-year follow-up meetings (see also Jeuring et al. 2018). Other longitudinal studies on the course of late-life depression show a worse prognosis compared to younger adults, with a more chronic course (Schaakxs et al. 2018). Therefore, a high remission percentage seems unlikely, and the dropout is probably partially caused by morbidity and mortality of our subjects. This means the subtypes and their longitudinal stability as found in **Chapter 4** are mainly based on a population with a chronic depression but relatively mild comorbidity, which could have caused the lack in differences in characteristics between subtypes.

Despite the large sample size of NESDO, the cohort size may have still been too limited to facilitate research into subtle differences in especially biological parameters. In addition, for the LTA, since only persons with MDD both at baseline and two-year follow-up could be included, persons experiencing remission either spontaneous or due to treatment were excluded. This select inclusion was needed in order to find subtypes based on symptoms and not on severity, but it may have further limited power to detect differences on characteristics of the subtypes when examining stability and transition. It could also be that our subtypes were still too broad and heterogeneous. Especially since we hypothesize that both inflammation, 'inflammageing', and biological disturbances can lead to this final common pathway of developing atypical depression, the pathophysiology of our atypical subtype might still be too heterogeneous for biological research.

A possible limitation of the MODECT study that might have hampered our results, is the homogeneity of the population. The amount of psychomotor disturbances and a response percentage to ECT were very high, probably because people enrolled in the study were already selected for ECT. This complicated the distribution of our cohort into meaningful

subgroups in **Chapter 5**, and might have meant a fast and broad symptom decline in **Chapter 6**.

Clinical implications

In several chapters, and in line with research on younger adults, we have shown the putative linking of atypical depression to metabolic disturbances, and its high stability over time. Although the direction of this correlation between atypical depression and metabolic disturbances is still unknown (see also 'Future directions for clinical research'), these results emphasize the importance of paying attention to metabolic syndrome in the doctor's office. As argued above, the relationship is probably complex and related to many other processes taking place simultaneously, but we think that optimizing the physical condition of the patient will affect their psychological state in a positive way. Patients might especially benefit from measures to prevent inflammatory processes that could eventually lead to cardiovascular disease and metabolic disturbances.

Furthermore, our results stress the importance of considering ECT as a first treatment option in depression with psychotic features, especially in older persons since age is positively correlated with ECT response and all symptoms rapidly improve during ECT treatment in the first two weeks.

Future directions for clinical research

Late-life depression subtypes in different groups of patients

Our findings warrant replications in other populations, to see to which extent our subtypes are applicable to other populations. For instance, these analyses could be repeated in hospitalized older patients, who often have a more severe depression or factors barring them from being treated at home, like (somatic) comorbidity or a lesser support system. This could provide information on both the applicability of our subtypes to other populations, the role of depression severity on identifying subtypes, and the role of (severe) somatic comorbidity and social factors like loneliness.

Biological pathophysiology of depression subtypes

As discussed in the above paragraphs, the inflammatory measures currently used are not specific enough to distinguish depression from aging, warranting a different approach. A way to circumnavigate this problem might be to shift focus from blood tests to genetic profiles of subtypes of depression, since these do not change over time. Milaneschi et al. (2015) have already examined the genetic overlap between atypical depression and metabolic disturbances. It would be interesting to repeat this study in an older population with atypical depression, to see whether a comparable genetic profile to the younger population will be found or if other risk factors are important in developing atypical depression in later life.

Melancholic depression has not been associated genetically (yet) to biological disturbances, but research suggests depression characterized by psychomotor disturbances, like melancholic depression, shows genetic overlap with bipolar disorder (Bellivier et al. 2013) and schizophrenia (Milaneschi et al. 2015). It would be interesting to examine whether this is also the case with our data-driven melancholic subtype. Furthermore, melancholic depression is often seen as a spectrum with catatonia and psychotic features at the far (severe) end (Taylor and Fink 2006; Parker et al. 2010) and it would be interesting to see whether patients suffering from catatonia and psychotic depression will indeed fit into our data-driven melancholic subtype.

Another interesting approach would be to increase insight into depression as a final outcome of a cascade of events. As argued above, psychiatric diseases should be regarded as part of an intricate network of symptoms rather than a static syndrome. Symptoms cluster together and branch out to other both psychiatric and somatic diseases. Network analyses are a relatively new and promising methodology for the mapping and visualisation of disease complexity and connections between symptoms. Better insight into these networks and its hubs could provide new insights into (patho)physiological processes related to late-life depression, and give information about the sequence of how disturbances develop and symptoms emerge.

Predicting treatment response

Another clinical problem that could benefit from better understanding depression subtypes is how to apply a treatment algorithm, and predicting which patient will benefit from which treatment. ECT is highly effective in some people, but unless a patient presents with (life-threatening) psychotic features or catatonia in depression, it is the last option in the protocol for treating depression whereas waiting lists for ECT in the Netherlands can be long. Predicting who will benefit and who will not, will diminish delay for responders and will spare non-responders an invasive treatment. To better identify factors predicting ECT response, larger and more heterogeneous cohorts are needed, for instance also including bipolar disorder and outpatients. It would also be interesting to explore whether other 'dopaminergic symptoms' like anhedonia, loss of motivation, and loss of interest have a predicting value in ECT response. Furthermore, increasing our knowledge about which patients will benefit from ECT will also help us to better understand the pathophysiology of depression, by studying structural, functional, and neurotransmitter-related changes ECT causes in the brain.

Another direction for future research is trying to find more adequate treatments for the atypical depression subtype. Its high stability over time and repeated identification in both younger and older cohorts makes it an increasingly well-defined subtype, facilitating research into treatment response. An observational study about atypical depression concludes that atypical depression seems to react well to mono-amine-oxidase inhibitors (MAOI) (Thase 2007), but results to date remain largely inconclusive. It would be very interesting to resume research on the treatment of atypical depression, since knowledge on the atypical depression subtype will have increased since then.

Final conclusions

Late-life depression is a heterogeneous condition, consisting of different subtypes with distinct symptom profiles and characteristics. We identified an atypical subtype, which was highly stable over time and correlated with metabolic symptoms. The melancholic subtype was correlated with low cardiovascular disease, which was similar to the melancholic subtype we identified in another cohort, and characterized by the presence of psychomotor disturbances. In contrast to studies in younger adults, we did not find a correlation between depression subtypes and biological disturbances. We think this is caused by the pathophysiology of aging and the often additional increase of both cortisol measures and inflammation due to ageing processes or somatic comorbidity, regardless of any co-existing psychopathology. This means that new approaches are needed to better understand pathophysiology of late-life depression. Given the poor prognosis of late-life depression, it also means that it is important to treat pathophysiological aging such as the development of somatic comorbidity rigidly, since this probably plays a role in both the development and persistence of late-life depression. Furthermore, it is important to know that in the presence of psychomotor disturbances and especially psychotic features in late-life depression, ECT will likely relieve all depressive symptoms rapidly.

Epilogue

The stories of the two patients described in the first chapter of this thesis, with their similar diagnosis of depression but vastly different symptoms, have sparked my interest in late-life depression and its diverse presentation. Their long-time suffering before sufficient treatment was found has convinced me of the necessity to improve treatment algorithms. During my clinical work I have treated older patients who did not recover as well as the two patients I have described here, which felt sad but not unexpected given the worse prognosis there is for depression in older adults. I have treated patients with an often very complex medical history, who sometimes suffered from a large amount of pharmacological side effects, and who have experienced a relapse into depression after a seemingly small stressor such as a cold or an argument with a loved one. Both my clinical work and my research have made me realize how incredibly complex late-life depression is. While my work with patients has motivated me to better understand the concept of depression, my research has taught me to increasingly regard the development and treatment of depression as complex and multifactorial, and how it might take multiple, and sometimes creative, solutions to try and restore my patients' mental balance. I hope this thesis will contribute to a better understanding of late-life depression, and will inspire further research into this urgent, sometimes Gordian, but always intriguing subject.

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Appendices

Nederlandstalige samenvatting

Subtypen van depressie bij ouderen en implicaties voor de klinische praktijk

Depressie bij ouderen

Samenvatting

Depressie bij ouderen is een veelvoorkomende aandoening met een hoge ziektelast voor patiënten, hun naasten, en de maatschappij (Gallo et al. 2007; Unützer et al. 2009). Meer kennis over het gericht behandelen en de prognose voor individuele patiënten is daarom van groot belang. Depressie is echter een heterogeen begrip met vele verschillende uitingsvormen, wat onderzoek bemoeilijkt alsmede de diagnostiek en behandeling in de klinische praktijk. De Diagnostic and Statistical Manual of Mental Disorders versie 5 (DSM-5) (American Psychiatric Association 2013) beschrijft verschillende subtypen van depressie, zoals atypische depressie welke gekenmerkt wordt door een toename van eetlust, gewicht en slaap. Een ander subtype dat wordt beschreven is de melancholische depressie, gekenmerkt door ondermeer een afname van eetlust, gewicht en slaap. Veel studies naar verschillen in pathofysiologie en behandeling hebben gebruik gemaakt van deze zogeheten DSM-gebaseerde klinische subtypen, maar de resultaten zijn tot op heden niet eenduidig.

In dit proefschrift is gebruik gemaakt van andere methodes om potentiële subtypen van depressie bij ouderen in kaart te brengen. Met zogeheten data-gedreven technieken, waarbij de rekenkracht van de computer gebruikt wordt om hypothesevrij onderzoek te doen naar subtypen, hebben we geprobeerd om de heterogeniteit van depressie verder in kaart te brengen. Hierbij is specifiek gefocust op de melancholische depressie. Daarna hebben we gekeken naar verschillen in klinische presentatie en biologische parameters tussen de subtypen. Om de klinische relevantie van de melancholische depressie te kunnen bepalen hebben we nagegaan in hoeverre het melancholische subtype, gekenmerkt door (ernstige) psychomotore symptomen, de uitkomst van electroconvulsietherapie (ECT) voorspelt. Ook hebben we onderzocht of clusters van depressieve symptomen, geïdentificeerd door factoranalyse, een verschil toonden in responssnelheid.

Subtypen van depressie en hun stabiliteit over de tijd

In **hoofdstuk 2** hebben we een latente-klassenanalyse uitgevoerd bij een cohort van 359 ouderen met een depressie. Hiervoor zijn data gebruikt van de Nederlandse Studie naar Depressie bij Ouderen (NESDO) (Comijs et al. 2011). In onze analyse werden drie groepen of subtypen geïdentificeerd: een matig ernstig subtype (prevalentie 46.5%), een ernstig melancholisch subtype (prevalentie 38.4%) en een ernstig atypisch subtype (prevalentie 15.0%). De meest onderscheidende karakteristieken tussen de drie subtypen waren eetlust en gewicht, en in mindere mate psychomotore symptomen en verlies van interesse. Vergeleken met het melancholische subtype had het atypische subtype het hoogste percentage vrouwen, de laagste gemiddelde leeftijd, de hoogste Body Mass Index (BMI), en de hoogste prevalentie van zowel hart- en vaatziekten als metabool syndroom.

In **hoofdstuk 3** hebben we onderzocht of de subtypen verschilden wat betreft biologische parameters. Resultaten van eerdere studies lieten zien dat depressieve subtypen verschillen in de hoogte van ontstekingswaarden en in het functioneren van de hypofyse-hypothalamus-bijnieras (hypothalamic-pituitary-adrenal (HPA) axis) (Gold en Chrousos 2002; Stetler en Miller 2012; Lamers et al. 2013; Penninx et al. 2013). Dit kan betekenen dat er verschillende pathofysiologische mechanismen aan deze subtypen ten grondslag liggen. In dit hoofdstuk onderzochten we verschillen in de ontstekingswaarden C-reactive proteïne (CRP), interleukine-6 (IL-6), neutrofiel-gelatinase-geassocieerd lipocaline (neutrophil gelatinase-associated lipocalin, NGAL), en in verschillende cortisolmetingen. Onze gevonden subtypen verschilden echter niet in de hoogte van de ontstekingsparameters en cortisolwaarden, ook niet na correctie voor mogelijke confounders.

Om de klinische relevantie van de gevonden subtypen verder te onderzoeken hebben we in **hoofdstuk 4** de stabiliteit van de subtypen over een periode van twee jaar nagegaan. We hebben wederom data van de NESDO-studie gebruikt, maar dit keer zijn alleen personen geïncludeerd die op zowel meetmoment T0 (baseline) als meetmoment T1 (na twee jaar) voldeden aan de criteria van een depressie (N=111). Op T0 en T1 is een latente-klassenanalyse uitgevoerd, en daarna een latente-transitieanalyse om de stabiliteit van de gevonden subtypen te meten over de tijd. Bij een latente-transitieanalyse wordt gekeken in hoeverre de subtypen vergelijkbaar zijn op T0 en T1, en hoe de onderlinge stabiliteit en verschuivingen van subtypen eruitzien. Wij vonden twee subtypen op zowel T0 als T1, namelijk een atypisch subtype (prevalentie 19.8% op T0 en 37.8% op T1) en een melancholisch subtype (prevalentie 80.2% op T0 en 62.2% op T1). Het atypische subtype had een stabiliteit van 0.93 en het melancholische subtype een stabiliteit van 0.86, wat wijst op een hoge stabiliteit over de tijd. Het matig-ernstige subtype dat werd gevonden in **hoofdstuk 2** werd niet teruggevonden.

Melancholische depressie en electroconvulsietherapie

In **hoofdstuk 5** onderzochten we of melancholische kenmerken van depressies bij ouderen een voorspeller waren voor een positieve respons op ECT. Hierbij is melancholische depressie gekarakteriseerd als een depressie gekenmerkt door ernstige psychomotore symptomen, waarbij deze symptomen gemeten werden met de CORE-vragenlijst (Parker et al. 1995). Er was sprake van een melancholische depressie als iemand 8 punten of hoger scoorde. In deze studie zijn 110 patiënten geïncludeerd vanuit de Mood Disorders in Elderly Treated with ECT (MODECT) studie (Dols et al. 2017). We vergeleken kenmerken van melancholische en niet-melancholische patiënten, en onderzochten of de CORE-score voorspellend was voor respons en remissie, en voor de tijd waarin dit behaald werd. We vonden dat patiënten met een melancholische depressie gemiddeld ernstiger depressief waren, slechter scoorden op cognitief en algemeen functioneren, en een lagere prevalentie hadden van hart- en vaatziekten. De relatie tussen melancholische depressie en hart-en vaatziekten werd ook gevonden in het data-gedreven melancholische subtype in **hoofdstuk 2**. Er werd echter geen relatie gevonden tussen CORE-score en remissie/ respons. Er was wel een significante relatie tussen remissie/ respons en psychotische symptomen, iets wat al eerder is gevonden (Van Diermen et al. 2018). In ons cohort was er sprake van een hoge prevalentie van psychotische symptomen (N=61). Dit kan ertoe

geleid hebben dat de CORE als voorspeller voor remissie/response niet meer significant was omdat deze door het effect van psychotische symptomen werd versluierd. We hebben daarom gekeken of de CORE wel een voorspellende waarde had in de groep mensen zonder psychotische symptomen (N=49). In deze groep was het remissiepercentage 62%, en de relatie tussen CORE-scores en remissie was bijna significant (p=0.057).

In de laatste studie in **hoofdstuk 6** hebben we nagegaan of ECT alle depressieve symptomen met dezelfde snelheid verbetert. Verschillen in responssnelheid zeggen mogelijk iets over het onderliggende werkingsmechanisme van ECT, en deze kennis kan helpen om de symptoomprofielen van depressie te identificeren die het meest zullen profiteren van ECT. In hoofdstuk 6 hebben we daarom gekeken naar de verbetering van depressieve symptomen in de eerste twee weken van ECT. Om zogeheten *multiple comparisons* te voorkomen hebben we een factoranalyse uitgevoerd, waarbij de tien depressieve symptomen samen zijn gevoegd tot enkele symptoomdimensies. Depressieve symptomen werden gemeten met de Montgomery-Asberg Depression Rating Scale (MADRS). Verschillen in de responssnelheid werden geanalyseerd met multilevel analyses. We vonden drie symptoomdimensies, te weten 'stemming', 'melancholisch', en 'suïcidaal'. 'Stemming' liet de grootste daling in ernst zien en verschilde na een week significant van de andere twee dimensies. Na twee weken waren zowel 'stemming' als 'melancholisch' significant gedaald ten opzichte van 'suïcidaal', maar alle symptoomdimensies lieten een snelle en grote daling zien van de ernst binnen twee weken.

Tot slot wordt in het hoofdstuk '**Summary, discussion and conclusions'** bediscussieerd hoe deze bevindingen te begrijpen zijn in het licht van de bestaande literatuur en welke klinische implicaties deze resultaten hebben. Ook wordt besproken welk vervolgonderzoek nodig is om het begrip over subtypen van depressie bij ouderen verder te verbeteren.

Een belangrijke bevinding is de identificatie van de melancholische, atypische, en matig ernstige subtypen in **hoofdstuk 2 en 3**. Opvallend is dat deze subtypen een eigen symptoomprofiel en onderscheidende karakteristieken hebben, en relatief stabiel zijn in de tijd. We vonden echter geen biologische correlaten van de subtypen, in tegenstelling tot studies bij jongere volwassenen. Dit komt mogelijk doordat (patho) fysiologische veroudering, bijkomende lichamelijke ziektes, en medicatiegebruik ook alle invloed hebben op ontstekingsparameters en cortisolwaarden, en zo de resultaten vertroebelen. Dit wordt waarschijnlijk verder versterkt door de toegenomen lichamelijke comorbiditeit en polyfarmacie bij depressie op oudere leeftijd, vergeleken met ouderen zonder depressie. Een beter begrip van depressie bij ouderen kan dan het beste bereikt worden door het complexe netwerk van fysiologische systemen te bestuderen. Deze benadering past ook bij de bevinding dat de prognose van depressie bij ouderen in het algemeen slechter is dan bij jongeren. Als in een complex systeem meerdere onderdelen uit evenwicht zijn is dit veel moeilijker te herstellen bij een kwetsbare oudere met weinig reservecapaciteit dan bij een veerkrachtige jongere volwassene. In de klinische praktijk moet dan ook altijd aandacht zijn voor de brede gezondheid van de oudere patiënt, zeker als de depressie moeilijk te behandelen blijkt.

In de **hoofdstukken 5 en 6** werd gevonden dat psychotische verschijnselen een voorspeller zijn voor een goede respons op ECT, en dat in de groep niet-psychotische depressieve patiënten de CORE net geen significante voorspeller is voor respons. Deze bevindingen sluiten aan bij de hypothese van Parker et al. (2010) dat psychose de overtreffende trap van ernst is binnen de melancholische depressie. Ondanks dat vooral psychomotore symptomen gerelateerd zijn aan een beter resultaat van ECT, vonden we dat alle symptomen verbeteren met ECT. Dit is verder bewijs dat ECT een snelle en effectieve behandelmanier is voor ouderen met een ernstige, melancholische depressie, en een belangrijke plaats verdient in het behandelprotocol van depressie bij ouderen.

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About the author

About the author

Eveline Margaretha Veltman was born on January 19th, 1989 in Roermond, the Netherlands. After graduation from high school at the Hermann Wesselink College in Amstelveen (2007), she studied medicine at the Vrije Universiteit in Amsterdam and finished her studies in September 2013. During her internships she was also a board member of the Co-Raad (intern council), and has done board membership in local (youth) politics. In December 2013 she started as a resident psychiatry at the Leiden University Medical Center and finished her training in May 2018. During this training she has specialized in old age psychiatry and liaison psychiatry, and has become qualified to treat patients with electroconvulsive therapy. She has combined training with her PhD program at the departments Psychiatry of the Leiden University and GGZinGeest/ VUmc in Amsterdam. Currently she works as an old age psychiatrist at GGZ Rivierduinen in Leiden, and as a liaison psychiatrist at the Alrijne hospital in Leiderdorp. She is also participating in several forums of the Dutch Psychiatrist's Association (Nederlandse Vereniging voor Psychiatrie, NVvP). She is a board member of the Society of Old Age Psychiatry, and a board member of the Scientific Committee. She lives in Amsterdam together with her partner Albert.

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Dankwoord

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List of publications

List of publications

This thesis

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