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

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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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