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

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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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