

Chapter one

Introduction

Late life depression, brain characteristics and response to ECT

In the near future, from now to 2050, the elderly population (aged above 60) worldwide is expected to increase from 12% to 22%. This is an expected absolute increase from 900 million to 2 billion people over the age of 60. Over 20% of the elderly suffer from neurological or mental health problems, of which dementia and depression are the most common disorders (WHO 2015).

Late life depression

Late life depression is a complex neuropsychiatric disorder with a high burden of disease in patients and their relatives (Beekman et al., 1997). Late life depression is diagnosed in older adults above a threshold ranging from 55 to 65 years, i.e. approximately 60 years, using the criteria for major depression of the American Psychiatric Association's Diagnostic Statistic Manual (DSM). Both early-onset, with an age of onset of a first episode before 60 years, and late-onset, with an age of onset after 60 years, may present with cognitive changes, somatic symptoms, executive dysfunction and loss of interest (Fiske et al., 2009; Alexopoulos, 2005).

Approximately five to ten percent of the population above 60 years suffers from one or more clinically relevant depressive episodes (Beekman et al., 1999; Fiske et al., 2009; Blazer et al., 2014), with serious consequences for functioning, disability and quality of life. Remarkably, the disease is often under-diagnosed and under-treated in primary care (van Beljouw et al., 2015; Stek et al., 2004), possibly explained by physical comorbidity, hampering detection by overlapping symptomatology (Blazer et al., 2014).

The aetiology of late life depression is heterogeneous. Age-related changes in endocrine, inflammatory or immune, cardiovascular, and neuroanatomical changes have been associated with increased incidence rates of late life depression, as well as psychological risk factors such as stressful life events, cognitive decline and lack of social support (Alexopoulos, 2005; Fiske et al., 2009).

Early-onset depression has particularly been associated with a family history of affective disorders (Heun et al., 2001), a higher prevalence of personality disorder, suicidal thoughts and poor social support (Sachs-Ericsson et al., 2013; Brodaty et al., 2001), whereas, late-onset depression has been associated with somatic comorbidities, personal losses, worse neurocognitive performances and vascular risk factors (Hickie et al., 2001; Mackin et al., 2014).

Normal aging (Figure 1) is accompanied by subcortical and cortical grey matter atrophy (respectively, Figures 2 and 4), as well as white matter hyperintensities (Figure 3) (Farkas et al., 2006). Grey and white matter abnormalities are thought to

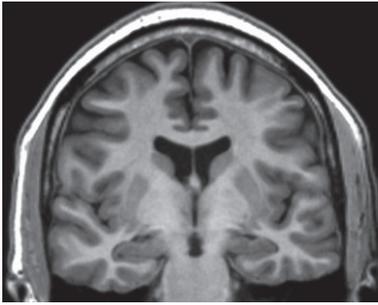


Figure 1. Normal brain on a coronal T1-weighted image

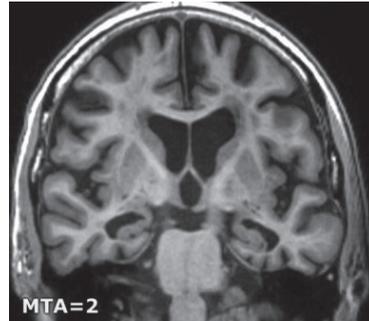


Figure 2. Medial temporal lobe atrophy grade 2 (white arrow) on a coronal T1-weighted image

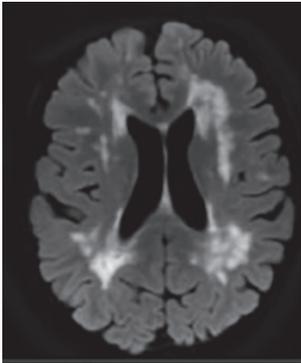


Figure 3. White matter hyperintensities, shown on a transverse fluid-attenuated inversion recovery (FLAIR) image

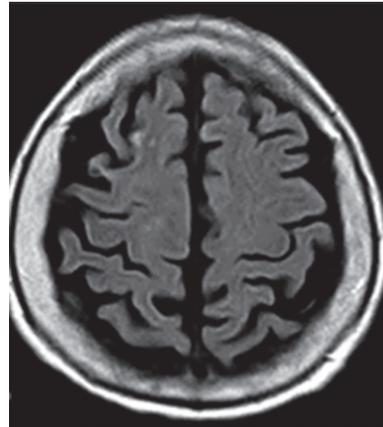


Figure 4. Global cortical atrophy on a transverse fluid-attenuated inversion recovery (FLAIR) image

be involved in the disease mechanism of late life depression (Alexopoulos et al., 1997; Tadayonnejad et al., 2014 and Allalade et al., 2011). Alexopoulos et al. (1997) first described the ‘vascular depression hypothesis’ stating “cerebrovascular disease may predispose, precipitate, or perpetuate some late life depressive syndromes”. Cerebral hypoperfusion and neuroinflammatory processes may contribute to the development of depression (Alexopoulos, 2002), as well as disease-related changes in the aging brain, such as neurodegeneration (Park et al., 2007; Reijnders et al., 2008).

Functionally, late life depression has been associated with frontostriatal, amygdalar, and hippocampal dysfunction (Alexopoulos, 2005). More recently the ‘disconnection hypothesis’ has been proposed, with strategic vascular lesions and

white matter lesions in the brain, disrupting neural connectivity leading to clinical symptomatology (Taylor et al., 2013).

Severe late life depression

Patients with severe late life depression are often admitted to specialized old age clinical facilities and treated with antidepressants. Electroconvulsive therapy (ECT) is recommended when patients are resistant to pharmacotherapy (Alexopoulos, 2011) or in cases where rapid recovery is life saving. ECT has shown to be significantly more efficient than pharmacotherapy in late life depression (Spaans et al., 2015; Salzman et al., 2002).

Patients with severe late life depression may suffer from catatonia, melancholic symptoms or psychotic symptoms. *Catatonia* in late life depression is characterized by motor abnormalities that occur in association with changes in thought, mood and vigilance. Malignant catatonia is the most severe form of catatonia, and can be complicated by life-threatening medical conditions, autonomic instability and systemic organ failure. Older adults are particularly susceptible to develop malignant catatonia and ECT can be life saving in these cases (Kerner et al., 2014). *Melancholic symptoms* present with anhedonia or lack of mood reactivity and at least three of the following symptoms; depressed mood that is subjectively different from grief or loss, severe weight loss or loss of appetite, psychomotor agitation or retardation, early morning awakening, excessive guilt, and worse mood in the morning (DSM-5). In addition, late life depression with *psychotic symptoms* is characterized by mood-congruent hallucination and/or delusions of personal inadequacy, guilt, disease, death, nihilism or deserving punishment (DSM-5). Both melancholic and psychotic symptoms profiles have been associated with higher incidence rates with increasing age (Parker et al., 2013; Birkenhager et al., 2003). Moreover, psychotic symptoms have been associated with a shorter illness duration (Birkenhager et al., 2003) and increased levels of cortisol and dopamine (Schatzberg et al., 1992), compared with non-psychotic depression.

Efficacy of electroconvulsive therapy in severe late life depression

Electroconvulsive therapy is used to treat severe depression since the 1930s and has proven to be a safe and valuable treatment option, especially in older adults (Dombrowski et al., 2007; O'Connor et al., 2001; Tew et al., 1999; Rhebergen et al., 2015). The administration rates of ECT have increased in the last decades due to improved anesthesia and improved information for patients, relatives and doctors. During ECT, an electric pulse is passed briefly through the brain, via electrodes applied to the head, to induce a generalized seizure. The patient treated with ECT

receives general anesthesia and muscle relaxants are given to prevent damage from epileptic seizures, especially bone fractures. The ECT electrodes are placed on one side of the head (unilateral) or on both sides of the head (bilateral or bi-frontal). Unilateral placement is principally to the non-dominant side of the brain, with the aim of reducing cognitive side-effects. According to the European protocol, patients treated with ECT receive a course of ECT, two times a week, preferably starting with right unilateral ECT. Generalized seizure activity of at least 20 seconds is considered adequate (Nice 2003, Nederlandse richtlijn ECT, NVVP, 2010). On average, patients with late life depression require 12 ECT sessions to achieve response (Tew et al., 1999) and remission rates range from 50% to 90% (van der Wurff et al., 2003; Tew et al., 1999), depending on previous pharmacotherapy failure and depression subtype (Heijnen et al., 2010).

Cognitive impairment and electroconvulsive therapy in severe late life depression

ECT is a relatively safe treatment (Philibert et al., 1995; Dombrovski et al., 2007). Nonetheless, all patients treated with ECT experience post-ECT confusion, which lasts several minutes to several hours and is transient in nature (Semkovska and McLoughlin, 2010; Tielkes et al., 2008) and some patients treated with ECT suffer from anterograde and retrograde amnesia after completion of ECT (Tielkes et al., 2008, UK ECT review group 2003). Moreover, frail elderly patients may suffer from transient cognitive impairment during an ECT course, which resolves at discharge (Rubin et al., 1993; Damm et al., 2010). Risk factors influencing cognitive impairment during or after ECT have been reported in various studies. These studies showed associations between electrode placement, pulse shape, treatment frequency, treatment dosage and incidence and duration of cognitive impairment (UK ECT review group 2003). Besides ECT modality, cognitive impairment during or after ECT may also be influenced by heterogeneity of patients' characteristics, such as age, the presence of prodromal or existing neurodegenerative diseases, different cognitive reserve capacities among patients, biological variability such as differences in known genetic risk factors for AD (Sutton et al., 2015) and possibly, pre-existing white and grey matter characteristics.

Mechanism of action of electroconvulsive therapy

Considering the mechanism of action of ECT, several hypotheses have been studied, but till now no theory has proven to be realistic. The first is the *monoamine hypothesis*, which states that ECT increases dopamine, noradrenalin and serotonin concentrations in the brain directly after the first ECT session. The second is the

neurochemical effect hypothesis, stating that ECT response is associated with an improved balance between Gamma-aminobutyric acid (GABA) and glutamate after ECT (Scott, 2011; Michael et al., 2003). The third is the *neurogenesis hypothesis*, based on the increase of neurotrophic factors necessary for the survival and function of particular neurons. Especially concentrations of Brain Derived Neurotrophic Factor (BDNF) showed elevations after a course of ECT (Scott, 2011; Bouckaert et al., 2014). Several studies evaluated the neurogenesis hypothesis, reported on post-ECT cortical and subcortical volume increases (Dukart et al., 2014; Joshi et al., 2015; Abbott et al., 2014; Nordanskog et al., 2010; Ota et al., 2015; Bouckaert et al., 2015; Nickl-Jockschat et al., 2015), though not all volume increases were associated with successful ECT (Bouckaert et al., 2015; Nickl-Jockschat et al., 2015).

Psychotic symptom profile and brain characteristics influencing ECT response

Various ECT studies have shown particular high remission rates and fast speed of remission in patients with psychotic symptoms (Tew et al., 1999; Birkenhager et al., 2003; Petrides et al., 2001; Spaans et al., 2015), possibly explained by specific biological characteristics of this depression subtype (Schatzberg et al., 1992; Fleming et al., 2004). However, a meta-analysis of studies evaluating ECT predictors does not fully support significant associations between psychotic symptoms and ECT response (Haq et al., 2015).

Biological markers such as brain characteristics of late life depression may help to predict the response to ECT. Yet, studies assessing this relation in late life depression are sparse and results show inconclusive associations between characteristics of grey (Lekwauwa et al., 2005) or white matter (Hickie et al., 1995; Simpson et al., 1998) and ECT response.

Clinical heterogeneity and small patients samples may explain the inconsistent results of the studies so far. Studies evaluating the relationship between clinical profile, brain characteristics and ECT response, in well defined samples are highly needed. Depression with psychotic symptoms in particular may add to this knowledge as psychotic symptoms are well defined in clinical practice.

Primary objective and outline of this thesis

Specialized clinical facilities of old age psychiatry provide an opportunity to evaluate the relation between brain characteristics, efficacy, safety and outcome of patients with severe late life depression treated with ECT to improve response prediction of ECT. The primary objective of the present thesis therefore is to evaluate the association between symptom profiles, especially psychotic symptoms, brain

characteristics, ECT response and cognitive impairment in late life depression after short and long term follow-up. The research goals arising from this objective are:

- I To assess the relation between level of medial temporal lobe atrophy, white matter hyperintensities, and global cortical atrophy and ECT response in patients with and without psychotic symptoms
- II To assess the relation between cognitive impairment during and directly after ECT and level of medial temporal lobe atrophy, white matter hyperintensities, and global cortical atrophy prior to treatment
- III To study how specific symptom profiles of late life depression, such as psychotic symptoms or late-onset depression, are related to structural characteristics and to efficacy of ECT
- IV To evaluate whether late life depression with psychotic symptoms is associated with specific functional brain characteristics
- V To evaluate whether symptom profiles and brain characteristics of patients with late life depression treated with ECT are related to long-term cognitive impairment and development of dementia

Structural MRI scans are part of the clinical work-up in the old age clinic before ECT is initiated. MRI is a non-invasive, safe and relatively patient friendly method to obtain information on grey and white matter structures of the brain. In both our naturalistic cohorts (see box 1) structural MRI scans were obtained before ECT. Visual rating scales were used to determine the level of white matter hyperintensities, as measure of vascular damage, and to determine local and global atrophy. Automatic voxel based morphometry (VBM) was used to relate regional grey matter volume with symptom profiles. In the second cohort resting state functional MRI (rsfMRI) scans were obtained for research purpose, as fMRI scans are not involved in the clinical work-up. Independent component analyses (ICA) were performed to evaluate pre-ECT resting state networks in relation to symptom profiles (see box 2 for the applied techniques).

Contents of the chapters

Chapter 2: Structural abnormalities in the brain, such as medial temporal lobe atrophy, white matter hyperintensities or global cortical atrophy, may influence ECT response. The respective value of these factors in response prediction is unclear.

In the second chapter the association between pre-ECT visually rated structural brain abnormalities and ECT response was evaluated. It was predicted that medial temporal lobe atrophy, white matter hyperintensities and global cortical atrophy negatively affect the short-term response to ECT.

Chapter 3: The third chapter describes the background and results of a study evaluating the association between white matter hyperintensities, medial temporal lobe atrophy and transient cognitive impairment during and directly after ECT. Visual rating scales and MRI were used to assess brain characteristics and MMSE scores were used to assess cognitive decline during ECT. We predicted that medial temporal lobe atrophy, white matter hyperintensities and global cortical atrophy influence cognitive impairment during or directly after a course of ECT.

Chapter 4: The fourth chapter describes the relationship between regional grey matter volumes, symptom profiles, and ECT response. Voxel-based Morphometry (VBM) on structural MRI was used to identify regional brain characteristics of psychotic (versus non-psychotic) symptoms and late-onset (versus early-onset) late life depression in relation to ECT response. We predicted that alterations of frontal, parietal and temporal GM volume relate to ECT response, since these regions are involved in the network that is activated during ECT-induced seizures.

Chapter 5: The fifth chapter evaluates resting state functional connectivity across symptom profiles in late life depression. Independent Component Analyses (ICA) was used to evaluate pre-ECT resting state functional connectivity in psychotic versus non-psychotic late life depression. We predicted that psychotic symptoms are related to hypoconnectivity of the frontoparietal networks and basal ganglia and insula, compared with patients without psychotic symptoms.

Chapter 6: The sixth chapter describes a naturalistic longitudinal study assessing the association between pre-ECT global cortical atrophy, medial temporal lobe atrophy, white matter hyperintensities and cognitive decline, dementia and survival after seven to 12 year naturalistic follow-up. We predicted that patients with late life depression and severe brain abnormalities (medial temporal lobe atrophy, white matter hyperintensities and global cortical atrophy) are at risk to develop dementia and live shorter than depressed patients without severe brain abnormalities.

Chapter 7: In the final chapter the findings are summarized and methodological strengths and limitations are discussed. The discussion integrates the main findings to shed a new light on the disease model of late life depression with psychotic

symptoms and the working mechanism of ECT in these patients. The chapter finishes with some thoughts about potential future directions and clinical recommendations.

Box 1. Cohorts of patients studied in this thesis

Study cohorts

The four studies (chapter 2, 3, 4, 6) which are described in this thesis were conducted in a cohort (first cohort) of patients recruited at the clinic for Late life Psychiatry of GGZ inGeest (formerly known as Stichting BuitenAmstel Geestgronden) from 2001 until 2006. The overall aim of the naturalistic cohort was to assess vascular grey and white matter characteristics and to evaluate these factors in relation to ECT response and cognitive impairment after short- and long-term follow-up.

Patients aged 55 years and over with severe unipolar late life depression and eligible for ECT were recruited from secondary referrals for ECT in the catchment area and tertiary referrals from throughout the Netherlands. A total of 81 patients provided informed consent and participated. Depression diagnosis was based on DSM-IV and clinical consensus. MRI scans were obtained pre-ECT to assess age-related grey and white matter characteristics with visual rating scales. Voxel-based morphometry (VBM) was used in 55 patients to compare regional grey matter differences between patients and healthy controls, between patients with and without psychotic symptoms and between late-onset and early-onset depression. Evaluations of depression and cognition were performed with the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Minimal Mental State Examination (MMSE), respectively, weekly before, during and after ECT, as well as clinical evaluations. ECT was administered using an age-dosing protocol. Patients were defined as initial responders if the MADRS score decreased by at least 50 percent from pre-treatment during the course of ECT. Patients were defined as remitters if the MADRS score decreased below 10 points after completion of ECT.

The patients and/or relatives were contacted again after seven to 12 year follow-up to obtain information on cognition and survival. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) was obtained from a proxy of the patients. The IQCODE presents a list of everyday situations where the person has to use their memory, of which each situation is rated for amount of change over the previous 10 years, using a five points scale. An average score from the 16 items is calculated and scores above 3.44 are indicative of cognitive

decline (Jorm et al. 2004). Information on survival and dementia diagnosis was obtained from the relative and confirmed by the general practitioner.

The fifth study of this thesis was conducted in a cohort (second cohort) of a two-site naturalistic longitudinal study named Mood Disorders in Elderly treated with Electro Convulsive Therapy (MODECT). Patients aged 55 years and over with severe unipolar depression and eligible for ECT were recruited from 2011 till 2013 from tertiary psychiatric hospitals GGZ inGeest, Amsterdam, the Netherlands (first site) and University Psychiatric Center, KU Leuven, Belgium (second site). The aim of MODECT was to identify clinical and neurobiological variables associated with ECT response in late life depression.

Patients with a unipolar late life depression diagnosis, with or without psychotic symptoms, based on DSM-IV-TR and MINI, were asked to participate. Forty-nine patients (23 in Amsterdam and 26 in Leuven) provided informed consent and structural MRI and functional MRI scans were obtained before and directly after ECT, as well as after six months follow-up. ECT was administered using a dose titration protocol and evaluations of depression (MADRS scores) and cognition (MMSE scores) were performed before during and after ECT.

The overall aim of the fifth study of this thesis was to evaluate functional resting state characteristics of late life depression with psychotic symptoms compared with patients without psychotic symptoms.

Box 2. The applied techniques**Structural Magnetic Resonance Imaging (MRI)**

MRI is a non-invasive technique to study brain structure and brain function. MRI uses a strong, permanent static magnetic field to align protons in the human brain. With the aid of a second magnetic gradient field the protons are brought to a higher energy level. Upon removal of the gradient field, the protons return to their original states, with different tissue-types emitting different radiofrequency waves. The emitted energy is measured with a coil and is used to reconstruct a structural image of the brain.

a) Visual rating scales

1. The Age-Related White Matter Changes (ARWMC) scale (Wahlund et al., 2001) was used to score white matter hyperintensities (WMH), caused by an atherosclerotic process in small vessels of the brain. The WMH are rated in the basal ganglia, infratentorial, frontal, parieto-occipital and temporal cortex, in left and right sides of the brain. The score per region ranges from 0 (no WMH) to 3 (severe WMH).
2. The Fazekas scale rates the white matter hyperintensities spread throughout the brain, not in separate regions. The total score ranges from 0 (no WMH) to 3 (severe WMH) (Fazekas et al., 1987).
3. Medial temporal lobe atrophy (MTA) was rated with a validated visual rating scale (Scheltens et al., 1992). The MTA scale ranges from 0 to 4 and was applied to the left and right medial temporal lobe. The score of the left and right lobe were summed and divided by two.
4. Cortical atrophy was rated with the Global Cortical Atrophy (GCA) rating scale (range 0 to 3) (Pasquier et al., 1996).

b) automated measures: Voxel-based morphometry (VBM)

VBM is a computerized algorithm to investigate grey matter volumes, white matter volumes or cerebrospinal fluid. VBM assesses the tissue type of every voxel in the brain, to obtain relative estimations of tissue type for each voxel for a group of participants. VBM and Statistical Parametric Mapping (SPM; www.fil.ion.ucl.ac.uk/spm) were used to perform voxel-wise statistical analyses on regional grey matter volumes in subgroups of depression (Ashburner and Friston, 2000).

Functional MRI:

Functional MRI (fMRI) uses the blood-oxygen-level-dependent (BOLD) contrast to map neuronal activity in the brain. Changes in local magnetization result from oxygen-rich opposed to oxygen-poor hemoglobin in blood. Increases in oxygen consumption and blood flow are related to neuronal activity and brain activation.

Resting state fMRI

Resting-state functional magnetic resonance imaging (rsfMRI) is used to study functional properties of the brain while patients are instructed to lay still with their eyes closed (not falling asleep). Spontaneous neuronal activity is recorded as localized changes in BOLD response.

Independent Component analyses (ICA)

Spatially distinct brain regions with co-varying resting state BOLD signals are considered to be functionally connected. Independent Component Analysis (ICA) decomposes whole brain multivariate signals into independent components, representing functional networks (Beckmann et al., 2005).

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