Chapter 1

General introduction

Depression is a highly prevalent and debilitating disorder that is expected to be the second-ranked disease burden in 2020 (WHO, 2004). In addition to personal suffering, depression is related to significant distress and higher morbidity in family and caregivers (Shahly et al., 2013). Electroconvulsive therapy (ECT) is the most effective treatment for depression (Kho et al., 2003; Pagnin et al., 2004; UK ECT Review Group, 2003) but its widespread use is hampered by the fear of cognitive side effects. The clinical effects with the cognitive side effects determine the patients' outcome of ECT. This thesis focuses on neurocognitive performance in electroconvulsive therapy (ECT) and is complementary to the thesis of Harm-Pieter Spaans "Efficacy of electroconvulsive therapy – too brief or not too brief?", whose thesis primary focuses on the efficacy of ECT. Several questions will be answered in this thesis: what is the nature and extend of changes across multiple domains of neurocognitive functioning in depressed patients after ECT? What is the evolution of these changes within six months after the last ECT? Is there any variability concerning cognitive performance between patients? Does ultrabrief pulse ECT reduce the cognitive side effects compared to brief pulse ECT?

Electroconvulsive therapy

Electroconvulsive therapy (ECT) has been used for more than 70 years. With the development of psychiatric medications and stigma associated with ECT in the 1960's, the use of ECT treatment declined. The use of ECT has increased since the 1970's because of improved treatment delivery methods, increased safety and comfort measures, and enhanced anaesthesia management. ECT is widely acknowledged as effective in the treatment of psychiatric disorders (Van den Broek et al., 2010). It is generally applied in persons with severe depression with psychotic features, psychomotor retardation, refusal to eat and drink, suicidal thoughts/ideation, or in case of pharmacotherapy resistance (Salzman et al., 2002). The absolute number of patients who receive ECT is large, annually estimated at 1 million worldwide (Leiknes et al., 2012; Weiner and Prudic, 2013). In the Netherlands approximately 700 patients a year are treated with ECT. Treatment with ECT produces rapid response and remission rates (Husain et al., 2004) and is somatically safe for patients across the adult life span.

Neurocognitive side effects

History

From the start of ECT on (in the last century), neurocognitive functioning in patients treated with electroconvulsive therapy, especially memory, was already brought to attention (Duncan, 1949; Zubin, 1948). Amnestic phenomena were described as the most prominent observable during and after ECT. Contrary to the present opinion, the amnesia for the ECT treatment itself was one of the reasons for its popularity. The ECT related cognitive side effects impressed some clinicians to such an extent that they proposed amnesia as a cornerstone for theoretical explanations of the therapeutic efficacy of ECT (Zubin, 1948). Nowadays, cognitive side effects are described as the major complications limiting the use of ECT. In the 50ties-60ties researchers like Cronholm (Cronholm and Blomquist, 1959; Cronholm and Lagergren, 1959; Cronholm and Molander, 1957, 1964; Cronholm and Ottosson, 1963) started to write a series of papers on memory disturbances after ECT focussing on the nature and changes of memory during and after ECT. After the opposition of society against diagnosis and treatment of psychiatric disorders from a biological perspective in the 70ties, comparative studies became important in the effort to optimise ECT to be efficacious with less cognitive side effects. Nowadays it is generally acknowledged that cognitive impairment may be an important side effect (Calev et al., 1995; Calev and Phil, 1994; Fraser et al., 2008; Ingram et al., 2008; Semkovska and McLoughlin, 2010; Tielkes et al., 2008). Optimising ECT treatment by comparing different methods of ECT on efficacy and neurocognitive side effects is still of major importance and a main focus in ECT research. Consequently, more attention is given to these comparative studies in search of limiting neurocognitive impairments after ECT. Unfortunately, to date much less attention is given to evaluating patients in the long term to study the prevalence, nature, extend and persistency of cognitive impairment. Hardly any quantified cognitive data are available which makes it difficult to estimate its clinical relevance. Therefore, in this thesis the neurocognitive changes are quantified with respect to their severity, their pattern and their persistence over a period of six months after ECT.

ECT neurocognitive profile

Immediately after the ECT session the ECT neurocognitive profile primarily includes decreased orientation in time and place. During and after an ECT course anterograde amnesia for recent information, and retrograde amnesia for long-term autobiographical and impersonal information are found (Ingram et al., 2008; Rami-

Gonzalez et al., 2001; Reisner, 2003; Sackeim et al., 2000; Semkovska et al., 2011) [*Box 2*]. Other neuropsychological domains that become inefficient or impaired include processing speed, attention, verbal fluency, and executive functioning. These cognitive impairments are transient in many cases but not in all. In the weeks and months after ECT, significant improvement in antero- and retrograde amnesia has been observed, but the moment at which full recovery after ECT, if any, has been achieved remains unclear (Ingram et al., 2008; Sackeim, 1992). Some studies suggest that especially retrograde amnesia of autobiographical information is rather persistent (Rami-Gonzalez et al., 2001; Reisner, 2003; Sackeim et al., 2000). In this thesis we focus on the persistence of these amnestic side effects and on its prevalence, nature and extend. Special attention is given to autobiographical amnesia and cognitive domains other than memory such as attention and executive functioning [*Box 3*].

Box 2

Amnesia
Anterograde amnesia Inability to acquire, store, or retrieve new information long-term and consciously after a memory-impairing incident. **Retrograde amnesia** Inability to consciously re-activate information that was stored long ago. **Autobiographical amnesia** Inability to recall events (and to a minor degree personal knowledge) from own life *(Markowitsch and Staniloiu, 2012)*

Neurocognitive effects of ECT in the elderly

Especially for the elderly patients with a depressive disorder, ECT is an effective and relatively safe treatment (Stek et al., 2009). The effects of ECT on neurocognitive functioning in elderly depressed patients are still unclear (Tielkes et al., 2008). It is generally assumed that, compared with younger adults, elderly patients are more vulnerable to cognitive side effects after ECT and that the side effects are more severe (Zervas et al., 1993). Most studies of ECT and neurocognitive functioning however have focused on younger and mixed-age populations. In this thesis special attention is given to elderly depressed patients.

Box 3

Neuropsychological tests used in this thesis
Domain **Global cognitive function** Mini Mental State Examination (MMSE) **Memory function** Visual AssociationTest (VAT) 10 Words Verbal Learning Task (10 WVLT) Amsterdam Media Questionnaire (AMQ) Kopelman's Autobiographical Memory Interview (AMI-Kopelman) **Attention and executive function** Digit span (forward and backward) Expanded Mental Control Test (EMCT) Wordfluency (category & letter) Stroop Color Word Test (STROOP) Trail Making Test (TMT A & B) Behavioural Assessment of the Dysexecutive Syndrome (BADS key search & rule shift cards)

ECT parameters influencing neurocognitive side effects

The exact aetiology of reported side effects of ECT is unclear but the extent of the memory problems has been shown to be dependent upon techniques used in the administration of ECT. Earlier treatment used sine wave stimuli, which produced more severe cognitive side effects compared to brief pulse ECT that is now commonly used. Right unilateral (RUL) ECT has been reported to result in less severe cognitive side effects, compared to bilateral (BL) ECT (Semkovska et al., 2011). Some recent studies suggest that the reduction of the pulse width of the electrical current to induce seizures in ECT – from brief pulse (BP) (0.5 ms and up) to ultrabrief pulse (UBP) (0.2–0.3 ms pulse width) – can be effective in minimizing cognitive impairment while maintaining efficacy (Loo et al., 2007; Sackeim et al., 2008; Sienaert et al., 2006). In this thesis BP ECT is compared with UBP ECT regarding the benefits on neurocognitive side effects.

Individual variability of neurocognitive side effects

In this thesis special attention is given to individual variability of neurocognitive side effects. Most of our knowledge about neurocognitive functioning after ECT is based on results analysed at group level. Nevertheless, there may be a variation and interplay in both individual vulnerability and treatment parameters explaining why cognition declines after ECT in some patients and improves in others (McClintock et

al., 2014; Sackeim et al., 2007). Two recent studies suggest that in spite of stable or improved neurocognitive performances at a group level, there may be neurocognitive impairments for a substantial minority of depressed patients receiving ECT (Dybedal et al., 2014; Hausner et al., 2011). Mean group scores can overlook inter-individual variability in neurocognitive performances which may limit clinical interpretation. This thesis describes the presence of inter-individual variability in neurocognitive performances after ECT.

Studies used in this thesis

This thesis is based on two studies:

A naturalistic prospective study of depressed elderly patients

This was conducted at the academic department of old age psychiatry of GGZinGeest/VU Medical Center in Amsterdam. Patients aged 55 years and older referred for an acute course of ECT treatment, suffering from a primary major depressive disorder or bipolar depression (with or without psychosis) were included in this study. Patients came for ECT from referrals in the catchment area and from tertiary referrals throughout the Netherlands. Over a five-year period (2002–2007), 72 patients were treated with ECT. The institutional review board of GGZinGeest approved the study. Baseline neuropsychological data before the first ECT, one week after the final ECT and six months after the final ECT were available for the present thesis.

A randomized controlled multicentre trial

From April 2007 until March 2011, a prospective, double blind, randomized multicenter trial was conducted comparing the efficacy and cognitive side effects of brief pulse and ultrabrief pulse RUL ECT (Netherlands National Trial Register number NTR1304). At three and six months after the randomized phase, naturalistic follow-up assessments were performed. Patients were recruited from 3 ECT centers: Parnassia (The Hague) and GGZ Delfland (Delft) in The Netherlands and the University Psychiatric Center KU Leuven, Campus Kortenberg (Kortenberg) in Belgium. All in and outpatients of 18 years and older suffering from major depressive disorder or bipolar depression (with or without psychosis) according to DSM-IV criteria who were referred for ECT were screened for inclusion in the study. The Institutional Review Boards (IRBs) of these hospitals approved the study. Four cognitive assessments were available for this thesis: a week before the first ECT (pre-ECT), one week after finishing the treatment course, and after a follow-up of three and six months.

Aims and outline of this thesis

This thesis outlines studies that examine the influence of ECT on neurocognitive performances in depressed patients undergoing ECT. The effects of different treatment parameters, e.g. brief pulse versus ultrabrief pulse are compared. Trajectories of neurocognitive performance before and after ECT are explored. During follow up differences were compared in neurocognitive change between patients receiving ECT and patients not receiving any ECT by using normative data of a representative sample. Finally, we tried to detect inter-individual variability in neurocognitive performances after ECT. This thesis specifically focusses attention on older adults and specific cognitive domains such as (auto)biographical retrograde memory and executive functioning.

Chapter 2 reviews all prospective studies using right unilateral (ultra) brief pulse index electroconvulsive therapy published up until February 2011, which used at least one instrument for cognitive assessment before and after ECT. The severity and persistence of neurocognitive side effects immediately (one to seven days post ECT), between one and six months and after six months post ECT were assessed by calculating effect sizes using Cohen's d.

In *Chapter 3*, global cognitive function, memory and executive function were assessed in 42 depressed elderly (≥ 55 years) patients. Assessments were done before ECT treatment started and one week and six months after ECT. Associations between cognitive functioning and electrode placement, total number of treatment sessions, age and the severity of depression on time of cognitive measurement were studied.

Chapter 4 focuses on a prospective, double blind, randomized multicenter trial in three tertiary psychiatric hospitals. We compared the efficacy and cognitive side effects of high dose unilateral brief pulse ECT with high dose unilateral ultrabrief pulse ECT in the treatment of major depression.

Chapter 5 describes the naturalistic follow up of the randomized multicentre trial. We compared the differences in relapse rate and cognitive performance three and six months after index ECT with unilateral brief pulse ECT or ultrabrief pulse ECT.

In *Chapter 6* the changes in retrograde amnesia for (auto)biographical memory and executive functioning of depressed patients treated with right unilateral ECT were

evaluated one week, 3 and 6 months after the last ECT session. The group of patients receiving ECT at any time during the follow up was compared to the group of patients not receiving any ECT after the index episode and the level of cognitive performances was compared with normative data of a representative normal population.

Finally, in *Chapter 7*, we tried to detect inter-individual variability in neurocognitive performances after ECT in two cohorts. We compared subgroups of patients whose cognitive function declined significantly after ECT with those that improved significantly. We examined whether specific demographic and clinical features discriminated between these two subgroups.

In *Chapter 8* and *9* the main findings of these studies are summarized, and methodological considerations and the clinical implications for the depressed patients treated with ECT are discussed.

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