# WHO BENEFITS MOST?

## Towards accurate prediction of electroconvulsive therapy outcome

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University of Antwerp

Faculty of Medicine and Health Sciences | 2019

Dissertation for the degree of doctor in medical sciences at the University of Antwerp

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# Who benefits most?

Towards accurate prediction of electroconvulsive therapy outcome

# Wie heeft het meeste baat bij behandeling?

Op weg naar nauwkeurige voorspelling van de effecten van elektroconvulsietherapie


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**Cover**
Luc Derck

**Layout**
Rein De Block

**Publisher**
Global Academic Press

**Printer**
Proefschriftmaken.nl

**ISBN**
978-94-6380-397-7

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# GENERAL INTRODUCTION


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## 1.1. Major depressive disorder

Major depressive disorder (MDD) is a psychiatric disorder characterized by negative and pessimistic thoughts, feelings of worthlessness and guilt. Psychomotor changes are important clinical features of a depressive episode as well. MDD adversely affects a person's family and work life, sleeping and eating habits and general health. A major depressive episode (MDE) is recurrent in the majority of patients and at its worst, depression can lead to suicide. According to DSM-5 (1), a person must experience five or more symptoms during the same 2-week period and at least one of the symptoms should be either depressed mood or loss of interest or pleasure:

- Depressed mood most of the day, nearly every day.
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
- Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day.
- Diminished ability to think or concentrate, or indecisiveness, nearly every day.
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

To be diagnosed as MDD, these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. They can also not be the result of substance abuse or another medical condition.

MDD is a relatively prevalent psychiatric disorder, with a 12-month prevalence of 5-7% in Belgium (2). At the European level, there are similar prevalence rates and it was calculated that MDD is responsible for 3.8% of all disability-adjusted life years, and for 11% of years lived with disability. That makes MDD the leading cause of disability worldwide, and a major contributor to the global burden of disease (3).

## 1.2. Psychomotor functioning in MDD

Psychomotor retardation and agitation are core symptoms of MDD (1). The relevance of psychomotor symptoms has been described in several reviews over the past few years (4–7). Psychomotor symptoms have unique significance. Because of their high discriminative validity, they may be the only symptom cluster in MDD that can distinguish depression subtypes.

Psychomotor signs have been defined as all those activities in which movement or action, i.e. planning, programming, and execution, is the principal component rather than thinking or feeling (5). The term 'psychomotor' encompasses wider involvement of perceptual processes and cognitive-control mechanisms, which underlines that motor control involves more than an adjustment of timing and initiating muscle contractions. To further fine-tune the definition, a combination of psychomotor assessment tools comprising psychomotor rating scales and experimental tasks from each domain, measuring motor as well as cognitive aspects should preferably be used (4–7).

Despite being a core symptom of MDD, psychomotor symptoms are difficult to measure and their clinical observation is rater-dependent and therefore subjective. The CORE Assessment of Psychomotor Change (CORE) is a rating scale developed to assess observable psychomotor symptoms in a uniform and standardized way in patients with MDD. The scale provides a global impression of psychomotor functioning (in three different domains – retardation, agitation, and non-interactiveness) and was designed to distinguish between non-melancholic (NMD) and melancholic depression (Mel-D) (8,9). However, the CORE relies on the subjective judgment of the investigator. Several other methods have been developed aiming to ensure more objective measurement of psychomotor functioning (5). This could allow the detection of abnormalities that escape the clinical eye. Such objective measurements could improve the classification of depressive subtypes, assist in monitoring the evolution of a depressive episode and play a role in treatment selection (7).

Many of the objective measurement methods that have been developed focus on the domains of gross and fine motor activity (5). Gross motor activity refers to the movement of the entire body that enables general movement and balance. Fine motor skills, on the other hand, are involved in fine movements such as writing and drawing. Previous research has applied drawing tasks in depressed samples to reveal substantial fine motor retardation in patients with MDD (10–14). Several studies have measured gross motor activity in psychiatric disorders by means of wrist accelerometry (15,16) and found lower gross psychomotor activity in depressed patients than in healthy controls (4,17–19). Psychomotor symptoms are also part of other psychiatric disorders, such as schizophrenia (20,21).

Several factors must be taken into account when studying psychomotor functioning in MDD. First of all, some authors claim that differences in psychomotor disturbance can be attributed to variations in symptom severity, rather than being distinguishing features of depression subtypes in themselves (22,23). Others do not agree, however (24,25). The second factor to take into account is age. Cognitive and psychomotor retardation often occur in the process of normal aging (7,26) and it has been suggested that aging and depression have an additive effect on psychomotor performance (12). The final factor that is believed to have an influence on psychomotor performance

in depressed populations is pharmacotherapy. Psychotropic drugs can contribute to improvements in psychomotor and cognitive performance in the long term, mostly due to clinical recovery. On the other hand, certain drugs such as benzodiazepines have been found to impair psychomotor performance (27,28).

Studies examining the role of psychomotor retardation in treatment outcome have found differential results. Current literature regarding antidepressants is inconclusive, though tricyclic antidepressants may be considered for the treatment of patients with psychomotor retardation (6). Available evidence also suggests that depressed patients with psychomotor retardation may respond well to electroconvulsive therapy (ECT)(29).

## 1.3. Depression subgroups

MDD is not a homogeneous disease. Several subtypes have been identified based on, amongst others, the presence of melancholic or psychotic symptoms. In patients with DSM-defined Mel-D, a loss of pleasure in (almost) all activities is seen with a mood that lacks reactivity. Besides that, patients with Mel-D often experience profound despair, they feel worse in morning hours, wake up early, have marked psychomotor retardation or agitation, significant anorexia and/or excessive feelings of guilt (1). In patients with psychotic depression, delusions and/or hallucinations are present that are either mood-congruent or mood-incongruent (1).

Parker et al. (2000) describe a hierarchical model for distinguishing depression subtypes by the presence of three specific features (30). A depressed mood is presumed to be present across all three subtypes and can therefore not provide distinction. The distinction between NMD and Mel-D is marked by the presence of psychomotor disturbance in melancholia (8,30,31). Psychomotor disturbance appears to be more prominent in the depressive subtype with psychotic symptoms than in patients who do not have psychotic symptoms (8,32). The latter subtype is however distinguished by the presence of psychotic symptoms. To summarize, psychomotor disturbance and psychotic symptoms construct the hierarchical model and members of the residual NMD subtype lack both features (30) (Figure 1-1). Underlying, each subtype is assumed to be characterized by disruptions in the three relevant neurotransmitter systems (serotonin, noradrenaline, and dopamine) but their relative contributions vary. Serotonin seems to play an important role in NMD, whereas melancholic and psychotic depression additionally have contributions from the noradrenergic and dopaminergic systems, respectively (33).

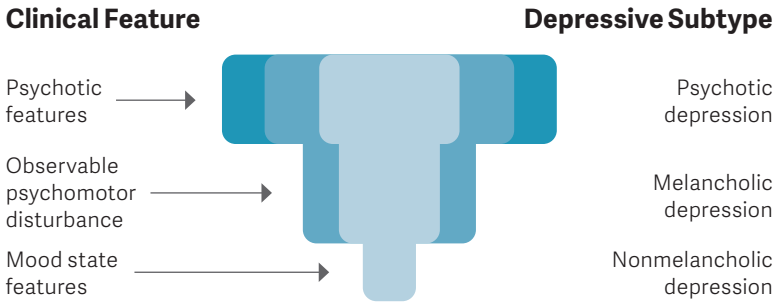


*Figure 1-1 - Hierarchical Model for Distinguishing Depression Subtypes (30)*

Among depressed inpatients, psychotic features are rather prevalent with approximately 35% meeting diagnostic criteria (34). Lifetime prevalence varies between 0.35% and 1% in the general population, with higher rates in older age (35). The hierarchical model used to distinguish depression subtypes implies that patients with psychotic symptoms also have psychomotor symptoms or melancholia (33). Although most of the depressed patients with psychotic features indeed have Mel-D or observable psychomotor disturbance, a small group of depressed patients with psychotic symptoms does not present with these melancholic features. The prevalence of psychosis is higher in melancholic patients (51.1%) than in nonmelancholic patients (17.7%), but patients with NMD and psychotic symptoms definitely exist (36).

Although motor retardation is considered to be one of the key elements of the melancholic subtype of depression (37), it remains unclear whether differences in objective psychomotor performance can actually distinguish between depression subgroups.

## 1.4. Treatment of MDD and the role of ECT

Psychopharmacological treatments are effective in cases of moderate or severe major depression. Unfortunately, there are three major problems with psychopharmacological interventions. First, often there is a delay of several weeks between the start of treatment and the first beneficial effects (38). The second issue is the limited adherence to the therapy (39) and last but not least, resistance to antidepressant treatment remains an important issue in clinical practice (40). Response rates for commonly used antidepressants are moderate and remission rates are even lower (41,42). Moreover, the patients that take more steps to respond or remit show more relapse in long-term follow up (42).

The search for a more effective treatment method, with a limited delay of onset and the possibility to control adherence to treatment, has led clinicians back to ECT. The efficacy of ECT (compared to placebo and simulated ECT) was convincingly demonstrated (43). Treatment with ECT is significantly more effective than pharmacotherapy as well (43,44).

Besides that, ECT has a faster onset of action than treatment with antidepressants. Only about a third of patients with MDD treated with any single antidepressant attains full symptom remission in 8-week medication trials, while the same percentage of patients achieve remission with ECT after 2 weeks of treatment (45).

In major depression treatment guidelines, ECT is generally recommended following non-response to pharmacotherapy. In case of very severe depressive symptoms, high suicidality, urgency (not eating or drinking), a good response in a past depressive episode or patient preference, ECT can be used as first-line treatment. Guidelines differ in whether or not they recommend ECT for specific subtypes of depression such as psychotic and melancholic depression (46).

## 1.5. Technical aspects of treatment with ECT

The duration of a treatment course with ECT is variable and depends on its effect, which is preferably evaluated every week during the course. Treatments should be continued until remission is reached or when there is no further improvement during the last three treatments and the patient had at least 10 treatments. The course can also be stopped when there is no clinical effect after 10 treatments (47). Treatments are given twice a week, based on literature concluding that treating three times a week has no advantage in antidepressant effect over twice weekly schedules (43,48). Because treating patients three times a week does seem to result in a somewhat faster response (with however more cognitive side effects)(49), increasing treatment frequency can be considered in life-threatening cases.

### Anesthetics

It is recommended to use a fast and short-acting hypnotic. The choice of a specific hypnotic has to be made by the anesthesiologist and the psychiatrist depending on the potential influence on the course of ECT and the expected side effects. There are several options, but it is not known which IV anesthetic medication leads to the greatest improvement in depression scores with minimal side-effects (50). Methohexital has long been the most widely used anaesthetic for ECT, but problems with its supply have led to an increased usage of other hypnotics. Compared to methohexital, advantages of Propofol are its short duration of effect, the relative hemodynamic stability and anti-emetic properties (51). Etomidate is slightly proconvulsive and also has no major hemodynamic effects (47,52). Ketamine is an alternative, which could accelerate the antidepressive effect (especially when used as add-on anesthetic). However, it should be cautiously used due to the increased risk of cardiovascular and psychiatric side-effects (53). According to a recent literature review, best quality seizures would be provoked with Etomidate as an anesthetic (54). Succinylcholine is the muscle relaxant routinely used in ECT.

### Electrode position

A recent meta-analysis showed no difference in efficacy between high-dose right unilateral (RUL) ECT and moderate-dose bitemporal (BT) ECT. RUL ECT has some advantages regarding cognitive side-effects (55). Because BT ECT does postulate a faster decrease in depressive symptoms (56), this treatment option is preferred when a rapid response is needed. RUL ECT should be given at five times and BT ECT at two times seizure threshold (47).

### Dosing

The stimulus dose is often based on the age method for RUL treatment and the half-age method for bilateral interventions (57). However, recent research suggests dose titration has advantages over the age-based methods with better response, lower peak doses and lower total cumulative dose (58). Therefore, dose titration is the dosing method of first choice.

### Stimulus parameters

Most frequently, a brief pulse (BP, 0.5-1.0ms) stimulus is used. Ultrabrief pulse (UBP, 0.3ms) ECT has recently been extensively investigated as a treatment option that can combine efficacy with limited cognitive side effects. However, a meta-analysis showed that BP ECT was slightly more effective than UBP ECT but led to more cognitive side-effects (59).

### Seizure adequacy

The therapeutic effect of ECT requires a stimulus above seizure threshold and a generalized motor seizure of at least 20 seconds. On the EEG one should see early onset slow waves, high amplitude, low frequency, postictal silence, waxing, and waning. Furthermore, accompanying tachycardia should be present. A study looking at seizure adequacy markers and prediction of ECT response found that higher quality of hemispheric brain wave synchronicity and wave amplitude were associated with higher symptomatology decrease (60).

## 1.6. Predictors of response to ECT

Administering ECT as a first-line treatment to depressed patients, whose clinical profile predicts a good response to ECT, can prevent patients from suffering from a severe depressive disorder for months or years while searching for the correct psychopharmacological treatment. ECT is well suited for a personalized approach that could increase its efficacy, as well as reduce the impact of side effects. This personalized approach could be based on the identification of subpopulations of patients sharing common clinical and biological features that predict a good ECT outcome (61). In this doctoral thesis, we mainly focus on clinical predictors of response to treatment with ECT, although data on both clinical and biological predictors were gathered. Therefore, the current literature on both biological and clinical ECT response predictors is discussed briefly in this section.

### 1.6.1. Biological predictors

Based on different hypotheses of mechanisms underlying depression, a few biological variables seem of interest in the prediction of treatment response.

Increasing evidence supports a stress-related model of depression. Limbic structures influence mood and decreased levels of brain-derived neurotrophic factor (BDNF) and other growth factors could result in atrophy of these structures. The hippocampus is one of the limbic structures with a supposed role in mood disorders, playing a role in learning and memory as well as regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Both of these functions are disturbed in major depression. Additionally, the hippocampus is connected to the amygdala and prefrontal cortex, two structures even more directly involved in emotion and cognition and thereby contributing to other depressive symptoms (62). Lowered serum BDNF seems to be a peripheral manifestation of depression, but serum concentrations do not correlate with depression symptom severity (63). BDNF seems to increase after treatment with ECT (64), suggesting that neurotrophic effects might be a final common pathway in MDD treatment. The neurotrophic action of electroconvulsive therapy could reverse neuronal atrophy and as a consequence contributes to the therapeutic effect (62). However, the increase of BDNF and hippocampal enlargement lack a correlation with an improvement of depressive symptoms suggesting that ECT has neurotrophic effects regardless of clinical response (64,65). Enhancing neurogenesis could enable a dysfunctioning hippocampus to restore control over the HPA-axis, allowing recovery (66).

To summarize, stress lowers BDNF expression and as a consequence, neuroplasticity is limited potentially resulting in (hippocampal) atrophy. Dysfunctioning of the hippocampus hampers control over the HPA-axis and higher cortisol levels limit BDNF expression. ECT seems to intervene by increasing BDNF levels (67) resulting in enhanced neuroplasticity and restored control over the HPA-axis (Figure 1-2).

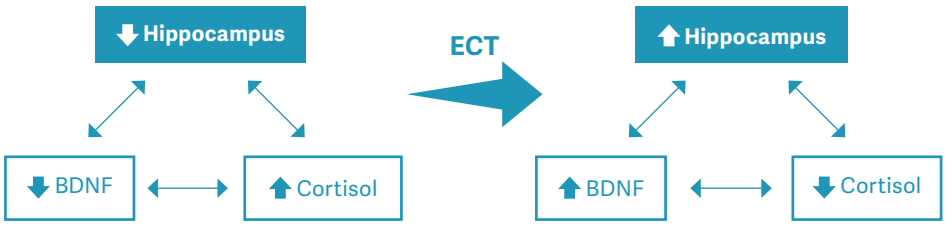


*Figure 1-2 – Stress-related changes in depression before, and after ECT.*

Although they are involved in the mechanism underlying depression and its treatment, the above factors have (as far as we know) not been studied in one and the same patient popu-

lation. To increase understanding of the role of the separate components and to determine whether or not they can play a role (alone or in combination) in ECT response prediction models, it could however be valuable to assess a combination of these factors in a severely depressed population scheduled for treatment with ECT: baseline BDNF serum levels and genotypes (68), brain volumetry (69) and functioning (70,71) and performance of the HPA-axis (72,73).

### 1.6.2. Clinical predictors

In clinical practice, the time and money to assess biological variables with a potential role in ECT response prediction are not always available. Therefore, easy-to-assess clinical variables associated with treatment outcome could be even more valuable. Consequently, this is the main focus of this doctoral thesis. Several large trials have addressed this subject in the past years.

In a recent meta-analysis (74) longer episode duration and presence of medication failure predicted a poor ECT outcome. Greater age and presence of psychotic symptoms only seemed to be weakly associated with a better response to ECT. Bipolar diagnosis, gender, age of onset and the number of previous episodes were not associated with treatment outcome. The analyses of depression severity and melancholic features were inconclusive due to heterogeneity between the studies.

Studies looking at the best way to use these predictors are scarce. Finding the best definition of a predictor for incorporation in prediction models is however of great importance for the adequacy and predictive capacity of these models. The most promising predictors are in our opinion age, depression severity, psychomotor functioning, psychotic symptoms, and treatment resistance.

Age can either be used as a continuous variable or in the form of age groups (75) and seems to be a predictor of rapid remission (76). The predictive value of the different subgroups of psychomotor symptoms (retardation, agitation) is not clear (6,77). In past projects, often only clinical judgment of the treating psychiatrist or the clinician-rated CORE (scale for assessment of psychomotor functioning)-scores were used to assess psychomotor functioning (6). One study found that CORE-defined melancholia predicted a beneficial ECT outcome (78). Research on more objectively measured psychomotor retardation and agitation could be of added value to determine the value of psychomotor functioning as a predictor of ECT outcome. Patients with psychotic symptoms also seem prone to respond to ECT (79,80). Up to recently, however, there was no instrument to measure the severity of the psychotic component of MDD. The development of the Psychotic Depression Assessment Scale (PDAS) changes this. The scale covers both the psychotic and depressive domains of psychotic depression (81,82). One could expect that increasing severity as measured by the PDAS is more sensitive as a predictor than the simple presence or absence of psychotic symptoms. The PDAS was however not tested on its capacity to predict ECT outcome. An-

other predictor that seems relevant is treatment resistance. Treatment resistance is usually defined as more than two failed antidepressant trails and as such its presence is associated with a relatively poor response to ECT (74). Instead of a dichotomous definition of treatment resistance, it can also be described as a continuum (83). The Maudsley Staging Method (MSM) differs from other staging models in that it incorporates two clinical factors associated with treatment resistance, i.e. depression severity and episode duration, in addition to treatment factors (84). According to Fekadu et al (2009), authors of the MSM, staging treatment resistance only in relation to the number of antidepressants used says little about the specific nature of the depression itself. The MSM has never been used specifically in an ECT population to test its predictive capacity.

Besides the relatively extensively investigated predictors mentioned above, there is limited evidence for a few others that are however promising. According to a recent review, high suicidality is associated with a better response to treatment with ECT (61). Presence of a borderline personality disorder is generally associated with poorer outcome (85).

## 1.7. Side-effects

Treatment with ECT is often well-tolerated. Adverse events such as nausea, headache, and myalgia after treatment are usually mild and self-limiting and can be treated symptomatically. Prolonged seizures can occur, but the most common cause of morbidity and mortality after ECT are cardiovascular complications, although they are often uneventful in patients without pre-existing risk factors (86). It is important to note that the ECT-related mortality rates were estimated at 2.1 per 100 000 treatments (87). Therefore we can conclude that death as a consequence of treatment with ECT is extremely rare, knowing that the mortality rate of general anesthesia related to surgical procedures is estimated at 3.4 per 100 000 (88).

Cognitive side-effects of treatment with ECT are rather common. Right after treatment, ECT can cause postictal confusion or even delirium. These conditions tend to resolve within 1 hour after the procedure (86). Subacute cognitive side-effects include anterograde and retrograde amnesia. Anterograde amnesia typically resolves within two months after an ECT course is completed (89,90). The assessment of cognitive deficits secondary to ECT is complicated by several issues related to the illness it is used to treat. Depression itself is associated with cognitive impairment (91). When depression is treated and the related cognitive impairment resolves, there can be impairment at the same time secondary to ECT, which makes interpreting cause and effect difficult. Besides that, many patients experience significant residual cognitive impairment even when recovered of their MDD (92). Cognitive side effects can impair the judgment of ECT response and possibly result in premature termination of the treatment (93).

Retrograde amnesia is the most common persistent adverse effect of ECT. Shortly after ECT, some of the patients have gaps in the memory of events that occurred before the

treatment, and retrograde amnesia may extend back several months or years. Although retrograde amnesia often improves during the first few months after ECT, for many patients, recovery is incomplete, with prolonged amnesia regarding events that occurred close to the time of treatment. Objective measures found the memory loss to be relatively short term (<6 months post-treatment), the subjectively reported memory problems are more persistent (>6 months post-treatment)(94). This would suggest that ECT as currently practiced does not cause significant lasting retrograde amnesia (95).

Cognitive impairment as a consequence of ECT can be reduced by using the unilateral placement of electrodes and by limiting the number of treatments (96–98). Given the difference between objectively measured cognitive function and subjectively experienced impairment, both have to be evaluated (99). At least one-third of patients report persistent memory loss (100).

## 1.8. General research goal

The current literature suggests that it may be possible to predict the ECT outcome based on clinical variables. For this reason, we used an extensive set of different measures to describe baseline patient and depression characteristics with the goal to test whether a successful response prediction model could be created with a combination of these clinical features and to develop a decision-making tool that would afford a more accurate indication of ECT outcome.

## 1.9. Outline of the thesis

Before starting our clinical studies, we reviewed the literature on promising ECT response and remission predictors, among which were age, psychotic symptoms, depression severity, and melancholia (Chapter 3). Based on the results of this meta-analysis, we began our search for the most accurate response prediction model, diving deeper into the separate predictors to try and disentangle their relative contributions. We look for the most accurate definition of treatment resistance (Chapter 4) and psychotic symptoms (Chapter 5) as potential predictors, with a third factor, psychomotor functioning (Chapter 6) being investigated more extensively: we explore its potential to distinguish depression subgroups (Section 6.1), look for correlations between the assessment methods used (Section 6.2) and, last but not least, evaluate its capacity to predict ECT outcome (Section 6.3). In the subsequent part of this doctoral dissertation, we focus on the relative contributions of the different predictors (Chapter 7), taking steps towards the creation of an adequate prediction model. In the final chapter (Chapter 8), we briefly describe the effect of ECT on cognitive functioning.

2

# METHODS


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## 2.1. Study design

We designed a prospective observational study for patients with a depressive disorder that are treated with ECT. The study name was PROTECT, an acronym for PRediction Of Treatment response to ECT in depression and cognitive side effects. Prior to the ECT course, depression characteristics such as episode duration and treatment resistance, psychotic symptoms, psychomotor functioning, cortisol levels, BDNF and inflammatory markers, brain structure, and vascular burden were assessed. Mood and cognitive functioning were measured before, during and one week after the ECT course. On top of that, a follow-up visit was planned at 3 and 6 months after the ECT course. The study was registered at ClinicalTrials.gov (identifier: NCT02562846). The study and main researcher were financed by a collaboration between Antwerp University and Duffel University Psychiatric Hospital. A time schedule of this project is displayed in Table 2-1.

*Table 2-1 - Time schedule PROTECT*

| | S | T-1 | T0 | T1 | T2 | T3 | -TW- | Tstop | Tfu1 | Tfu2 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Socio-demographics** | X | | | | | | | | | |
| **Clinical characteristics** | | | | | | | | | | |
| Somatic and psychiatric history | X | | | | | | | | | |
| VBI + AB-index | X | | | | | | | | | |
| MINI | X | | | | | | | | | |
| MSM | X | | | | | | | | | |
| HDRS | X | | X | X | X | X | X | X | X | X |
| MADRS | | | X | X | X | X | X | X | | |
| PDAS | X | | | | | | | X | | |
| Apathy scale | | X | | | | | | X | | |
| MANSA | | X | | | | | | X | X | X |
| **Psychomotor functioning** | | | | | | | | | | |
| BFCRS | | X | | | | | | X | | |
| CORE | | | X | X | X | X | X | X | | |
| Drawing tasks | | X | X | X | X | X | | X | | |
| 24hr motionwatch | | X | | X | X | X | | X | | |
| CPT | | X | | X | X | X | | X | | |

*(Table continues on page 20)*

| | S | T-1 | T0 | T1 | T2 | T3 | -TW- | Tstop | Tfu1 | Tfu2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Cognition | | | | | | | | | | |
| MOCA | | X | | X | | | | X | X | X |
| HVLT-R | | X | | | X | | | X | X | X |
| AMI-part C | | X | | | | | | X | X | X |
| SDST | | X | | | X | | | X | X | X |
| PRMQ | | X | | | | | | X | X | X |
| Orientation recovery time | | | After each ECT | | | | | | | |
| ECT procedure & seizure characteristics | | | After each ECT | | | | | | | |
| MRI | | X | | | | | | X | | |
| Blood sample | | X | | | | | | X | | |
| Hair sample | | X | | | | | | | X | |

*S= Screening. T-1 = the week before the start of ECT. T0 = the day before ECT starts. T1 = after 1 week (2 ECTs). T2 = after 2 weeks (4 ECTs). T3 = after 3 weeks (6 ECTs). -TW- = weekly after T4. Tstop is the week after the last ECT, cognitive testing and the blood sample will be done exactly one week after the last ECT. Tfu1 is the follow-up visit after 3 months. Tfu2 is the follow-up visit after 6 months. Medication use will be registered throughout the duration of the project. ECT procedure = electrode placement, type of anesthesia and dosage. Seizure characteristics = motor and EEG duration. The other abbreviations are explained under the heading 2.6 (Assessment).*

## 2.2. Recruitment

All psychiatrists providing patients with ECT treatment were informed about the study. The psychiatrists planning ECT treatment and the ECT-team receiving the patient names briefed the main researcher when a patient was planned to be treated with ECT for MDD. All these patients were screened for inclusion in our study and when eligible, asked for their informed consent. Patients were recruited between August 2015 and August 2017.

## 2.3. Selection of patients

### 2.3.1. Inclusion criteria

To be eligible for study inclusion, patients must meet the following inclusion criteria:

- Admitted to University Psychiatric Hospital Duffel or consulting for ambulatory ECT.
- ECT indication is major depressive disorder or major depressive episode in bipolar disorder (according to DSM-5 criteria).
- Male or female between 18 and 85 years of age.

- Baseline HDRS-score ≥ 17.
- Be medically stable on the basis of physical examination and vital signs performed during the pre-ECT screening procedure.
- Have signed an IC form indicating that they understand the purpose of and procedures required for the study and are willing to participate in this study. In case of incapacity, a close relative will be asked to give informed consent.

### 2.3.2. Exclusion criteria

Potential patients who meet one or more of the following criteria will be excluded from participating in the study:

- Drug or alcohol dependence or a primary psychotic disorder as detected in the MINI interview at screening (<6 months before ECT).
- Currently enrolled in a study with an investigational study drug.
- Has any condition that, in the opinion of the investigator, would compromise the wellbeing of the subject or prevent the subject from meeting or performing study requirements.

## 2.4. Participant flow

We screened 120 patients that were scheduled for ECT for a depressive disorder between August 1, 2015, and September 1, 2017. Forty-seven patients were not included for several reasons. Eight patients did not start ECT and 5 started too soon to do all necessary study assessments. Sixteen patients were not considered eligible because of screening failure (not meeting inclusion criteria or presence of one of the exclusion criteria) and 18 patients refused participation in the study (Figure 2-1).

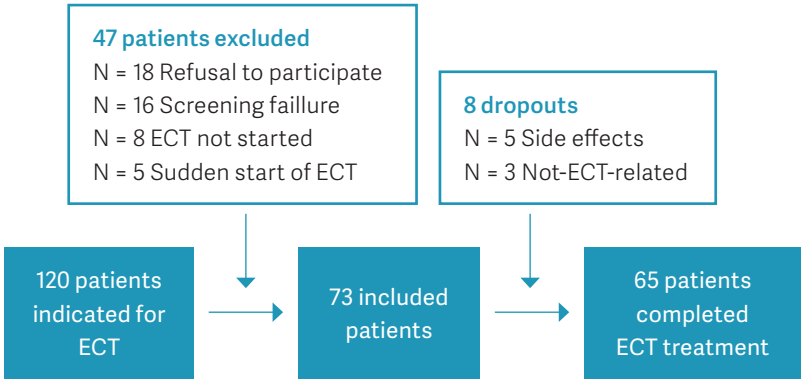


*Figure 2-1 – Participant flow. ECT = electroconvulsive therapy.*

There were several reasons for screening failure (Figure 2-2). Three patients were too severely depressed to participate, mostly because of catatonic states in which they did not speak or interact with caregivers. One patient did not speak Dutch and two were excluded because of recent (<6 months) dependency on alcohol and/or cannabis. The other patients were excluded because they did not have the -correct- diagnosis. They were either not that severely depressed (HDRS<17; N=2), had a depression in the light of a schizo-affective disorder (N=6) or had rapid cycling bipolar disorder (N=2).

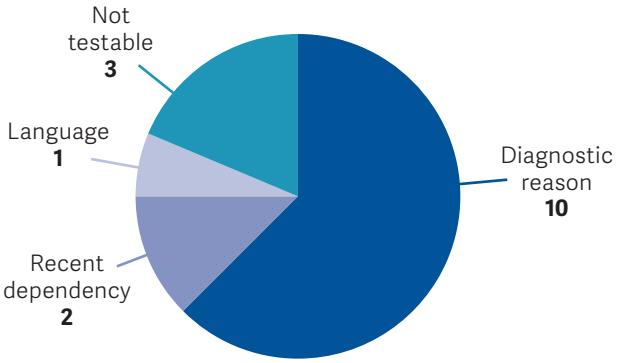


*Figure 2-2 - Reason for screening failure*

Seventy-three patients signed informed consent forms and participated in the study, they will be referred to as the intention-to-treat (ITT) sample. Eight patients could not complete the ECT course because of side-effects (N = 5) or reasons not related to the ECT (N = 3). The completer sample accordingly comprised 65 patients (Figure 2-1, Figure 2-3).

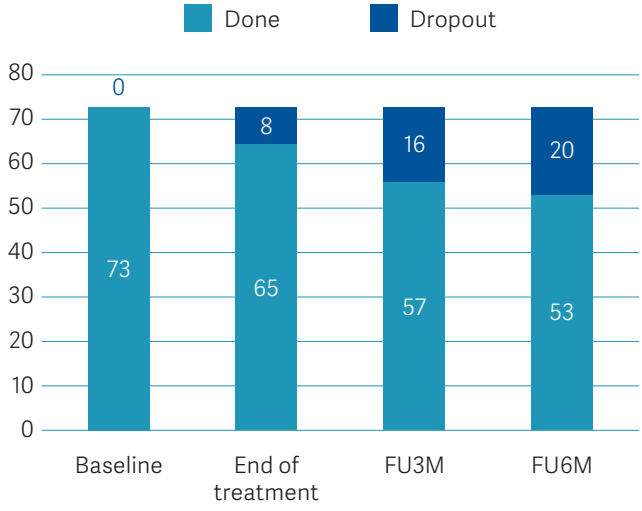


*Figure 2-3 - Dropout during the study.*

A follow-up visit was scheduled 3 months after the last ECT, and another one three months later. Of the completer sample, 57 patients could be retested at three months (87.7%) and 53 at six months (81.5%). Patients were either asked to come back to the psychiatric hospital for retesting or visited at home when they were not able or willing to come back to the psychiatric hospital.

## 2.5. Treatment

### 2.5.1. Drugs

During the ECT course, patients continued their antidepressant and/or antipsychotic medication. Agents and doses were preferably not changed 4 weeks prior to and during ECT (including the final assessment).

### 2.5.2. ECT

ECT was delivered twice weekly according to recent guidelines (101) using a brief-pulse (0.5ms) constant-current Thymatron IV system (Somatics LLC, USA). Electrodes were placed right unilateral (RUL), bifrontal (BF) or bitemporal (BT) when a fast antidepressant effect was needed (55). Patients that were initially treated with RUL ECT were switched to BT ECT if the response was inadequate after six treatments. In the case of intolerable (cognitive) side effects as a consequence of BT ECT, patients that started with BT ECT sometimes switched to RUL electrode positions. Prior to the ECT start, the stimulus dose was established by means of the age method for RUL-electrode placement and the half-age estimation method for bilateral electrode positions(57). Etomidate was the anesthetic of first choice (0.15mg/kg), with propofol (1mg/kg) being used when etomidate was not (well) tolerated. Ketamine (1-2mg/kg) was sporadically used at the request of the treating psychiatrist in case of a lack of clinical response (decrease in mood ratings < 50%) after 12 sessions. Succinylcholine (0.5mg/kg) was used as a muscle relaxant.

When patients agreed, mood and side-effect ratings were briefed to the treating psychiatrist. The endpoint of the ECT treatment was determined by the clinician, who based the decision on these ratings. During the ECT course, the mood was rated weekly and ECT was continued until patients were either asymptomatic (HDRS17 ≤ 7) or showed no further improvement during the last three sessions. Another reason to stop ECT was the occurrence of intolerable side-effects.

## 2.6. Assessment

### 2.6.1. Diagnostic procedure

The diagnosis of MDD or a major depressive episode in bipolar disorder according to DSM 5 was confirmed by consensus between an experienced psychiatrist and the main inves-

tigator, based on observations, patient interviews, and data from the referring GP or psychiatrist. To support the diagnosis and to screen for psychiatric comorbidity, a Mini-International Neuropsychiatric Interview 6.0 (MINI 6.0) was completed (102). This is a short but accurate validated structured diagnostic interview.

### 2.6.2. Measures of depression severity and definition of treatment outcome

Different scales were used to measure baseline depression severity, the evolution of depressive symptoms and the treatment outcome: The Hamilton Rating Scale for Depression (HDRS), the Montgomery-Asberg Depression Rating Scale (MADRS) and the Psychotic Depression Assessment Scale (PDAS).

The HDRS-17 items is one of the most commonly used instruments for assessing depression severity. It is a valid and reliable clinician-rated measure that has been used extensively in clinical research and in clinical practice for assessment of the severity of depression, changes in its severity over time and efficacy of treatment (103). Based on a large study of psychiatric outpatients with major depressive disorder, the following severity ranges were suggested: no depression (0–7); mild depression (8–16); moderate depression (17–23); and severe depression (≥24) (104). Response according to the HDRS-17 is defined as a decline of at least 50% on the scale, remission as a score ≤ 7.

The MADRS was designed to be particularly sensitive to treatment effects and consists of 10 items. Higher MADRS scores indicate more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60. Its capacity to differentiate between responders and non-responders to antidepressant treatment seems to be better than the HDRS (105). Response is defined as a decline of at least 50% on the MADRS, remission is defined as a MADRS score < 10 (106).

Since psychotic depression is an important indication for ECT, we considered it important to quantify psychotic symptoms. The PDAS is a composite rating scale, covering both the psychotic and depressive domains of psychotic depression. It consists of 6 items of the HDRS and 5 items of the Brief Psychiatric Rating Scale (BPRS) and is a sensitive measure of treatment response in psychotic depression (81,82).

The HDRS was done as part of the screening procedure for eligibility, right before the start of ECT, weekly during the course and after the last ECT. The MADRS was also done at baseline, weekly during ECT and after the last ECT. The PDAS was administered before the first and after the last ECT of the acute treatment course.

### 2.6.3. Psychomotor assessment

Patients had been observed for about one hour before psychomotor functioning was assessed by the main researcher, an MD trained in psychiatry. For patients on two of the

participating wards (approximately 10% of measurements), psychomotor functioning was (when possible) assessed by the psychomotor therapists of these wards that were trained to rate the CORE. The CORE is used to measure observable psychomotor functioning, the cardinal feature of melancholia (9). It was developed as a diagnostic tool, to classify melancholic and non-melancholic subtypes of depression (8,31). During the assessment, eighteen observable clinical features related to psychomotor functioning are scored on a 4-point scale based on severity ranging from 0 (absence of symptom) to 3 (severe). The CORE generates scores in three psychomotor categories: retardation, agitation, and non-interactiveness. A cut-off of 8 is used to define melancholic depression. The validity of the Dutch version of the CORE as a measure of psychomotor disturbance has been confirmed (107).

Besides observer-rated psychomotor functioning, psychomotor functioning was also objectively measured as described in the following two sections. The whole psychomotor test battery was completed at baseline, after 1, 2, and 3 weeks of treatment with ECT and at the end of the ECT course. The CORE was completed every week during the ECT course.

## Gross motor performance

Gross motor performance was measured by means of the MotionWatch8 (CamNtech Inc, UK), which registers the movement of the limb to which it is attached and can be used to quantify the intensity and duration of physical activity. Earlier studies support the use of accelerometry tools as an objective measure of gross psychomotor functioning (108).

During our study, the MotionWatch (Figure 2-4) was worn around the wrist of the patient's non-dominant arm for 24 consecutive hours (109). Activity counts were stored in 2-second intervals. Analyses were performed using the most recent version of the MotionWare software. Approximate wake-up and bedtimes were set so that the software could calculate daytime and nighttime activity levels.

*Figure 2-4 - Motionwatch 8*

### Fine motor performance

We used a digital drawing task to measure fine motor performance. In the line copying task (LCT), patients were asked to copy straight lines that had one of four possible orientations (vertical, horizontal or oblique in both directions). Besides a simple line copying task, a copying task with complex letters, figures and patterns was done (FCT). The lines and figures were presented on a standard monitor positioned in front of the patient and had to be copied as fast as possible within the confines of one of 20 target boxes (40 x 50 mm) on a sheet of paper placed on a graphic tablet. The stimuli appear on the screen when the subjects place the pen in a start circle below the target box's lower left-hand corner. Once the pen lands in the target box, the stimulus disappears. After the subjects have completed the reproduction, they have to place the pen in a similar-sized finish circle above the box´s upper right-hand corner, thereby ending the trial. Next, they need to move the pen into the start circle of the adjacent box to start off the next trial (Figure 2-5).

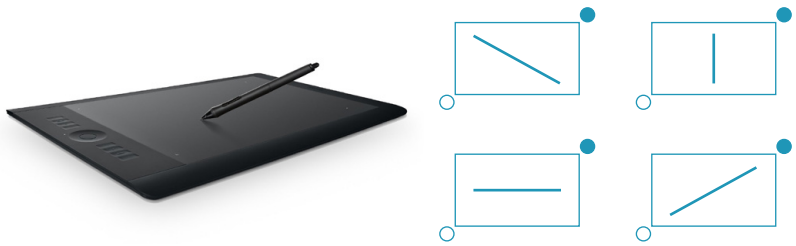

*Figure 2-5 - Wacom graphic tablet, line copying task.*

The use of a graphic tablet (WACOM Intuos Pro) and a pressure-sensitive pen connected to a laptop allowed us to calculate variables such as initiation time and movement time (IT and MT). IT mainly reflects the cognitive component of the performance and is defined as the time between the presentation of the stimulus and the beginning of the first drawing movement. MT reflects the motor component and is defined as the time between the beginning of the first drawing movement and the end of the last drawing movement. Motor retardation affects both cognitive and motor processes, as reflected by increases in both IT and MT (7).

Although we strived to do all psychomotor testing in the morning (since there are daily fluctuations in psychomotor functioning), this proved not to be feasible given the other challenges of testing in between ECT-sessions sometimes only 2 days apart.

## 2.6.4. Cognitive assessment

Cognitive function has to be assessed on a regular basis when treating patients with ECT (101,110). Our test battery was based on recommendations of earlier research (92). We focus

on cognitive measurements within the domains relevant to our ECT population. We limited the number of cognitive tests to make it better tolerable for our population.

These are the elements of the cognitive testing battery:

- The **Montreal Cognitive Assessment** (MOCA) is used to test global cognitive function (111). With a cut off of 26/30, the MOCA is sensitive with regard to tracing cognitive decline. The MOCA is a scale that proved useful in monitoring cognitive impairment in depressed patients receiving ECT (112).
- The **Symbol Digit Substitution Test** (SDST) was done to test processing speed. A series of symbols is presented that has to be decoded as fast as possible within 90 seconds, based on a key translating the nine different symbols into the digits 1 to 9. The SDST is executed on a sheet of paper placed on a digitizer with a special pressure-sensitive pen, both connected to a laptop. The digitized recordings allow the computation of separate matching and writing times. The matching and writing times resemble the efficiency of a chain of cognitive and motor processes.
- The **Hopkins Verbal Learning Test-Revised** (HVLT-R) was used to test anterograde memory, or the ability to learn new information. Three sets of 12 words (instead of five sets of 15 words at the Rey Auditory Verbal Learning Test (RAVLT)) were used. This test was originally developed for the elderly, but also seems to be better tolerated than the RAVLT by the depressed population(92). The outcome measure is the number of remembered words after each of the 3 times they are offered. Delayed recall of the words was tested 20 minutes later.
- To measure retrograde amnesia, section C (the recent period - concerning memories of the past year) of the **Autobiographic Memory Interview** (AMI) was used. We selected the section recent memory since these are the memories that are most frequently affected by ECT (94,113). The specificity of the questions makes it possible to assess the answers objectively and to verify the accuracy of memories.

Besides the above tests, we let the patient fill in the **Prospective Retrospective Memory Questionnaire** (PRMQ) (114) to know more about subjective memory complaints. The PRMQ has 16 questions, 8 retrospective, and 8 prospective items.

### 2.6.5. Assessment of treatment resistance

Treatment resistance in this study was assessed by the main researcher, completing the Maudsley Staging Method (MSM, Table 2-2)(84) prior to the start of ECT. This points-based staging model evaluates three elements of treatment resistance: the duration of the current episode, the severity of the illness and treatment history. Treatment history comprises three elements: the number of failed antidepressants, whether or not augmentation strategies (with antipsychotics or lithium) and/or ECT had been applied during this episode. Antidepressant trials for the current depressive episode were evaluated for adequacy according

to the instructions provided in the original MSM paper (84). When the patient was unable to provide the required data on treatment history and episode duration, the treating psychiatrist or the family doctor was consulted.

*Table 2-2 - Maudsley Staging Parameters and Suggested Scoring Conventions (84)*

| Parameter/Dimension | Parameter Specification | Score |
|---|---|---|
| Duration | Acute (≤ 12 months)<br>Sub-acute (13-24 months)<br>Chronic (> 24 months) | 1<br>2<br>3 |
| Symptom severity (at baseline) | Subsyndromal<br>Syndromal<br>Mild<br>Moderate<br>Severe without psychosis<br>Severe with psychosis | 1<br><br>2<br>3<br>4<br>5 |
| Treatment failures | | |
| Antidepressants | Level 1: 1-2 medications<br>Level 2: 3-4 medications<br>Level 3: 5-6 medications<br>Level 4: 7-10 medications<br>Level 5: > 10 medications | 1<br>2<br>3<br>4<br>5 |
| Augmentation | Not used<br>Used | 0<br>1 |
| Electroconvulsive therapy | Not used<br>Used | 0<br>1 |
| Total | | (15) |

## 2.6.6. Biological assessment

Because the literature on vascular risk factors and ECT response is scarce, we chose to collect data about the vascular burden of our patients. A Vascular Burden Index (VBI) can help to identify individuals with increased vascular burden linked to decreased cognitive function indicating neurodegenerative processes. The following factors were evaluated:

- Lifetime diagnosis of diabetes, additional intake of antidiabetic medication and HbA1c levels ≥ 6.5%.
- Lifetime diagnosis of hypertension, intake of antihypertensive medication.
- Positive medical history of hypercholesterolemia and/or intake of lipid-lowering medication.
- Lifetime diagnosis of atherosclerosis, atrial fibrillation, cardiac arrhythmia, myocardial infarction, congestive heart failure, and/or coronary heart disease.
- A body mass index (BMI) above 30.
- Personal history of smoking by "pack years" quantifying the packs (of 20 cigarettes) smoked per day multiplied by years as a smoker. Threshold at 15 pack years.

In that way, a patient can have a VBI of 0, 1, or 2+ (115). Besides that, the ankle-brachial index (AB-index) was assessed to confirm chronic arterial obstructive disease. The patient is lying down (for 5-10 minutes) in a comfortable room. The blood pressure in the left and right arm and the left and right leg is measured. The highest systolic ankle pressure is divided by the highest systolic arm pressure. If there is good arterial circulation, the AE-index in rest is bigger than 1. If the index is smaller than 0.9, chronic arterial obstructive disease is suspected.

Blood samples were taken from patients before and approximately one week after the last ECT. CRP, cytokines, and growth factors were measured in these samples. DNA extraction was done to assess BDNF polymorphisms.

A subset of patients (N=19) underwent an MRI scan at baseline and at the end of the ECT course, to assess vascular damage, do volumetric analyses and to assess brain related ECT changes. The MRIs were done at a 3-Tesla scanner, at the University Hospital of Antwerp.

Last but not least, a 10-20mg hair sample from the back of the head was taken in the week before ECT and at the follow-up assessment 3 months after the last ECT. The cortisol-exposure of the last 3 months was determined in this sample (116) in collaboration with the laboratory of Prof. van Rossum (Erasmus MC, The Netherlands).

## 2.7. Ethical considerations

After ECT had been indicated by the treating psychiatrist, the cognitive abilities of the patient had to be evaluated to decide on whether or not the patient was capable of providing IC. If so, the patient was informed about the study, including the procedures. After that, the patient was granted time to decide about participation, and the opportunity to ask questions. When the patient wanted to participate, written consent was required to proceed. When there was doubt about the capacity of the patient to give informed consent (for example due to the presence of severe psychotic features), a close relative was also informed and asked for the written consent. A copy of the IC form was given to the patient. The IC could be withdrawn by the patient or a relative at any time without a given reason and without consequences for further treatment.

The Guidelines on Good Clinical Practice (GCP) were respected. GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The study protocol, IC form, subject recruiting materials and other requested material were provided to the local (Emmaus VZW) and independent ethics committee (University Hospital Antwerp). They were approved with study number EC 15/10/93. For all protocol changes

after that (excluding purely administrative ones, with no consequence for the patients, data or trial conduct), the change and adapted IC form have been submitted to the ethics committees for review and approval before implementation of the change.

3

# CLINICAL PREDICTORS OF ECT RESPONSE: CONTRIBUTION OF LITERATURE

Published as: van Diermen L, van den Ameele S, Kamperman AM, Sabbe BCG, Vermeulen T, Schrijvers D, et al. Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. Br J psychiatry [Internet]. 2018 Feb;212(2):71–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29436330

BJPsych The British Journal of Psychiatry (2018)
212, 71–80. doi: 10.1192/bjp.2017.28

Review article

# Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis

Linda van Diermen, Seline van den Ameele, Astrid M. Kamperman, Bernard C.G. Sabbe, Tom Vermeulen, Didier Schrijvers and Tom K. Birkenhäger

**Background**

Electroconvulsive therapy (ECT) is considered to be the most effective treatment in severe major depression. The identification of reliable predictors of ECT response could contribute to a more targeted patient selection and consequently increased ECT response rates.

**Aims**

To investigate the predictive value of age, depression severity, psychotic and melancholic features for ECT response and remission in major depression.

**Method**

A meta-analysis was conducted according to the PRISMA statement. A literature search identified recent studies that reported on at least one of the potential predictors.

**Results**

Of the 2193 articles screened, 34 have been included for meta-analysis. Presence of psychotic features is a predictor of ECT remission (odds ratio (OR) = 1.47, $P = 0.001$) and response (OR = 1.69, $P < 0.001$), as is older age (standardised mean difference (SMD) = 0.26 for remission and 0.35 for response ($P < 0.001$)). The severity of depression predicts response (SMD = 0.19, $P = 0.001$), but not remission. Data on melancholic symptoms were inconclusive.

**Conclusions**

ECT is particularly effective in patients with depression with psychotic features and in elderly people with depression. More research on both biological and clinical predictors is needed to further evaluate the position of ECT in treatment protocols for major depression.

**Declaration of interest**

None.



There is no consensus on the position of electroconvulsive therapy (ECT) in current depression treatment protocols. For depression with psychotic features, ECT is the first-line treatment according to several guidelines,[1–3] whereas others recommend antidepressant monotherapy[4] or in combination[5] with antipsychotics. In clinical practice ECT is often used to treat patients with treatment-resistant depression. In a recent meta-analysis the response rate was 58% for patients with treatment-resistance depression and 70% for those without.[6] Despite many studies on possible predictors of response to ECT, Kellner *et al*[7] recently concluded that no useful clinical predictors have emerged. A possible explanation for this apparent lack of clinical predictors is the fact that many studies investigating predictors are underpowered to find an effect. Furthermore, heterogeneity between studies may mask the ability of a clinical variable to predict ECT response. Since many relatively small studies have been performed, meta-analysis may be useful to calculate effect sizes of possible predictors. A more accurate prediction of response and remission would be helpful to guide decision-making and preferably treat those patients likely to respond to ECT. This could substantially shorten depressive-episode duration.[8] To our knowledge, there have been no meta-analyses that look at prediction of response and remission separately. The difference between the two is, however, clinically relevant. Remission has become the gold standard for depression treatment, because patients who do not remit have a poorer prognosis than those who do. They have a greater chance of relapse and recurrence.[9]

## Method

Age, depression severity, psychotic and melancholic features were selected as potential predictors in this meta-analysis. They were selected because of their possible clinical relevance and because their role in the prediction of response and remission of depression after ECT is unclear. In an earlier meta-analysis,[6] older age and psychotic features were weakly associated with greater ECT response rates, but heterogeneity was notable. Analyses of symptom severity and melancholic features were inconclusive as a result of study heterogeneity in the same analysis.

This meta-analysis was conducted and reported according to the PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) and MOOSE guidelines[10,11] (supplementary Table 1; available at http://dx.doi.org/10.1192/bjp.2017.28). Objectives and eligibility criteria were specified in advance and documented in a protocol (available from the authors on request).

### Eligibility criteria

In order to obtain details of recent original studies on the predictive effect of age, severity of depression, melancholic and psychotic symptoms on the effectiveness of ECT (as it is currently practised) in patients with depression we applied the following eligibility criteria:

(a) studies assessing the effect of brief- or ultrabrief-pulse ECT on depression severity, published in or after 1995, articles are written in English;
(b) adults (>18 years of age) diagnosed with uni- or bipolar depression as confirmed by Research Diagnostic Criteria , DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5 or ICD-10 criteria;
(c) presence of psychotic or melancholic symptoms as confirmed by a structured diagnostic or clinical interview;
(d) classification of patients as 'responder/non-responder' or 'remitter/non-remitter' based on scores on valid clinician-rated depression scales (Hamilton Rating Scale for Depression (HRSD) or Montgomery–Åsberg Depression Rating Scale (MADRS)) that were administered before and soon after the end of the ECT course;

(e) effect sizes (or raw data enabling calculation of the effect size) of single-response predictors were provided or could be obtained by contacting the authors.

### Data sources and study selection

We searched Embase, Medline, Web of Science, Cochrane, PubMed publisher and Google scholar up to 17 February 2017. Articles published before 1995 were discarded. We chose to select studies from 1995 onward to get an overview of predictors of ECT as it is currently practised. The indication for, and practice of ECT has changed substantially over the years. This implies that including older studies means increased heterogeneity.

Combinations of the words depression, electroconvulsive therapy, response, remission and the four predictors (age, depression severity, psychotic and melancholic symptoms) were used. References from reviews and relevant articles were searched for additional studies. The titles and abstracts were screened for relevance. We selected articles in English. Searches were combined and duplicates removed. To maintain statistical independence of effect sizes, studies that reported on the same population were identified. When redundancy was obvious, the most comprehensive report with the largest sample size was used.

The inclusion of papers in the meta-analysis was evaluated separately by two independent researchers, the first (L.v.D.) and second author (S.v.d.A.). Disagreements were resolved via consensus. If no agreement was obtained, there was further discussion with two senior researchers (T.B. and D.S.).

### Data-collection process

When reported results were insufficiently detailed but the remaining inclusion criteria were fulfilled, corresponding authors were contacted for clarification and re-contacted if necessary. Authors were contacted if an email address was available and the author had published in the past 10 years. If data on only response or remission were available, authors were contacted to ask if data on the other outcome measure could also be provided. In total, 62 authors were contacted, 21 of the responding authors provided us with the data necessary to use their study in the meta-analysis.[12–32]

### Data extraction

The information was independently extracted from each article by two investigators (L.v.D. and S.v.d.A.) using a data extraction sheet with the following data:

(a) study characteristics: year, country and design of the study, diagnostic classification and depression severity scale used;
(b) characteristics of the study sample: number of participants, percentage female participants, percentage of patients with psychotic symptoms, mean age of the participants, average episode duration and percentage with medication resistance;
(c) ECT related: the average number of ECT sessions, electrode position used;
(d) outcome measure: general response and remission rates, response and remission rates for patients with depression with and without psychotic symptoms, for patients with and without melancholic symptoms, average age (and s.d.) and depression severity score (and s.d.) for 'responders/non-responders' and 'remitters/non-remitters'.

### Quality assessment

There was a strict use of eligibility criteria to select studies for the meta-analysis. Diagnostic criteria had to be used and an objective measurement of response based on one of the clinician-rated depression scales was required.

Furthermore, two of the reviewers (L.v.D. and T.B.) independently assessed several other quality aspects of the included studies based on the GRADE method[33] and the Newcastle–Ottawa Quality Assessment Scale[34] for cohort studies. The following three quality criteria were assessed:

(a) design of the study (pro- or retrospective);
(b) observational or interventional study;
(c) completeness of outcome data (more *v.* less than 20% drop-out).

### Outcome measures

The primary outcome was remission, the secondary outcome was response. The use of continuous data would be a more sensitive method to detect differences. However, we chose to use remission as primary outcome measure because it is often used as such in clinical practice. Remission is associated with a lower full symptomatic recurrence rate compared with achieving treatment response.[9,35] In all the selected studies, response was defined as a reduction of at least 50% from the baseline HRSD or MADRS score. Remission was usually defined as a depression scale score equal to or below 7 (for HRSD-17) or 10 (for HRSD-21, HRSD-24 and MADRS).

### Statistical analyses

The predictors were analysed separately with Comprehensive Meta-Analysis (CMA version 3). The effect size was analysed as an odds ratio (OR) for the dichotomous variables psychotic and melancholic symptoms. For age and severity of depression, the effect size was represented by the standardised mean difference (SMD). For each predictor, a random-effects model was computed since we expect the true effect to vary from study to study dependent on the composition of the study population.[36] The Stata 'metan' package was used for part of the analyses on publication bias.

Without consideration of the study weights in the random-effects model, we calculated the average age of all 'responders/non-responders' and 'remitters/non-remitters'. In the same way, response and remission percentages were calculated for those with and without psychotic and melancholic symptoms.

### Publication bias

When there were ten or more studies in an analysis,[37] funnel plots were used to visualise whether or not the effects found were dependent on the sample size.[36] Publication bias was formally assessed with the Egger's test in CMA for age and depression severity given their continuous outcome[38] and with the Harbord's test in Stata for the dichotomous predictors.[39]

### Heterogeneity and sensitivity analysis

Heterogeneity was assessed using Cochran's $Q$-test and $I^2$ statistics. An $I^2$ statistic of 0–40% was interpreted as heterogeneity that might not be important, 30–60% may represent moderate heterogeneity, 50–90% may represent substantial heterogeneity and 75–100% is considerable heterogeneity.[37]

Heterogeneity was further explored conducting sensitivity analyses. Therefore, we calculated the effect using fixed-effect and random-effects modelling and evaluated the effect of the modelling procedure on the overall effect per predictor. A substantial difference in the effect calculated by the fixed- and random-effects model will be seen only if studies are markedly heterogeneous.[40]

Furthermore, we compared the overall effects based on potential clinical sources of heterogeneity such as the continent of origin (according to World Health Organization classification), the study population (average age and episode duration of the sample, the

percentage of patients with psychotic features, percentage with medication resistance) and treatment parameters (length of ECT course and electrode position used). The effects were also compared based on the before mentioned study quality criteria.

## Results

### Selection of studies

After removal of duplicates and studies published before 1995 (Fig. 1), the literature search yielded 2193 potentially relevant articles. We excluded 1991 articles after review of titles and abstracts. The full texts of the 202 remaining studies were analysed; 171 of them did not meet eligibility criteria and were excluded, 2 articles were added through reference lists and 1 through cross-reference. In total, 34 articles were selected and used in this meta-analysis.[12–32,41–53] The interrater reliability was good, with an interrater agreement of 96.1% (kappa (κ) = 0.87, 95% CI 0.78–0.96).

### Study characteristics

Overall, the selected studies reported on 3276 participants that received an ECT course (supplementary Table 2). More than half of the studies (52.9%) were carried out in Europe. A total of 25 studies included psychotic symptoms, 28 had data on age, 28 on depression severity and 7 on melancholic symptoms.

Studies had between 15 and 414 participants (on average 99 per study). The majority of the participants (64.3%) were women (range 27.0–77.8%) and 32.6% had psychotic symptoms (range 6.7–70.6%). Patients were on average 57.1 years of age (range of mean age was 33.1–74.8). Three studies reported on the same large sample, but on a different predictor.[19,31,54] The data of the largest sample were used for the above calculations of study characteristics. One of the three was eventually excluded[54] because data on psychotic symptoms were provided by the authors of the largest sample.[19]

Results of the quality assessment can be found in the supplementary material (supplementary Table 3). There were 7 retrospective studies and 27 had a prospective design. In total, 26 studies were observational, 8 of them were interventional. Eight studies had a drop-out rate of more than 20%.

### Psychotic symptoms

#### Remission

Data on the presence of psychotic symptoms and remission following ECT were provided in 21 studies. For remission, the OR under the random-effects model was 1.47 (95% CI 1.16–1.85, $P = 0.001$, $I^2 = 36.6$) (Fig. 2(a)). The remission rate for patients with depression and psychotic symptoms was 57.8%; for those without psychotic symptoms it was 50.9%.

#### Response

Data on the presence of psychotic symptoms and response to ECT were provided in 21 studies. Psychotic features were positively associated with a higher ECT response rate under the random-effects model (Fig. 2(b)). The OR was 1.69 (95% CI 1.27–2.24, $P < 0.001$, $I^2 = 25.8$). The response rate for patients with depression and psychotic symptoms was 78.9% and for those without psychotic symptoms it was 70.6%.

### Age

#### Remission

In total, 24 papers provided data on age and remission. Age was positively associated with higher ECT remission rates under the

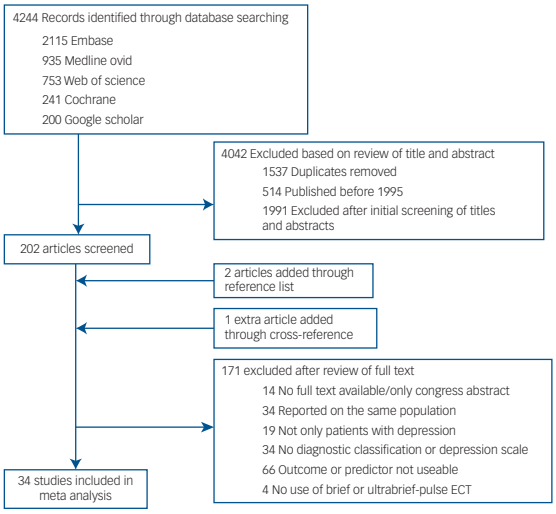


**Fig. 1** Study selection.

ECT, electroconvulsive therapy.

random-effects model (Fig. 2(c)). The SMD was 0.26 (95% CI 0.13–0.38, $P < 0.001$, $I^2 = 53.4$). The average age of those whose condition remitted was 59.7 years, compared with 55.4 years for those whose condition did not.

### Response

Data on age and response to ECT could be extracted from 25 papers. Age was positively associated with a higher ECT response under the random-effects model (Fig. 2(d)). The SMD was 0.35 (95% CI 0.23–0.47, $P < 0.001$, $I^2 = 29.7$). The average age of those who responded was 58.2 years, compared with 54.9 years for those who did not respond.

## Melancholic symptoms

### Remission

There were seven studies that provided data on presence of melancholic symptoms and remission after ECT. The OR under the random-effects model was 1.24 (95% CI 0.69–2.22, $I^2 = 63.9$, Fig. 2(e)). The difference was, however, not significant ($P = 0.467$). The remission rate for patients with depression and melancholic symptoms was 62.9%, for those without melancholic symptoms it was 65.5%.

### Response

Data on melancholic symptoms and response could be obtained from five studies. The OR under the random-effects model was 1.71 (95% CI 0.43–6.84, $I^2 = 85.9$, Fig. 2(f)). The difference was, however, not significant ($P = 0.452$) and there was considerable heterogeneity. The response rate for patients with depression and melancholic symptoms was 71.1% and for those without melancholic symptoms it was 64.7%.

## Depression severity

### Remission

Data on depression severity and remission could be extracted from 23 studies. Remission following ECT was less likely in patients with

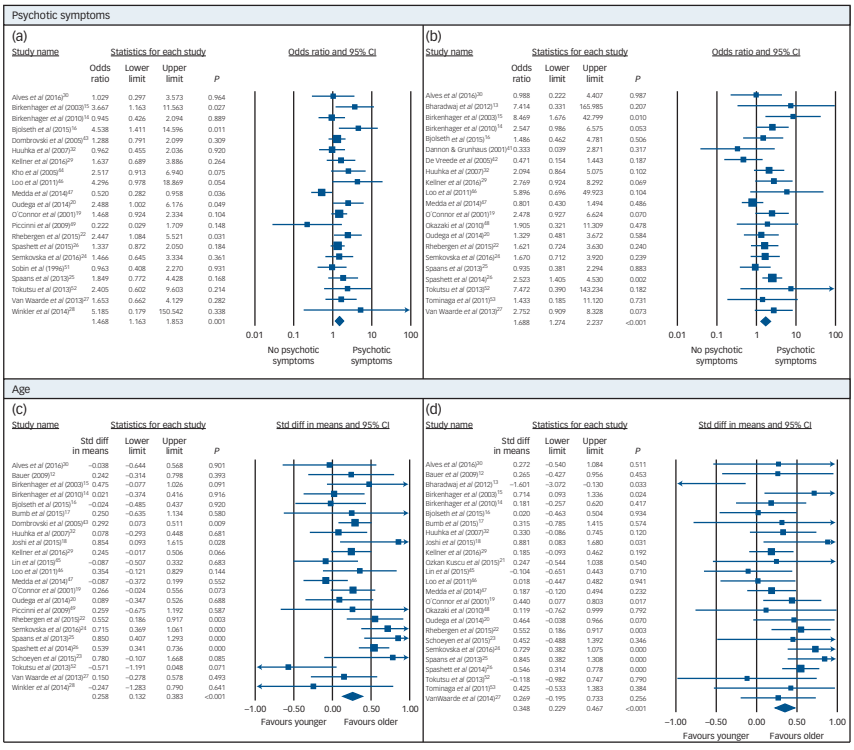


**Fig. 2** Random-effects meta-analyses.

Effect of psychotic symptoms on remission (a) and response (b) and age on remission (c) and response (d) of depression after electroconvulsive therapy (ECT). Random-effects meta-analyses of the effect of melancholic symptoms on remission (e) and response (f) and depression severity on remission (g) and response (h) of depression after ECT. Std diff, standardised difference.

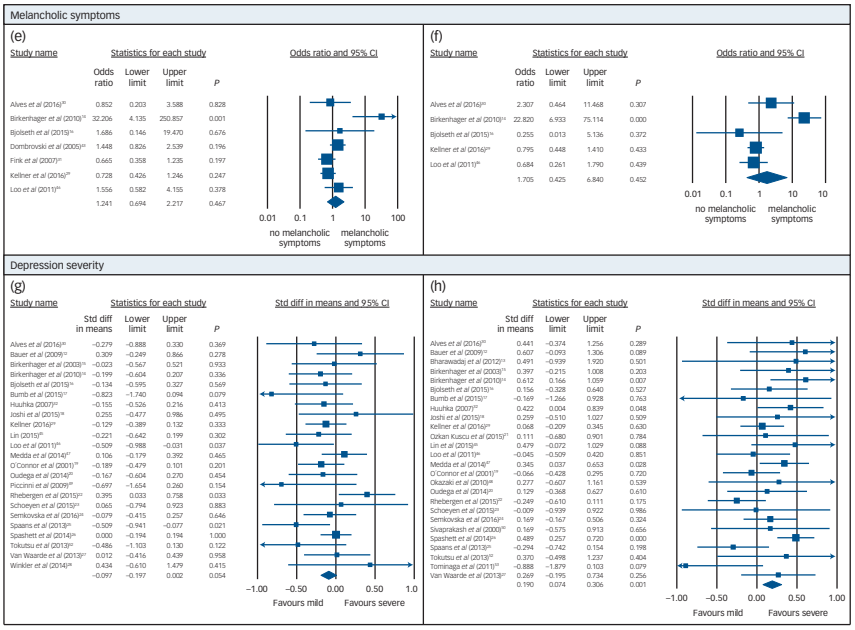


**Fig. 2** Continued.

higher depression severity scores, although the effect was not significant under the random-effects model (SMD = −0.10, 95% CI −0.20–0.002, $P = 0.054$, $I^2 = 29.7$, Fig. 2(g)).

### Response

In total, 26 studies reported on depression severity and response to ECT. A small but significant association was found between response and baseline symptom severity scores on the HRSD or MADRS, under the random-effects model (SMD 0.19, 95% CI 0.07–0.31, $P = 0.001$, $I^2 = 28.1$, Fig. 2(h)). Patients with higher scores were more likely to respond to ECT.

## Publication bias

The funnel plots that could be generated revealed no obvious asymmetry (see supplementary Fig 1). Given the limited number of studies in the melancholia analyses, no funnel plots were generated for this predictor. According to Egger's and Harbord's test there was also no significant publication bias in all of these analyses (Table 1).

## Heterogeneity and sensitivity analysis

A group of observational studies often shows considerable heterogeneity, regardless of the number of included studies. The Cochran's Q-test and $I^2$ statistics were used to quantify heterogeneity. There was evidence of moderate heterogeneity in all of the analyses that were done (Table 2), and substantial heterogeneity in the analyses on melancholic symptoms.

Heterogeneity was further explored conducting sensitivity analysis. Therefore, we calculated the effect using both fixed-effect and random-effects modelling and evaluated the effect of the modelling procedure on the overall effect per predictor. The difference between results of fixed- and random-effects analyses were small (Table 2), confirming that heterogeneity in our analyses was limited.

Besides that, we compared the overall effects based on the potential clinical sources of heterogeneity and study quality criteria (as discussed). Continuous variables were analysed with meta-regression, categorical variables were subjected to mixed-effects subgroup analysis. Studies were excluded from the analyses if data on the variable was not available. This can explain differences found in overall effects.

**Table 1** Results of tests for publication bias

| | Intercept | 95% CI | *P* |
|---|---|---|---|
| Harbord's test | | | |
| Psychosis – remission | 0.563 | −0.289 to 1.415 | 0.182 |
| Psychosis – response | 0.011 | −0.529 to 0.550 | 0.968 |
| Melancholia – remission | 1.739 | −1.112 to 4.590 | 0.178 |
| Melancholia – response | 0.630 | −4.641 to 5.900 | 0.729 |
| Egger's test | | | |
| Age – remission | −0.626 | −2.164 to 0.912 | 0.408 |
| Age – response | −0.787 | −1.960 to 0.386 | 0.178 |
| Severity – remission | −0.546 | −2.014 to 0.922 | 0.447 |
| Severity – response | −0.350 | −1.517 to 0.817 | 0.542 |

**Table 2** Sensitivity analyses – results of random- and fixed-effect models and heterogeneity tests

| Predictor | Studies, *n* | *n* | Random effects | | | Fixed effect | | | Heterogeneity test | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | OR (95% CI) | SMD (95% CI) | *P* | OR (95% CI) | SMD (95% CI) | *P* | *Q* | d.f. | $I^2$ | *P* |
| *Dichotomous* | | | | | | | | | | | | |
| Psychosis | | | | | | | | | | | | |
| Remission | 21 | 2787 | 1.468 (1.163 to 1.853 | | 0.001** | 1.399 (1.179 to 1.660) | | <0.001*** | 31.54 | 20 | 36.59 | 0.048* |
| Response | 21 | 2396 | 1.688 (1.274 to 2.237) | | <0.001** | 1.659 (1.321 to 2.083) | | <0.001*** | 26.96 | 20 | 25.82 | 0.136 |
| Melancholia | | | | | | | | | | | | |
| Remission | 7 | 1242 | 1.241 (0.694 to 2.217) | | 0.467 | 1.027 (0.762 to 1.386) | | 0.859 | 16.64 | 6 | 63.93 | 0.011* |
| Response | 5 | 524 | 1.705 (0.425 to 6.840) | | 0.452 | 1.269 (0.823 to 1.956) | | 0.282 | 28.37 | 4 | 85.90 | <0.001*** |
| *Continuous* | | | | | | | | | | | | |
| Age | | | | | | | | | | | | |
| Remission | 24 | 2863 | | 0.258 (0.132 to 0.383) | <0.001*** | | 0.285 (0.206 to 0.363) | <0.001*** | 49.32 | 23 | 53.36 | 0.001** |
| Response | 25 | 2633 | | 0.348 (0.229 to 0.467) | <0.001*** | | 0.364 (0.272 to 0.457) | <0.001*** | 34.15 | 24 | 29.73 | 0.082 |
| Severity | | | | | | | | | | | | |
| Remission | 23 | 2531 | | −0.097 (−0.197 to 0.002) | 0.054 | | −0.086 (−0.169 to −0.003) | 0.043* | 27.69 | 22 | 20.54 | 0.186 |
| Response | 26 | 2663 | | 0.190 (0.074 to 0.306) | 0.001** | | 0.203 (0.112 to 0.294) | <0.001*** | 34.75 | 25 | 28.06 | 0.093 |

*n*, total number of participants; OR, odds ratio (predictor present/predictor absent); SMD, standardised mean difference ('responders' – 'non-responders' or 'remitters' – 'non-remitters').
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

### Psychotic symptoms

Age and medication resistance were clinical sources of heterogeneity in the remission analysis (Table 3). The predictive effect of psychotic symptoms was stronger in samples with older patients and those with lower levels of medication resistance. The results were not significantly influenced by the other potential clinical sources of heterogeneity (length of the ECT course, episode duration, electrode position and location of the study, supplementary Table 4).

The study quality criteria had no significant influence on the results of the remission analysis (design of the study, drop-out and whether or not it was an observational study, supplementary Table 4). The length of the ECT course was a clinical source of heterogeneity in the response analysis. It was significantly related to the effect size, with longer courses corresponding to a greater predictive effect of psychotic symptoms on ECT response (Table 3). The results were not significantly influenced by the other potential clinical sources of heterogeneity (age, episode duration, therapy resistance, electrode position, location of the study) or the study quality criteria (design of the study, drop-out and whether or not it was an observational study, supplementary Table 4).

### Age

The most important clinical source of heterogeneity in the analyses on the effect of age on response and remission after ECT, was the average episode duration (Table 3). SMDs were greater in studies with longer episode duration. Moreover, the predictive effect of age was significantly higher in studies that used right unilateral or variable electrode positions, compared with those only using bilateral ECT in the remission analysis (Fig. 3a).

In the remission analysis, the SMD was also influenced by whether it was an observational study, or an interventional study. Interventional studies found on average higher SMDs than observational studies (Fig. 3b). The results were not influenced by the other potential clinical sources of heterogeneity (psychotic symptoms, medication resistance, length of the ECT course, location of the study), or the other study quality criteria (design of the study and drop-out, supplementary Table 4).

In the response analysis, the results were not significantly influenced by the other potential clinical sources of heterogeneity (psychotic symptoms, electrode position, location of the study, medication resistance, length of the ECT course), or the study quality criteria (design of the study, drop-out and whether or not it was an observational study, supplementary Table 4).

### Melancholic symptoms

Because of low patient numbers in part of the analyses and different definitions of the concept of melancholia, results of the response and remission analyses were considered to be inconclusive. Therefore, sensitivity analyses were not performed.

### Depression severity

In the remission analysis, there was no significant influence of the potential clinical sources of heterogeneity (age, psychotic symptoms, episode duration, medication resistance, length of the ECT course, location of the study). Drop-out was a source of heterogeneity in the remission analysis (Fig. 3c). Studies with drop-out rates above 20% found that lower depression scale scores favoured remission after ECT. Those with limited drop-out found no effect at all of depression severity. There was no significant effect of the other study quality criteria (design of the study and whether or not it was an observational study, supplementary Table 4).

**Table 3** Tests of heterogeneity – results of meta- regression

| | Beta | 95% CI | *Q* | *P* |
|---|---|---|---|---|
| Psychosis | | | | |
| Response, length course | 0.089 | 0.001 to 0.176 | 3.89 | 0.05* |
| Remission, age | 0.040 | 0.006 to 0.073 | 5.32 | 0.02* |
| Remission, medication resistance | −0.019 | −0.036 to −0.003 | 5.20 | 0.02* |
| Age | | | | |
| Response, episode duration | 0.037 | 0.005 to 0.068 | 5.30 | 0.02* |
| Remission, episode duration | 0.044 | 0.016 to 0.073 | 9.15 | <0.01** |

* $P < 0.05$, ** $P < 0.01$.

The results of the response analysis were not significantly influenced by any of the potential clinical sources of heterogeneity (age, electrode position, length of ECT course, episode duration, therapy resistance, location of the study). The SMD in the response analysis was influenced by the design of the study. Retrospective studies found remarkably higher SMDs than prospective studies (Fig. 3d). The results were not influenced by the other study quality criteria (drop-out and whether or not it was an observational study, supplementary Table 4).

## Discussion

### Main findings

This meta-analysis provides evidence for the superior efficacy of ECT in patients with depression with psychotic features, in older patients and in those with a more severe depression, whereas data on melancholic symptoms were inconclusive. This is an important finding, because identification of reliable predictors could contribute to more targeted patient selection, consequently increased ECT response and remission rates and limited episode duration.

We included 34 studies reporting on 3276 patients with a depressive disorder treated with ECT. There were relatively strict inclusion criteria to select only high-quality studies and, in contrast to previous meta-analyses on prediction of ECT efficacy, we made a distinction between data on response *v.* remission.

Presence of psychotic symptoms had an OR of 1.69 ($P < 0.001$) for response and 1.47 ($P = 0.001$) for remission. The SMD for older age was 0.35 ($P < 0.001$) in the response analysis, for remission it was 0.26 ($P < 0.001$). These are all rather small effect sizes.[55] When we look at the average age of patients whose condition remitted (59.7) and compare this with the age of those who did not remit (55.4), the difference is only 4.3 years. One could hypothesise that the age of 57 somehow resembles a turning point in remission following ECT. However, it is clear that not every person older than 57 will experience remission after treatment with ECT, just as remission will not occur in every patient with depression with psychotic symptoms. Therefore, age and psychotic symptoms are no waterproof predictors of ECT efficacy. They can, however, serve as one of several factors that can guide treatment decision-making.

A weaker association was detected between the severity of depression and response to treatment (SMD 0.19, $P = 0.001$). Depression severity was not associated with remission. This appears logical, since higher scores pre-ECT need a larger decrease than lower scores to attain remission.

Psychomotor disturbance is a key marker not only of melancholia but also of psychotic depression.[56] Thus, those with depression with psychotic features often have melancholic symptoms. Consequently, the finding that depression with psychotic features is a predictor of ECT response and remission indirectly points to melancholic symptoms also having predictive potential. However, this does not result from our analysis. The few studies that reported on melancholic symptoms did not use the same definition of melancholia. Furthermore, one of the studies had a very low number of patients without melancholic features,[16] and another one had very low numbers of individuals who responded/remitted in patients without melancholic symptoms.[14] This resulted in very large confidence intervals and considerable heterogeneity. We conclude that

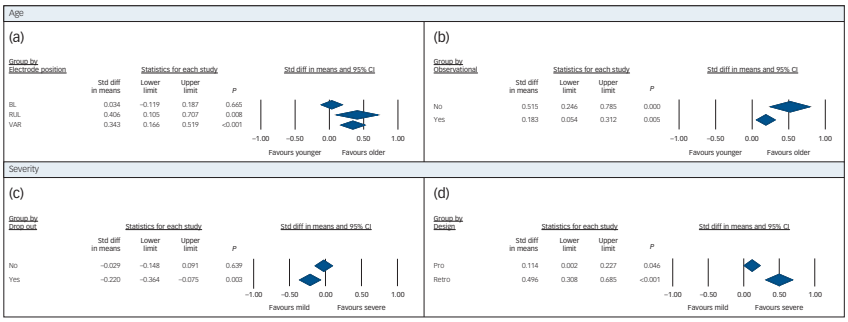


**Fig. 3** Significant results of subgroup analyses.

Mixed-effects analysis of electrode position in the remission analysis of the predictor age (a), of the study quality criterion observational/interventional in the remission analysis of the predictor age (b), of dropout in the remission analysis of the predictor severity (c) and of study design in the response analysis of the predictor severity (d). BL, bilateral; RUL, right unilateral; VAR, variable; Pro, Prospective; Retro, Retrospective; Std diff, standardised difference.

this predictor is insufficiently investigated to draw solid conclusions on its predictive effect.

Several relevant factors have emerged from the heterogeneity analysis. Presence of psychotic symptoms was a stronger predictor of remission in older patients and in patients with limited medication resistance. Psychotic symptoms were a stronger predictor of response for those with a longer ECT course. A stronger predictive effect of psychotic symptoms in patients receiving a longer ECT course could mean that patients with depression with psychotic symptoms might benefit from longer ECT courses.

A limited episode duration is known to predict a good response to ECT.[6] However, in studies with longer episode duration, the predictive effect of age on response and remission was stronger. This is remarkable, since we have no reason to expect that episode duration *per se* has an influence on the strength of the predictive effect of age. The value of the predictor age was also considerably higher in studies that used right unilateral or variable electrode positions in the remission analysis. As we look further, this result might be mediated by the location at which the study was performed. Age was a strong predictor of response and remission in studies carried out in the USA and Europe, and although the difference was not significant, the predictive effect was not that clear in studies carried out in Asia. An explanation could be that studies from Asia all use the standard bilateral electrode position, administer relatively short ECT courses and participants had a lower average age. The question therefore remains if the predictors that show a significant effect are relevant independent of the already known predictors and other confounders.

Besides the four predictors we investigated, there are several other potential clinical predictors that have been subject to previous meta-analyses. The predictive effect of the number of episodes, the age of onset, gender and a bipolar diagnosis on the efficacy of ECT appears to be non-existent.[6] The lack of predictive value of a bipolar diagnosis was confirmed by a second meta-analysis.[57] There was a significant influence of episode duration (SMD −0.43, $P < 0.001$; $I^2 = 35\%$) on ECT response. The weighted mean episode duration for those who responded was 6.6 months and 14 months for those who did not respond. Medication failure was the second significant predictor (OR 0.57, $P = 0.002$; $I^2 = 35\%$) for poorer ECT response, as mentioned in the introduction. This result was also confirmed by a second meta-analysis.[58]

Data on known response predictors (episode duration and medication failure) and the percentage of patients with psychotic symptoms were not always provided and could therefore not always be accounted for in the current analyses. The results of the heterogeneity analyses therefore have to be interpreted with care.

The effect size of psychotic symptoms as predictor of response and remission was considerably higher than the effect found in a recent meta-analysis on ECT response prediction by Haq *et al* (OR = 1.34, $P = 0.12$).[6] The same holds true for age (SMD 0.112, $P = 0.25$) and depression severity (SMD −0.022, $P = 0.90$). Differences between the meta-analyses were that, in our study response and remission rates were separated and strictly defined by HRSD or MADRS score. In addition, we retrieved unpublished data from 21 authors, contributing to a more complete analysis of those studies. To recapitulate, our study probably analysed a more homogeneous sample that facilitated detection of significant differences.

## Strengths

There are several strengths to this comprehensive meta-analysis. To make sure we based our analysis on reliable data, we used relatively strict criteria for selection of studies (use of a diagnostic instrument and a validated clinician-rated depression scale). The second strength is the separate analysis for response and remission. This distinction enabled us to confirm the findings of one outcome criterion by a second one. Our findings lead to the conclusion that age and psychotic symptoms are stronger predictors of response than of remission. The fact that we contacted a number of authors for extra data contributed to a large sample to study and a more complete data analysis of studies concerned, limiting publication bias. Furthermore, it enabled us to find sources of heterogeneity.

## Limitations

There are several limitations to our meta-analysis. Where strict selection criteria can be considered a strength, they can also be considered a limitation. As a consequence, a number of (often large) studies have been excluded. An example is a large Swedish study ($n = 990$)[59] that has only used Clinical Global Impression – Improvement scores and not a clinician-rated depression scale (HRSD or MADRS) to distinguish between individuals who responded and those that did not. The results of this study are, however, in line with our findings – a higher proportion of older patients responded (84.3%) as compared with younger ones (74.2%, $P < 0.001$) and patients with severe, depression with psychotic features had the highest response rate (88.9%) compared with patients with severe, non-psychotic depression (81.5%) and patients with mild/moderate depression (72.8%, $P < 0.001$). Furthermore, several seemingly suitable studies[60,61] could not be used because they have not reported on the value of predictors for responders *v.* non-responders and could not provide us with these data.

As mentioned before, we did not only use data from studies that were designed specifically to look at the predictive effect of psychotic symptoms or one of the other predictors. Part of the data could be abstracted from studies with a different objective. Considering publication bias, this is an advantage. On the other hand, this is an extra source of heterogeneity between the studies. Different populations were studied, the studies had divergent designs, several depression scales and versions of these scales were used and the definition of remission can therefore not be exactly the same in every study. Moreover, ECT practice and patient selection for ECT differs all around the world.[62] We tried to minimise the impact of this heterogeneity by including some of these parameters in heterogeneity analysis to determine their effect on outcome.

Despite the fact that more effective forms of ECT exist,[63] we have chosen not to exclude studies that use ultrabrief-pulse ECT. Given its cognitive advantages it can be the preferred treatment for a subgroup of patients with depression. The predictor results of the studies that use only ultrabrief-pulse ECT[29,46] are in line with the overall results of our meta-analysis.

## Clinical implications

Besides episode duration and treatment resistance, which are established predictors for the efficacy of ECT, age, depression severity and the presence of psychotic symptoms can also be of value in the ECT treatment decision-making process. Previous studies found a favourable response to ECT in patients with a short episode duration and limited treatment resistance. When episode duration is longer, age might be able to guide decision-making.

ECT could be suggested relatively early to those prone to respond or remit, thereby limiting depression duration and preventing a chronic trajectory of depressive symptoms. Other treatment options can first be considered for those with lower response and remission chances.

## Research implications

We have used the general definition of melancholia in our meta-analysis. Another strategy could be to investigate psychomotor disturbance as measured by the CORE Assessment of Psychomotor Functioning or the score on HRSD retardation and agitation item scores as a more specific marker.[64] Observable psychomotor disturbance has been suggested as an essential criterion in making a diagnosis of melancholia[65] and proved to be a predictor of ECT response in previous studies.[66,67] For future projects, it could be valuable to incorporate measurement of the severity of psychomotor disturbance next to the general definition of melancholia so that the predictive effect of the presence of melancholia and more specific psychomotor disturbance can be evaluated.

Our analysis examined a lot of (often) small studies that report on two or three of the factors that are known to be relevant. Larger studies that report on all of the identified predictors (and the presence of personality disorder[68]) could be valuable to get a clearer view on the combined effect of several predictors.

A combination of these clinical variables with their biological underpinnings could further improve response and remission prediction and could serve as more objective tools to guide patient treatment matching.

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First received 30 Nov 2016, final revision 19 Sep 2017, accepted 27 Oct 2017

## Acknowledgements

We thank the authors mentioned in the Method section for sharing unpublished data. Besides that, we thank data specialist Wichor Bramer for the literature search.

## Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2017.28.

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EXTRA CONTENT ONLINE

*Table DS1 - PRISMA checklist*

| Section/ topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 2 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 2 |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | NA |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 2 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 2/3 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Contact author |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 2 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 3 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 2 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 3 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 3 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 3/4 |

*(Table continues on page 44)*

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 3 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 3/4 |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 4 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 4 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 6 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figure 2 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 4, 5, Figure 2, Table 2 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 6, Table 1, Online supplement DS4 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 6, 7, 8, Table 2, Table 3, Figure 3, online supplement DS5 |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9, 10 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 9, 10 |
| FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 3, 11 |

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit:* www.prisma-statement.org.

*Table DS2. Studies included in the meta-analyses*

| Study | Design | Country | Trial size | Age (years) | Psychotic symptoms (%) | Episode duration (months) | Medication resistance (%) | Length ECT course (#) | Electrode position | Response rate (%) | Remission rate (%) | Predictors included |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alves (2016) | PRO | Brazil | 43 | 51.1 | 41.5 | X | X | 8.7 | RUL | 84.3 | 58.1 | A, M, P, S |
| Bauer (2009) | PRO | Denmark | 52[a] | 52.1[a] | X | X | X | 11.6[b] | BL | 80.8 | 59.6 | A, S |
| Bharadwaj (2012) | RET | India | 37 | 43.7 | 56.8 | 5.91 | 62.2 | 7.4 | BL | 91.9 | 75.6 | A, P, S |
| Birkenhager (2003) | RET | Netherlands | 55 | 50.4 | 47.3 | 23.1 | 74.5 | 14.7 | VAR | 74.5 | 40.0 | A, P, S |
| Birkenhager (2010) | RET | Netherlands | 104[a] | 55.7[a] | 46.2[a] | 17.0[a] | 81.4[a] | 13.5[b] | BL | 69.1[a] | 44.0[a] | A, M, P, S |
| Bjølseth (2015) | PRO | Norway | 73 | 74.8 | 24.7 | 6.5 | 38.4 | 9.2 | VAR | 65.8 | 45.2 | A, M, P, S |
| Bumb (2015) | PRO | Germany | 20 | 51.7 | X | X | X | 11.3 | VAR | 80.0 | 55.0 | A, S |
| Dannon (2001) | PRO | Israël | 17 | 62.4 | 70.6 | 10.7 | X | 9.3 | VAR | 41.2 | X | P |
| De Vreede (2005) | RET | Netherlands | 53 | 59.0 | 47.2 | X | 72.0 | X | BL | 41.5 | X | P |
| Dombrovski (2005) | PRO | USA | 328 | 57.4 | 28.4 | 13.7 | 54.3 | 11.2 | VAR | X | 55.8 | A, M, P |
| Fink (2007) | PRO | USA | 385[b] | 55.5[b] | 29.5[b] | 10.6b | 52.2[b] | 7.2[b] | BL | X | 86.5 | M |
| Huuhka (2007) | PRO | Finland | 119 | 57.7 | 42.9 | X | X | 9.4 | BL | 74.8 | 37.8 | A, P, S |
| Joshi (2015) | PRO | USA | 29[a] | 41.0[a] | X | X | 100 | 11.5 | VAR | 65.5[a] | 48.3[a] | A, S |
| Kellner (2016) | PRO | USA | 240 | 70.2 | 11.6 | X | X | X | RUL | 70.4 | 86.0 | A, M, P, S |
| Kho (2005) | RET | Netherlands | 73 | 57.7 | 46.6 | 52.8 | 77.0 | 7.0 | VAR | X | 65.8 | P |
| Kuscu (2015) | PRO | Turkey | 58 | 42.0 | 0.0 | X | X | 8.0 | BL | 87.9 | X | A, S |
| Lin (2015) | PRO | Taiwan | 104 | 47.3 | X | 15.7 | 86.7 | 9.5 | BL | 85.7 | 70.5 | A, S |
| Loo (2011) | PRO | Australia | 75 | 46.2 | 12.0 | 14.9 | X | 9.7 | RUL | 61.3 | 36.0 | A, M, P, S |

*(Table continues on page 46)*

| Study | Design | Country | Trial size | Age (years) | Psychotic symptoms (%) | Episode duration (months) | Medication resistance (%) | Length ECT course (#) | Electrode position | Response rate (%) | Remission rate (%) | Predictors included |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medda (2014) | PRO | Italy | 208 | 52.0 | 38.9 | 8.8 | 100 | 7.3 | BL | 73.1 | 34.6 | A, P, S |
| O´Connor (2001) | PRO | USA | 394[a] | 56.3[a] | 29.9[a] | 11.4b | X | 7.8[b] | BL | 91.9 | 86.5 | A, S |
| Okazaki (2010) | PRO | Japan | 24 | 64.2 | 54.2 | 7.8 | 100 | 6.0 | BL | 70.8 | X | A, P, S |
| Oudega (2014) | PRO | Netherlands / Belgium | 81 | 74.0 | 42.0 | 10.2 | 33.3 | 12.8 | VAR | 74.1 | 48.1 | A, P, S |
| Piccini (2009) | PRO | Italy | 18 | 44.9 | 44.4 | 7.4 | 100 | 8.3 | BL | X | 44.4 | A, P, S |
| Rhebergen (2015) | PRO | Netherlands / Belgium | 120 | 60.5 | 41.7 | 20.0 | 60.2 | 13.0 | VAR | 54.2 | 45.8 | A, P, S |
| Schoeyen (2015) | PRO | Norway | 23 | 48.0 | X | X | 100 | 10.6 | RUL | 73.9 | 34.8 | A, S |
| Semkovska (2016) | PRO | Ireland | 138 | 56.7 | 21.0 | X | 72.8 | 7.8 | VAR | 55.8 | 44.2 | A, P, S |
| Sivaprakash (2000) | PRO | India | 30 | 33.1 | 40.0 | X | 0 | X | BL | 63.3 | X | S |
| Sobin (1996) | PRO | USA | 100 | 57.4 | 46.0 | X | X | 9.6 | VAR | X | 70.0 | P |
| Spaans (2013) | PRO | Netherlands | 87 | 62.0[a] | 43.7[a] | 20.2[b] | X | 9.5 | RUL | 66.7 | 57.5 | A, P, S |
| Spashett (2014) | RET | UK | 414 | 57.4 | 30.0 | X | X | X | X | 77.2 | 55.6 | A, P, S |
| Tokutsu (2013) | RET | Japan | 42 | 61.3 | 31.0 | 9.7 | 100 | 10.5 | BL | 85.7 | 54.8 | A, P, S |
| Tominaga (2011) | PRO | Japan | 18 | 70.9 | 66.7 | 8.0 | 100 | 6.0 | BL | 38.9 | X | A, P, S |
| Van Waarde (2013) | PRO | Netherlands | 84[a] | 59.1[a] | 33.3[a] | X | X | 17.4[b] | VAR | 69.0 | 48.8 | A, P, S |
| Winkler (2014) | PRO | Austria | 15 | 47.9 | 6.7 | X | 100 | 9.8 | VAR | X | 40.0 | A,P, S |

*PRO, prospective; RET, retrospective; BL, only bilateral electrode position; RUL, only right unilateral electrode position; VAR, different electrode positions were used; A, age; M, melancholic symptoms; P, psychotic symptoms; S, depression severity; X, data not available.*

*(a) Number and averages of the completer sample extracted from additional data were used. Therefore, numbers in the table above may not match numbers in the original papers.*

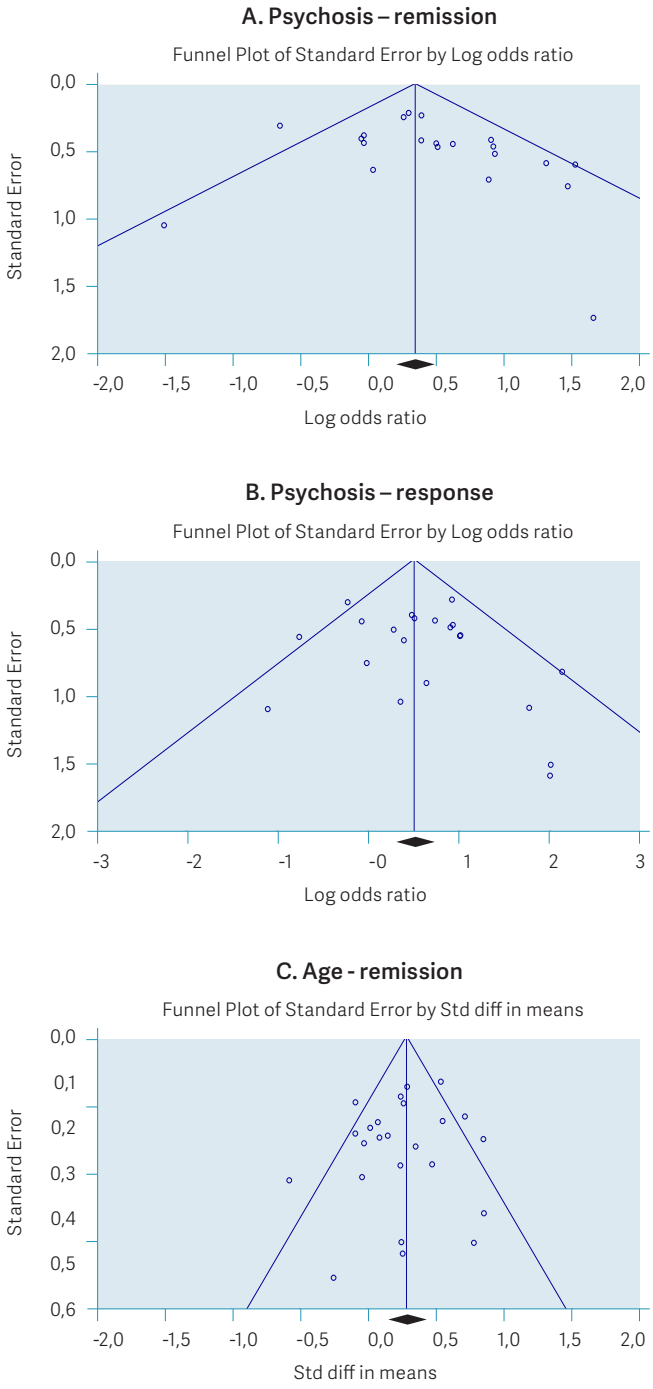
*(b) Data from the original paper (of for example course length) were used if these data were not available for the completer sample.*

*Table DS3. Results of study quality assessment*

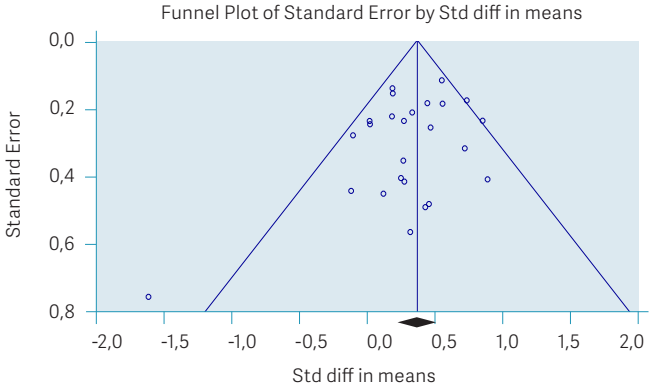
| | Design | Observational | Dropout (>20%) |
|---|---|---|---|
| Alves 2016 | Pro | Yes | Yes |
| Bauer 2009 | Pro | No | No |
| Bharadwaj 2012 | Retro | Yes | No |
| Birkenhager 2003 | Retro | Yes | No |
| Birkenhager 2010 | Retro | Yes | No |
| Bjølseth 2015 | Pro | No | No |
| Bumb 2015 | Pro | Yes | No |
| Dannon 2001 | Pro | Yes | No |
| De Vreede 2005 | Retro | Yes | No |
| Dombrovski 2005 | Pro | Yes | No |
| Fink 2007 | Pro | Yes | Yes |
| Huuhka 2007 | Pro | Yes | No |
| Joshi 2015 | Pro | Yes | Yes |
| Kellner 2016 | Pro | Yes | Yes |
| Kho 2005 | Retro | Yes | No |
| Kuscu 2015 | Pro | No | No |
| Lin 2015 | Pro | Yes | Yes |
| Loo 2011 | Pro | Yes | Yes |
| Medda 2014 | Pro | Yes | No |
| O´Connor 2001 | Pro | Yes | Yes |
| Okazaki 2010 | Pro | Yes | No |
| Oudega 2014 | Pro | Yes | No |
| Piccinni 2009 | Pro | Yes | No |
| Rhebergen 2015 | Pro | No | No |
| Schoeyen 2015 | Pro | No | Yes |
| Semkovska 2016 | Pro | No | No |
| Sivaprakash 2000 | Pro | Yes | No |
| Sobin 1996 | Pro | No | No |
| Spaans 2013 | Pro | No | Yes |
| Spashett 2014 | Retro | Yes | No |
| Tokutsu 2013 | Retro | Yes | No |
| Tominaga 2011 | Pro | Yes | No |
| Van Waarde 2013 | Pro | Yes | No |
| Winkler2014 | Pro | Yes | No |

*Pro, prospective; Retro, retrospective*

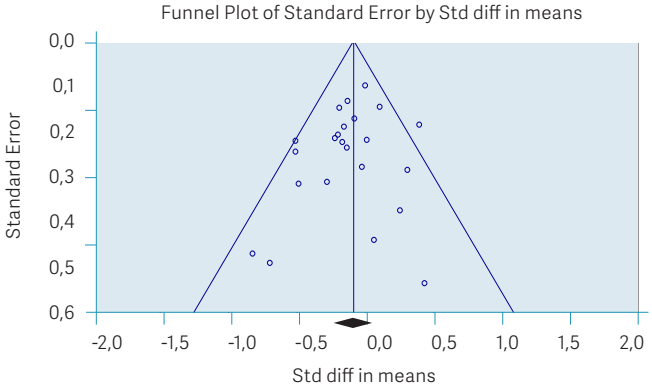
*Figure DS4. Funnel plots of the effect size according to the standard errors*



**D. Age - response**




**E. Depression severity - remission**




**F. Depression severity – response**

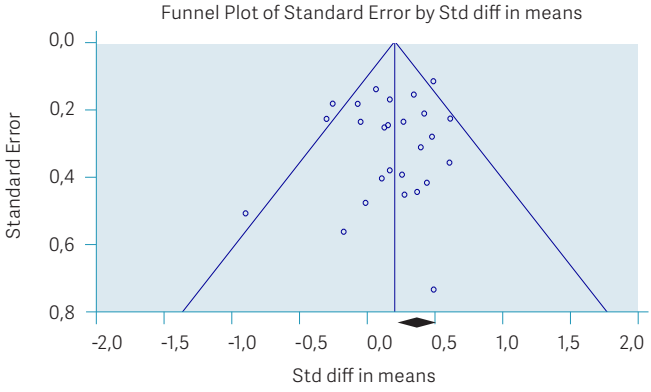


*Table DS5. Results of heterogeneity and sensitivity analyses*

| | | Remission | | | Response | | |
|---|---|---|---|---|---|---|---|
| Psychotic symptoms | | Q | df | P | Q | df | P |
| | Location | 3.16 | 4 | 0.531 | 3.90 | 4 | 0.420 |
| | Electrode position | 5.37 | 2 | 0.068 | 0.18 | 2 | 0.914 |
| | Design | 0.23 | 1 | 0.630 | 1.30 | 1 | 0.255 |
| | Observational | 1.14 | 1 | 0.285 | 0.79 | 1 | 0.375 |
| | Dropout | 0.21 | 1 | 0.646 | 0.03 | 1 | 0.861 |
| | | Beta | 95% CI | P | Beta | 95% CI | P |
| | Age | 0.040 | 0.006-0.073 | 0.021* | -0.013 | -0.054-0.029 | 0.543 |
| | Psychotic symptoms | -0.013 | -0.036-0.010 | 0.271 | -0.020 | -0.043-0.003 | 0.087 |
| | Episode duration | 0.018 | -0.015-0.050 | 0.296 | 0.034 | -0.037-0.105 | 0.346 |
| | Medication resistance | -0.019 | -0.036- -0.003 | 0.023* | -0.002 | -0.021-0.017 | 0.859 |
| | Length course | 0.063 | -0.034-0.160 | 0.203 | 0.089 | 0.001-0.176 | 0.048* |
| Age | | Q | df | P | Q | df | P |
| | Location | 6.64 | 4 | 0.156 | 7.55 | 4 | 0.110 |
| | Electrode position | 8.81 | 2 | 0.012* | 5.22 | 2 | 0.074 |
| | Design | 0.19 | 1 | 0.667 | 0.22 | 1 | 0.639 |
| | Observational | 4.75 | 1 | 0.029* | 2.53 | 1 | 0.112 |
| | Dropout | 0.75 | 1 | 0.387 | 0.03 | 1 | 0.860 |
| | | Beta | 95% CI | P | Beta | 95% CI | P |
| | Age | -0.004 | -0.020-0.012 | 0.609 | 0.002 | -0.013-0.016 | 0.830 |
| | Psychotic symptoms | -0.001 | -0.014-0.012 | 0.874 | 0.003 | -0.007-0.013 | 0.585 |
| | Episode duration | 0.044 | 0.016-0.073 | 0.003** | 0.037 | 0.005-0.068 | 0.021* |
| | Medication resistance | -0.002 | -0.011-0.007 | 0.647 | -0.001 | -0.010-0.009 | 0.919 |
| | Length course | 0.006 | -0.049-0.061 | 0.828 | 0.013 | -0.035-0.062 | 0.586 |
| Depression severity | | Q | df | P | Q | df | P |
| | Location | 5.31 | 4 | 0.257 | 3.32 | 4 | 0.506 |
| | Electrode position | 4.24 | 2 | 0.120 | 4.91 | 2 | 0.086 |
| | Design | 0.11 | 1 | 0.744 | 11.63 | 1 | 0.001** |
| | Observational | 0.49 | 1 | 0.483 | 0.10 | 1 | 0.749 |
| | Dropout | 3.99 | 1 | 0.046* | 0.07 | 1 | 0.790 |
| | | Beta | 95% CI | P | Beta | 95% CI | P |
| | Age | -0.001 | -0.014-0.012 | 0.875 | -0.009 | -0.020-0.003 | 0.150 |
| | Psychotic symptoms | 0.002 | -0.008-0.011 | 0.730 | 0.002 | -0.009-0.012 | 0.754 |
| | Episode duration | 0.008 | -0.027-0.042 | 0.666 | -0.008 | -0.044-0.029 | 0.683 |
| | Medication resistance | <-0.001 | -0.007-0.006 | 0.966 | 0.003 | -0.003-0.008 | 0.389 |
| | Length course | 0.022 | -0.022-0.067 | 0.321 | 0.016 | -0.029-0.061 | 0.487 |

*(*) P<0.05, **P<0.01, ***P<0.001*

4

# PREDICTING ECT RESPONSE: THE ROLE OF TREATMENT RESISTANCE

Published as: van Diermen L, Hebbrecht K, Schrijvers D, Sabbe BCG, Fransen E, Birkenhäger TK. The Maudsley Staging Method as predictor of electroconvulsive therapy effectiveness in depression. Acta Psychiatr Scand [Internet]. 2018 Oct 1;1–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30270433

Acta Psychiatrica Scandinavica

*Acta Psychiatr Scand 2018: 1–10*
DOI: 10.1111/acps.12962



# The Maudsley Staging Method as predictor of electroconvulsive therapy effectiveness in depression

van Diermen L, Hebbrecht K, Schrijvers D, Sabbe BCG, Fransen E, Birkenhäger TK. The Maudsley Staging Method as predictor of electroconvulsive therapy effectiveness in depression

**Objective:** To investigate the potential role of the Maudsley Staging Method (MSM) in the prediction of electroconvulsive therapy (ECT) outcome in severely depressed adults.
**Method:** Between August 2015 and August 2017, 73 consecutive patients with a major depressive episode (DSM-IV-TR) scheduled for ECT were recruited. Prior to their first ECT session, the MSM was completed to assess the level of therapy resistance. To determine the reduction in depression severity and response and remission rates, symptom severity was assessed at baseline and within one week after the last ECT session using the 17-item Hamilton Depression Rating Scale (HDRS17).
**Results:** The percentage of symptom reduction following ECT was best predicted by the MSM episode duration and depression severity factors ($R^2$ completer sample 0.24). Episode duration alone was the best predictor of remission (area under the ROC curve for completers: 0.72). Adding age to the models increased their predictive capacity.
**Conclusion:** An adapted version of the MSM gauging shorter episode duration, more severe depressive symptoms and older age is significantly associated with ECT effectiveness in adults with severe recurrent depression and is thus highly suitable for use in clinical practice, promoting the shared treatment decision-making process.

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Key words: major depressive disorder; electroconvulsive therapy; decision-making

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***Clinical Trials Registration***: ClinicalTrials.gov identifier: NCT02562846.

Accepted for publication August 23, 2018

**Significant outcomes**

- The percentage of HDRS decrease can be predicted by an adapted version of the MSM, evaluating baseline depression severity and episode duration.
- Remission was best predicted by depressive episode duration.
- Adding age to the models improved their predictive capacities.
- The adapted MSM has the potential to contribute to the treatment decision-making process in patients with depression.

**Limitations**

- Although the adapted MSM is a significant predictor, it can only explain part of ECT effectiveness.
- The sample size of our study is limited.
- Due to our observational design, there is substantial heterogeneity in patient and treatment characteristics.

## Introduction

Despite the availability of a broad range of pharmacological treatments for major depressive disorder (MDD), response rates are rather low. Results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study show a response rate of less than 50% and a remission rate of less than 30% to the first antidepressant trial (1). Furthermore, remission rates decrease with each subsequent antidepressant trial, with a steep decline after two trials. The core assumption in treatment resistance is the failure of adequate treatment (in terms of adequate dose and duration) to bring about improvement. The STAR*D results prompted a categorical definition of treatment-resistant depression (TRD), that is an MDD episode that does not respond to a minimum of two adequate trials of antidepressant monotherapy (2). Several other definitions have however also been proposed, ranging from non-response to a single antidepressant to non-response to at least two antidepressants from different classes (3). Instead of a dichotomous definition of treatment resistance (presence or absence), TRD can also be described as a continuum based on the number and types of failed treatments (2). Examples of such continuous staging models are the Antidepressant Treatment History Form (1990), the Thase and Rush staging model (1997) and the Maudsley Staging Method (MSM; 2009) (2, 4–8).

The difference between the MSM and other staging models is that it incorporates two clinical factors associated with treatment resistance, that is (depression severity and episode duration) in addition to treatment factors (7). According to Fekadu et al. authors of the MSM, staging treatment resistance only in relation to the number of antidepressants used says little about the specific nature of the depression itself. A moderately severe major depression that does not respond to treatment is distinct from a severe psychotic depression that is also resistant to treatment. Fekadu et al. conclude that a more severe depression and longer episode duration are associated with non-remission after treatment (9). Therefore, these two factors were included in the MSM. A higher number of failed antidepressants and a higher total MSM score were also associated with non-remission (9). The MSM consequently takes into account the complex and multidimensional character of TRD. Other advantages of the MSM are its clinical usability and the equal consideration of between-class and within-class switching of antidepressants (7).

To date, electroconvulsive therapy (ECT) is the most effective biological treatment for severe MDD (10, 11). However, its overall clinical use is limited due to its potential cognitive side-effects (12, 13), its limited availability and its limited acceptability to a proportion of patients. Furthermore, response to ECT varies between 65% and 80% (10, 14). In the last few decades, numerous predictors of ECT outcome have been proposed. In their 2010 meta-analysis, Heijnen et al. found the absence of medication failure to predict a higher efficacy of ECT (15), while in their more recent meta-analysis Haq et al. confirmed this and also concluded that a shorter episode duration was a good outcome predictor (16). In our 2018 meta-analysis, we found three additional clinical predictors of good outcome: old age, presence of psychotic symptoms and higher baseline severity of depressive symptoms (14).

### Aims of the study

The three fundamental MSM elements, that is antidepressant treatment failure, depression severity and episode duration, are all proven predictors of ECT outcome in populations with severe recurrent MDD. In the present study, we will be investigating whether combinations of these elements will increase the predictive power of the MSM in a population of depressed patients treated with ECT.

## Material and methods

### Study population

A total of 73 consecutive patients (56 women, 17 men; mean age 58.8 (±15.1) years) awaiting ECT at the University Psychiatric Hospital of Duffel (Belgium) participated in our prospective longitudinal study. This study is part of a larger research project on ECT response predictors, the so-called PROTECT cohort. All patients had been diagnosed with MDD or a severe depressive episode in bipolar disorder according to the Diagnostic and Statistical Manual, the DSM-IV-TR version (APA 2000). The diagnoses were confirmed by the Mini-International Neuropsychiatric Interview (MINI 6.0) (17). The large majority of the participants were inpatients of our hospital (92%, $N = 67$), with the remaining patients received ECT on an ambulatory basis. Prior to ECT, the 17-item Hamilton Depression Rating Scale (HDRS17) was completed, a score of at least 17 was required for inclusion (18). Exclusion criteria were a history of substance abuse (<6 months ago) or the presence of a primary psychotic or schizoaffective disorder.

All participants provided their written informed consent prior to the start of the study procedures. The study was approved by the Ethics Committee of the University Hospital of Antwerp (project number 15/10/93) and registered at clincaltrials.gov (trial registration number NCT02562846).

### Treatment

*Pharmacological therapy*. During the ECT course, patients continued their antidepressant and/or antipsychotic medication. Agents and doses were preferably not changed 4 weeks prior to and during ECT (including the final assessment). Seven percent of patients was not treated with antidepressants, 73% was on antidepressant monotherapy and 20% of patients used more than one antidepressant. In total, 68% took a tricyclic antidepressant, 26% a selective serotonin reuptake inhibitor, 3% a serotonin–noradrenaline reuptake inhibitor and 16% other antidepressants. Seventy-nine percent of patients were concurrently treated with antipsychotics and 26% with a mood-stabilizer (mainly lithium), with 73% taking short-acting benzodiazepines (an average 8.4 mg diazepam equivalent dose) that were withheld 12 h prior to each ECT session.

*Electroconvulsive therapy*. ECT was delivered twice weekly according to recent guidelines (19) using a brief-pulse (0.5 ms) constant-current Thymatron IV system (Somatics LLC, Lake Bluff, IL, USA). Electrodes were placed right unilateral (RUL), bifrontal (BF) or bitemporal (BT) when a fast antidepressant effect was needed (20). Patients that were initially treated with RUL ECT were switched to BT ECT if response was inadequate after six treatments. Prior to ECT start, the stimulus dose was established by means of the age method for RUL-electrode placement and the half-age estimation method for bilateral electrode positions (21). Etomidate was the anaesthetic of choice (0.15 mg/kg), with propofol (1 mg/kg) and ketamine (1–2 mg/kg) being used when etomidate was not (well) tolerated or in case of a lack of clinical response after the first 12 sessions. Succinylcholine (Myoplegine®, 0.5 mg/kg) was used as a muscle relaxant.

The endpoint of the ECT treatment was determined by the clinician, who based the decision on ratings of mood and side-effects of treatment. During the ECT course, the mood was rated weekly and ECT was continued until patients were either asymptomatic (HDRS17 $\leq$ 7) or showed no further improvement during the last three sessions. Another reason to stop ECT was the occurrence of intolerable side-effects.

### Clinical assessment

*Mood and effect of treatment*. The baseline HDRS17 rating was performed on the last weekday prior to the first ECT session while the last assessment was generally conducted one week after the last ECT. The HDRS17 was rated by the main researcher (LVD), MD and psychiatry resident or (in case of absence) by another member of the research team. All raters had received an HDRS training session delivered by an experienced investigator (TB) and once every 3 months attended a Hamilton rating session during which they independently scored a video-recorded case and discussed their ratings. ECT efficacy was defined in three ways. The primary outcome measure was the pre- to post-ECT change (in percentages) in HDRS17 scores. The secondary outcome measures were response and remission, defined as a HDRS17 decrease of >50% and an HDRS17 score $\leq$7 after the last ECT, respectively.

*Treatment resistance*. Treatment resistance was assessed by the main researcher, completing the MSM (7) prior to the start of ECT. This points-based staging model evaluates three elements of treatment resistance: the duration of the current episode, the severity of the illness and treatment history (Table 1). Because none of the participants in our study had subsyndromal or mild depressive disorders, all had a score of 3 (moderate), 4 (severe without psychotic symptoms) or 5 (severe with psychotic symptoms) on the depression severity item, as based on their baseline HDRS scores (where scores of 17–23 are classified as moderate and scores $\geq$24 as severe). In the original MSM, treatment history comprises three elements: the number of failed antidepressants, whether or not augmentation strategies (with antipsychotics or lithium) and/or ECT had been applied during this episode. We only used the number of failed antidepressants in our analyses as this was the only factor linked to non-remission in the original MSM evaluation (7). Antidepressant trials for the current depressive episode were evaluated for adequacy according to the instructions provided in the original MSM paper (7).When the patient was unable to provide the required data on treatment history and episode duration, the treating psychiatrist or the family doctor was consulted.

### Statistical analysis

Statistical analyses were performed with JMP 13.0. One participant refused testing after the last ECT,

Table 1. Original and adapted Maudsley staging parameters and suggested scoring conventions

| Original MSM | | | Adapted MSM | | |
|---|---|---|---|---|---|
| Parameter | Specifications | Score | Parameter | Specifications | Score |
| Duration | Acute (≤12 months) | 1 | Duration | Acute (≤12 months) | 1 |
| | Subacute (13–24 months) | 2 | | Subacute (13–24 months) | 2 |
| | Chronic (>24 months) | 3 | | Chronic (>24 months) | 3 |
| Symptom severity (at baseline) | Subsyndromal | 1 | Symptom severity (at baseline) | Severe with psychosis | 1 |
| | Syndromal | | | Severe without psychosis | 2 |
| | Mild | 2 | | Moderate | 3 |
| | Moderate | 3 | *Age** | *≥65 years* | *0* |
| | Severe without psychosis | 4 | | *50–65 years* | *1* |
| | Severe with psychosis | 5 | | *< 50 years* | *2* |
| Treatment failures | | | | | |
| Antidepressants | Level 1: 1–2 medications | 1 | | | |
| | Level 2: 3–4 medications | 2 | | | |
| | Level 3: 5–6 medications | 3 | | | |
| | Level 4: 7–10 medications | 4 | | | |
| | Level 5: >10 medications | 5 | | | |
| Augmentation | Not used | 0 | | | |
| | Used | 1 | | | |
| ECT | Not used | 0 | | | |
| | Used | 1 | | | |
| Total | | (15) | Total excluding age | | (6) |
| | | | Total including age | | (8) |

ECT = electroconvulsive therapy.
*Age can be added to the model to increase its predictive ability.

for whom we used the last-observation-carried-forward method.

To identify variables associated with the percentage of HDRS decrease, simple linear regression models were fitted. When more than one of the variables was associated with the percentage of HDRS decrease ($P < 0.10$), multiple linear regression models were fitted. Variables not reaching significance in the multiple regression were removed from the model before presentation of the final results. The same approach was used with response and remission, for which we used logistic rather than linear regression since it concerns dichotomous outcome variables.

When multicollinearity was observed between the predictor variables, only the strongest predictor was maintained in the multiple regression model.

## Results

Demographic and clinical characteristics for the intention-to-treat (ITT) sample and completers are shown in Table 2. The average number of ECT sessions was 11.2 (±5.7), with 40 patients receiving RUL and 11 BT treatment only, while two patients were treated with BF ECT. In the remaining 18 patients, electrode positions were switched during the course (mostly from RUL to BT). Etomidate was used in 65, propofol in 17 and ketamine in 14 patients. The most common switch was from

Table 2. Demographic and clinical characteristics of the study population

| Demographic characteristics | ITT (*N* = 73) | Completers (*N* = 65) |
|---|---|---|
| Age, years (mean ± SD) | 58.8 (±15.1) | 58.4 (±15.6) |
| Biological sex, female % (*N*) | 76.7 (56) | 76.9 (50) |
| Clinical characteristics | | |
| Baseline HDRS score (mean ± SD) | 24.8 (±6.0) | 24.9 (±6.1) |
| Endpoint HDRS score (mean ± SD) | 8.5 (±5.0) | 8.0 (±4.7) |
| Average HDRS decrease % (mean ± SD) | 63.9 (±22.9) | 66.1 (±22.5) |
| Responders % (*N*) | 73.9 (54) | 76.9 (50) |
| Remitters % (*N*) | 56.2 (41) | 61.5 (40) |
| CORE-defined melancholia % (*N*) | 63.0 (46) | 63.1 (41) |
| Bipolar % (*N*) | 17.8 (13) | 18.5 (12) |
| Episode duration in months | | |
| Mean ± SD | 14.3 (±18.1) | 13.3 (±17.8) |
| Median, range | 6.5, 1–84 | 6.0, 1–84 |
| Maudsley staging method (MSM) | | |
| Episode duration | | |
| Acute (<12 months, *N*) | 48 | 44 |
| Subacute (12–24 months, *N*) | 12 | 11 |
| Chronic (> 2 years, *N*) | 13 | 10 |
| Failed treatments (*N*) | | |
| 1–2 | 22 | 21 |
| 3–4 | 29 | 27 |
| 5–6 | 13 | 9 |
| 7–10 | 5 | 5 |
| >10 | 0 | 0 |
| Depression severity | | |
| Moderate (HDRS 17–23, *N*) | 25 | 22 |
| Severe without psychosis (HDRS ≥ 24, *N*) | 17 | 12 |
| Severe with psychosis (HDRS ≥ 24, *N*) | 31 | 31 |
| Augmentation % (*N*) | 90.4 (66) | 89.2 (58) |
| Previous electroconvulsive therapy course % (*N*) | 2.7 (2) | 3.1 (2) |

ITT, Intention-to-treat; HDRS, Hamilton Depression Rating Scale; CORE, Scale to assess psychomotor functioning, patients with a score ≥ 8 were classified as melancholic.

Table 3. Predictors of percentage of HDRS decrease, response and remission for the ITT ($N$ = 73) and the completer ($N$ = 65) samples

| | ITT | | | Completers | | |
|---|---|---|---|---|---|---|
| Outcome = percentage of HDRS decrease | *F*-ratio | Prob > F | $R^2$ | *F*-ratio | Prob > *F* | $R^2$ |
| Simple linear regression | | | | | | |
| Shorter episode duration | 11.61 | <0.001*** | 0.14 | 11.82 | <0.01** | 0.16 |
| More severe depression | 10.51 | <0.01** | 0.13 | 9.61 | <0.01** | 0.13 |
| Failed antidepressants | 7.94 | <0.01** | 0.11 | 6.47 | 0.01* | 0.1 |
| Multiple linear regression | | | 0.23 | | | 0.24 |
| Shorter episode duration | 8.95 | <0.01** | | 9.14 | <0.01** | |
| More severe depression | 7.8 | <0.01** | | 7.05 | 0.01* | |
| Outcome = non-response vs. response | Unit odds ratio | 95% CI | Significance | Unit odds ratio | 95% CI | Significance |
| Simple logistic regression | | | | | | |
| Shorter episode duration | 2.17 | 1.14–4.14 | 0.02* | 2.27 | 1.10–4.69 | 0.03* |
| More severe depression | 0.53 | 0.28–1.00 | 0.05* | 0.51 | 0.26–1.00 | 0.05 |
| Failed antidepressants | 1.92 | 1.03–3.58 | 0.04* | 1.66 | 0.86–3.21 | 0.13 |
| Multiple logistic regression | | | | | | |
| Shorter episode duration | 2.02 | 1.04–0.92 | 0.04* | | | |
| More severe depression | 0.58 | 0.30–1.11 | 0.1 | | | |
| Outcome = non-remission vs. remission | Unit odds ratio | 95% CI | Significance | Unit odds ratio | 95% CI | Significance |
| Simple logistic regression | | | | | | |
| Shorter episode duration | 3.14 | 1.55–6.35 | <0.001*** | 4.13 | 1.81–9.43 | <0.001*** |
| More severe depression | 0.71 | 0.42–1.22 | 0.21 | 0.75 | 0.43–1.32 | 0.32 |
| Failed antidepressants | 2.61 | 1.38–4.93 | <0.01** | 2.75 | 1.38–5.46 | <0.01** |

ITT, Intention-to-treat.

etomidate to ketamine ($N$ = 14) and from propofol to etomidate ($N$ = 10). Eight patients could not complete the ECT course because of side-effects ($N$ = 5) or reasons not related to the ECT ($N$ = 3). The ITT sample accordingly comprised 73 and the completer sample 65 patients.

### Predictors of treatment effect

To calculate the results for the three MSM factors with an alleged predictive effect (14–16) (episode duration, depression severity and the number of failed antidepressants during the current episode), we used the scoring method prescribed by the model (see Treatment resistance section).

*Separate predictors*. The results of the linear regression analyses performed on the data with the percentage of HDRS decrease as outcome variable are presented in Table 3.

All three factors were significantly associated with HDRS decrease in the ITT as well as the completer sample. A strong correlation between episode duration and the number of failed antidepressants ($r$ = 0.56, $P$ < 0.001) was found. The multiple linear regression model therefore only includes depression severity and the strongest of the two correlated variables – episode duration. The regression model with episode duration and depression severity as independent variables explained 23% of the variance in HDRS decrease in the ITT sample and 24% in the completer sample.

The part of the variance that can be explained by a combination of depression severity and failed antidepressants is similar (ITT: 0.23; completer sample: 0.24) to the variance explained by depression severity and episode duration. A shorter episode duration and a lower number of failed antidepressant treatments individually predicted remission both in the ITT and the completer sample (Table 3). The fact that depression severity was no significant predictor in this analysis is inherent to the definition of remission in that higher baseline symptom severity implies that a greater decrease in HDRS is needed to reach remission than when baseline HDRS scores are lower. Because of the correlation between episode duration and failed antidepressant treatments, the final model has only one predictor, that is episode duration. A ROC curve was fitted that had an area under the ROC curve (AUC) of 0.69 in the ITT and 0.72 in the completer sample. The results of the response analyses differed slightly. All three predictors individually predicted response in the ITT sample while in the completer sample only episode duration reached significance. In the ITT

Table 4. Percentage of HDRS decrease, response and remission rates for each possible score on the adapted MSM scale (excluding age) for the ITT ($N = 73$) and completer ($N = 65$) samples.

| | *N* | | Percentage of HDRS decrease (95% CI) | | Response rate (%) | | Remission rate (%) | |
|---|---|---|---|---|---|---|---|---|
| Adapted MSM score | ITT | Completers | ITT | Completers | ITT | Completers | ITT | Completers |
| 2 | 24 | 24 | 77 (71–84) | 77 (71–84) | 92 | 92 | 79 | 79 |
| 3 | 13 | 11 | 66 (55–77) | 69 (58–81) | 69 | 73 | 62 | 73 |
| 4 | 22 | 19 | 58 (48–69) | 60 (49–72) | 73 | 74 | 43 | 47 |
| 5 | 8 | 6 | 53 (35–70) | 60 (42–77) | 63 | 83 | 38 | 50 |
| 6 | 6 | 5 | 36 (9–76) | 36 (0–73) | 33 | 20 | 33 | 20 |

ITT, Intention-to-treat.

Table 5. Regression model of adapted MSM scores (excluding age) vs. percentage of HDRS decreases for the ITT ($R^2 = 0.23$) and completer ($R^2 = 0.24$) samples

| | | 95% confidence interval | | |
|---|---|---|---|---|
| | Point estimate | Lower limit | Upper limit | *P* |
| ITT | | | | |
| Intercept | 93.15 | 79.48 | 106.81 | |
| Adapted MSM score | −8.50 | −12.22 | −4.77 | <0.0001 |
| Completers | | | | |
| Intercept | 94.95 | 81.12 | 108.78 | |
| Adapted MSM score | −8.64 | −12.51 | −4.77 | <0.0001 |

ITT, Intention-to-treat.

Table 6. Regression model of adapted MSM scores (excluding age) vs. response (non-responder/responder) and remission (non-remitter/remitter) for the ITT (AUC for both = 0.70) and completer (AUC response = 0.71, AUC remission = 0.70) samples

| | | | 95% confidence interval | | |
|---|---|---|---|---|---|
| | Point estimate (log scale) | Estimated Odds Ratio | Lower limit | Upper limit | *P* |
| Response | | | | | |
| ITT | | | | | |
| Intercept | −3.32 | | | | |
| Adapted MSM score | 0.62 | 1.86 | 1.19 | 2.92 | 0.0067 |
| Completers | | | | | |
| Intercept | −3.55 | | | | |
| Adapted MSM score | 0.65 | 1.92 | 1.17 | 3.14 | 0.0095 |
| Remission | | | | | |
| ITT | | | | | |
| Intercept | −2.31 | | | | |
| Adapted MSM score | 0.59 | 1.81 | 1.20 | 2.73 | 0. 0047 |
| Completers | | | | | |
| Intercept | −2.62 | | | | |
| Adapted MSM score | 0.63 | 1.87 | 1.20 | 2.92 | 0.0057 |

ITT, Intention-to-treat.

sample, we performed a multiple logistic regression with episode duration and severity as predictors. Although depression severity was no longer a significant contributor in the regression, the AUC of the model was 0.71 and the AUC of the simple logistic regression model with episode duration in the completer sample was 0.65.

*Adapted MSM.* As we found shorter episode duration and severe depressive symptoms to be the most consistent independent predictors of a higher efficacy of ECT in our ECT sample, we constructed a composite score of these two treatment-resistance factors. To make sure the effects of the predictors had the same direction, we transformed the depression severity score by awarding the minimal score of 1 to severe depression with psychotic symptoms, a score of 2 to severe depression without psychotic symptoms and a score of 3 to moderate depression (Table 1). In this way, lower scores on episode duration (corresponding with shorter episode duration) and on depression severity (corresponding with a more severe depression) are both related to a greater reduction in HDRS scores. In Table 4, the percentage of HDRS decrease and response and remission rates are presented for each of the possible scores on this adapted MSM scale.

There is a clear decrease in ECT effectiveness with increasing adapted MSM scores. Details of the regression model for the ITT and completer samples with the percentage of HDRS decreases can be found in Table 5.

When looking at the outcome variable percentage of HDRS decrease, we found that the adapted MSM renders results comparable to the multiple regression model with depression severity and episode duration as two separate predictors (both have an $R^2$ of 0.23 in the ITT and 0.24 in de completer sample).

The adapted MSM score is significantly associated with the percentage of HDRS decrease as well as with the occurrence of remission and response. When remission is taken as outcome variable, the use of the adapted MSM has no clear advantage over the use of episode duration as the only remission predictor (AUC of both was 0.70, Table 6). For response, the adapted MSM score also shows no clear advantage over the multiple logistic

regression model with separate predictors in the ITT sample. The adapted MSM score rendered a somewhat better model in the completer sample with an AUC of 0.71 compared to 0.65 in the simple logistic regression model of Table 3.

Compared to the total original MSM score, the adapted MSM is an improvement as a predictor of ECT treatment effect for both percentage HDRS decrease and response as outcome variables. In the ITT sample, there was no significant influence of the original MSM total score in the analyses with the percentage of HDRS decrease ($R^2$ of 0.01) or treatment response (AUC of 0.57) as outcome variables. The original MSM total score did significantly predict remission (AUC of 0.66), but the adapted MSM yielded an AUC of 0.70. Results in the completer sample were comparable, with total MSM scores not affecting the percentage of HDRS decrease/response but showing a significant predictive effect on remission (AUC: 0.68), with the adapted MSM score only slightly improving the AUC (0.70).

*Improving the adapted MSM*. Considering what is already known about the prediction of the effect of ECT, we realized that our model was incomplete. Of the predictors we considered 'confirmed' (14, 16), only four are covered by the MSM. The only known ECT-response predictor that has no place in the MSM is age. We created a categorical variable for age, adding 2 points for patients under 50 to the adapted MSM score, 1 point for those between 50 and 65 years and no points for patients aged 65 years and older. The score of the adapted MSM including the variable 'age' thus ranges between 2 and 8 (Table 1). When we added age to the prediction model of the completer sample, $R^2$ of the percentage of HDRS decrease increased from 0.24 to 0.31 and the AUC for response and remission increased from 0.71 or 0.72 to 0.77 or 0.76, respectively (with older age corresponding to a better treatment effect).

#### Discussion

Since the future of a more accurate patient-treatment matching lies in practical clinician- and patient-friendly assessment tools, we evaluated the predictive capacity of the three key factors of the Maudsley Staging Method (MSM) and constructed an alternative, adapted version that affords a more accurate prediction of the efficacy of electroconvulsive therapy (ECT) for severe persistent depression.

We found that shorter episode duration and more severe depressive symptoms, two core factors of the MSM, most consistently predicted a larger effect of ECT in patients with recurrent severe depression. The number of failed antidepressant treatments did not significantly improve the prediction model that already included data on episode duration because these variables (episode duration and the number of antidepressant trials) correlated strongly. Of the three key factors in the original MSM evaluation, the number of failed antidepressants also had the weakest association with remission (7). Adding age to the analyses improved the prediction models.

In our clinical practice, we find that a substantial part of the patients referred for ECT is too ill to participate in clinical studies. However, our study confirms the effectiveness of ECT especially for the most severely and urgently depressed part of the patient spectrum (i.e. those patients with lower adapted MSM scores reflecting a shorter episode duration and more severe depressive symptoms), with remission rates of 79% (Table 4) for those with the lowest MSM scores. Note that more severe depressive symptoms predict a higher efficacy of ECT. This is not in agreement with findings of the original MSM report (7) in which more severe depressive symptoms significantly lowered chances of remission. An explanation for these contrasting results can be found in differences in study design and patient population. The original paper measured treatment outcome at discharge after administration of a variety of treatment options while our study specifically investigates the effect of treatment with ECT. As a consequence, our population is a selection of more severely depressed patients and not a reflection the whole spectrum of depression severity as one of our inclusion criteria was a HDRS score $\geq$ 17. Another explanation for this contrasting finding could be that patients with a severe depressive disorder relatively often show psychotic symptoms. Patients with psychotic depression have been reported to show a remarkably good response to ECT (14). The MSM does not evaluate the presence of psychotic symptoms as a separate factor but as a constituent part of the severity component. As this implies only a one-point difference between patients with and those without psychotic symptoms, this predictor might be insufficiently valued in the MSM for use in a depressed population eligible for ECT.

Although lower adapted MSM scores predict higher symptom reductions, we do not discourage the use of ECT for people with higher or even maximum adapted MSM scores (reflecting a longer episode duration and moderate depression severity) as in our trial 20% (Table 4) of the completers with a maximum adapted MSM score still

reached remission. Overall, ECT might still be the best treatment option for individuals suffering from persistent MDD, although other treatment options should also be considered in this patient group.

Although none of the predictors assessed is novel or unexpected, the relevance of our report lies in the fact that we composed a prediction model that incorporates different (known) predictors. Using the categories posed by the MSM increases the reliability of the collected data, which is desirable in research as well as clinical practice. Since the predictor episode duration is, by definition, always assessed retrospectively, its exactness is inherently doubtful. The chance that the registered episode duration is situated in the correct MSM category is considerable, compared to the estimation of episode duration in months. Together with its ease of use, this makes the MSM a highly applicable tool for clinical practice.

### Comparison with previous studies

Although numerous studies have investigated predictors of ECT efficacy, few attempted to create an actual prediction model that unites the known predictors while still being clinically applicable. De Vreede et al. (22) proposed a prediction index for poor ECT response consisting of four independent factors: age, presence of a personality disorder, psychotic symptoms and treatment resistance. Their model is more complex than the adapted MSM we suggest since, during a depressive episode with ECT being imminent, it is often hard to diagnose the presence of a personality disorder. Still, the precision of their remission prediction model (AUC = 0.76) was comparable to ours (AUC = 0.77). Another noteworthy model is the 3-item ECT Appropriateness Scale (EAS) developed by Kellner et al. (23). Founding their selection of relevant variables, that is depression severity, heritability and episodic nature of depression, on the literature, their model was not validated in a patient sample. Just like we do in our model, they pose that more severe depression is a reason to consider treatment with ECT.

We chose the MSM as a starting point for our predictive ECT-efficacy model mainly because of its straightforward rating system. With their Dutch Measure for the quantification of Treatment Resistance in Depression (DM-TRD) (24) Peeters et al. recently suggested an extension of the MSM, adding functional impairment, comorbid anxiety, personality disorder and psychosocial stressors to the model. The DM-TRD outperformed the MSM in the prediction of future depressive symptomatology and equalled the MSM in the prediction of remission. Nevertheless, besides the presence of a personality disorder (25), we expect their model to have no added value for patients eligible for ECT.

### Limitations

A limitation of the study is the relatively small sample size. Replication of our findings in a larger ECT sample would be valuable. With about one-third being moderately depressed, the patients in our study were, on average, somewhat less severely depressed (HDRS17 of 24.8) than the rates reported in most ECT studies (HDRS17 of 27.6 (26)). Due to the observational design of our study, our sample inevitably comprised a combination of severely depressed patients with an acute ECT indication and depressed patients with often less severe but longer-lasting depressive symptoms that had proved resistant to multiple antidepressant treatments. It is not unlikely that part of this group had not responded to these previous treatment strategies as a consequence of the presence of psychiatric comorbidities, such as personality disorders. As we did not systematically assess the presence of personality disorders prior to initiating ECT in our naturalistic design, it is impossible to determine the role of such comorbidity in our sample. Moreover, the observational design of our study implied that the inpatients were not all staying at the same treatment unit and that the outpatients were seen by different clinicians. Our participants were, therefore, not necessarily offered the same psychological/psychiatric or antidepressant therapies. Although we do not expect a major influence of electrode positions (27), anaesthetics used (28, 29) or the length of the treatment course on ECT effectiveness, the heterogeneity in our treatment protocols should be taken into account when interpreting our results. Given that we had opted for a naturalistic study design, besides heterogeneous in treatment, our sample was also rather heterogeneous in composition, consisting of mainly female patients, unipolar as well as bipolar patients, patients with and without melancholic symptoms and with varying degrees of suicidality. Several of these factors have been linked to ECT responsiveness in the past (30). However, as meta-analyses have not found any confirmation of an influence of gender, polarity or melancholia on ECT responsiveness (14, 16, 31), we chose not to account for these factors in our analyses but do consider the heterogeneity they cause to be a limitation of our study. The severity of suicidal intent is a predictor worth investigating in future studies.

Still, although heterogeneous, our sample is a good reflection of depressed patients seen in daily clinical ECT practice.

To conclude, an accurate prediction of the efficacy of ECT for depression will facilitate the shared treatment decision-making process. For some patients, it may prevent a detrimental delay in effective treatment and for others exposure to needless (cognitive) side-effects. Starting from the MSM, we propose a model that predicts symptom-severity reductions and symptom remission following ECT. Evaluating baseline depression severity and episode duration in a treatment-resistant sample, our adapted model was successful in predicting the percentage of HDRS decrease, while episode duration alone was best at predicting remission. Adding the age of the patient to these two models further improved their predictive capacity. Given its simplicity, this adapted model has the potential to be used as a clinical instrument supporting treatment decisions.

#### Declaration of interest

The authors report no financial or any other relationship relevant to the subject of this article.

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5

# PREDICTING ECT RESPONSE: THE ROLE OF PSYCHOTIC SYMPTOMS

van Diermen L, Versyck P, van den Ameele S, Madani Y, Vermeulen T, Fransen E, Sabbe B, van der Mast R, Birkenhäger T, Schrijvers D. Performance of the Psychotic Depression Assessment Scale as a predictor of ECT outcome. Journal of ECT. *In press.*

# Performance of the Psychotic Depression Assessment Scale as a predictor of ECT outcome

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Declarations of interest: none.

## Abstract

**Objectives:** The presence of psychotic symptoms is an important predictor of responsiveness to electroconvulsive therapy (ECT). This study investigates whether a continuous severity measure, the Psychotic Depression Assessment Scale (PDAS), is a more accurate predictor.

**Methods:** Depression severity was assessed before and after the ECT course using the Montgomery-Asberg Depression Rating Scale (MADRS) in 31 patients with psychotic depression and 34 depressed patients without psychotic symptoms. Logistic regression models for MADRS response and remission were fitted, with either the PDAS total score or the dichotomous predictors 'absence/presence of psychotic symptoms' as the independent variables. Age, episode duration, and treatment resistance were added as covariates.

**Results:** Both the asserted presence of psychotic symptoms and a higher PDAS total score reflected MADRS response (AUCs: 0.83 and 0.85, respectively), with MADRS remission also being predicted by the presence of psychotic symptoms and higher PDAS scores (AUCs: 0.86 and 0.84, respectively). Age was a contributor to these prediction models with response and remission rates being highest in the older patients. PDAS scores decreased significantly during ECT: at endpoint 81.5% of the patients showed significant response and 63.9% had achieved remission.

**Conclusions:** The PDAS indeed accurately predicts response to and remission after ECT in (psychotic) depression and most pronouncedly so in older patients but appears to have no clear advantage over simply verifying the presence of psychotic symptoms. This could be the consequence of a ceiling effect as ECT was extremely effective in patients with psychotic depression.

**ClinicalTrials.gov**: Identifier: NCT02562846.


*Keywords:* major depressive disorder; psychotic depression; electroconvulsive therapy; response prediction

# Introduction

A major depressive disorder (MDD) can occur with or without psychotic features (34,117). The associated delusions and/or hallucinations in psychotic depression (PD) are often mood-congruent with a prevailing sense of guilt, sin, or poverty. Epidemiological studies of PD show a prevalence of 0.35% to 1%, with higher rates in older age (35). Since the risk of suicide is high in people coping with MDD and even higher in those also experiencing psychotic symptoms (118), it is clear that we need to optimize the treatment for both conditions.

Current treatment guidelines for PD are highly heterogeneous. Although some recommend antidepressant-antipsychotic combination therapy, others recommend antidepressant monotherapy or consider electroconvulsive therapy (ECT) equally appropriate as first-line treatment (119). In a meta-analysis our group recently conducted, we could conclude that ECT was effective in patients with PD (120). Furthermore, the relapse rates after successful ECT were lower than those documented for persons with nonpsychotic depression (121).

Besides its implementation in persisting and urgent cases, optimal effectiveness predictors could support the choice for ECT in other circumstances. Bearing in mind that in PD the severity of psychotic symptoms can vary from mild to very severe, we wondered whether the widely used practice of merely establishing their presence or absence is the best way to predict clinical response to ECT. As a more severe depression predicts better ECT response (120), one could argue that more severe psychotic symptoms may likewise predict higher response rates and that merely dichotomizing their manifestation then causes an unnecessary loss of information. We were hence curious to find out whether more continuous measures of psychotic symptom severity would be a more sensitive predictor of ECT response. In current literature, we found no studies on this subject. Also, scales to evaluate these symptoms in depression are scarce. The Psychotic Depression Assessment Scale (PDAS) is the only empirically derived rating tool covering both the depressive and psychotic symptoms of PD (81,82).

In the present study we investigate whether in depression, as hypothesized, the psychotic symptom severity as measured with the PDAS is a more sensitive predictor of responsiveness to ECT than the dichotomous measure of the presence or absence of psychotic symptoms. The secondary aim of our investigation was to determine whether the scale is sensitive enough to differentiate the response to ECT of patients with PD from that of persons without psychotic symptoms. We also compare the speed of response of these two patient groups, expecting the first group to respond faster (80,122).

# Materials and Methods

## Study design

The study was a single-site, prospective ECT study. The study was registered in the online clinical database ClinicalTrials.gov (Identifier: NCT02562846). Patients were included between August 2015 and August 2017.

## Study population

A total of 73 patients (56 women, 17 men; mean age of 58.0 (±14.9) years) diagnosed with MDD or bipolar disorder, current major depressive episode, according to the DSM-IV-TR and scheduled for ECT participated in the study. The presence of psychotic symptoms was confirmed by consensus between an experienced treating psychiatrist and the main investigator (LVD), and were based on the observations of the psychiatrist and psychiatric nurses, as well as on patient interviews and data from the family, referring GP or psychiatrist. The Mini-International Neuropsychiatric Interview 6.0 (MINI 6.0) was completed to support the diagnosis and to screen for psychiatric comorbidity (102). When the clinical diagnosis did not match the MINI-diagnosis, the clinical diagnosis was decisive for inclusion in the PD or non-PD group. To be eligible for participation, patients referred for ECT had to score at least 17 on the Hamilton Depression Rating Scale – 17 items (HDRS17) (103). Patients with a history of recent substance abuse (<6 months ago) or a primary psychotic or schizoaffective disorder were excluded.

This study is part of the so-called PROTECT cohort study, a research project on ECT-response predictors carried out in Duffel Psychiatric Hospital (Belgium) (123–125), which entails that there may be some overlap in our descriptions of the procedures with earlier studies of our group. Most of the participants were hospitalized (91%) at the time of the study. Indications for ECT were treatment resistance, the presence of severe melancholic or psychotic symptoms, and acute suicidality. The study was approved by the Ethics Committee of the University Hospital of Antwerp (project number 15/10/93). All participants provided their written informed consent.

## Treatment

### Pharmacological treatment

All participants continued their antidepressant and/or antipsychotic medication during the ECT course, with drugs and doses not being changed (where possible) for four weeks prior to and during the ECT course.

**Electroconvulsive therapy**

ECT was administered twice weekly using a brief-pulse (0.5ms) constant-current Thymatron IV system (Somatics LLC, Lake Bluff, IL, USA). The electrodes were placed unilaterally over the right hemisphere (RUL), bifrontal (BF) or bitemporal (BT) when a fast antidepressant effect was required or when patients did not respond to unilateral ECT (55). Before the first session, the stimulus dose was determined using the age method for RUL treatment and the half-age method for the bilateral interventions (57). Etomidate (0.15mg/kg) was the anesthetic routinely used, but propofol (1mg/kg) was deployed when etomidate was not (well) tolerated and ketamine (1-2mg/kg) was used when a clinical response was lacking after 12 consecutive sessions. Succinylcholine (Myoplegine®, 0.5mg/kg) was used as the muscle relaxant.

The treating clinician determined the endpoint of the ECT based on the patient's ratings of mood and ECT side effects. Mood was rated weekly throughout the ECT course using the Montgomery-Asberg Depression Rating Scale (MADRS) and ECT was continued until the patient was either in remission or showed no further improvement during the last three sessions.

## Assessment of mood, predictors, and outcome measures

Depression severity was assessed at baseline (before the start of ECT) and within one week after the last ECT session using the HDRS17 (103), the MADRS (105) and the PDAS. The PDAS was used to assess the severity of (psychotic) depression and, more particularly, to quantify the severity of psychotic symptoms. The PDAS consists of a depression subscale (HAM-D6) covering the items depressed mood, feelings of guilt, work and activities, psychomotor retardation, psychic anxiety, and general somatic symptoms, and a psychosis subscale (BPRS-5) covering the items emotional withdrawal, suspiciousness, hallucinatory behavior, unusual thought content, and blunted affect. The PDAS was found to be clinically valid, unidimensional, and responsive to change (81,82). Severity ranges are 8-15 for mild, 16-23 for moderate, and >23 for severe symptoms. A PDAS score <8 is taken to indicate remission (126).

The primary outcome measure for our study is remission in terms of a post-ECT score of ≤ 10 on the MADRS, while we defined response as a pre-post MADRS reduction of at least 50% (106,127).

The episode duration of depression was assessed in months. Patients were considered to be treatment resistant when they had had more than two failed antidepressant treatments (128). Age was registered as a continuous variable because of its potential influence on treatment outcome (120). Presence of psychomotor symptoms was assessed at baseline by means of the CORE assessment of psychomotor functioning (78) and the Montreal Cognitive Assessment (MOCA)(111,129) to be able to evaluate differences in cognitive functioning between patients with and without psychotic symptoms.

## Statistical analysis

Statistical analyses were performed with JMP 13.0. We used the last-observation-carried-forward method for one participant who refused testing after the last ECT session.

Comparisons between participants with and without psychotic symptoms were conducted on the intention-to-treat sample (ITT, *n*=73) using a one-way ANOVA for continuous variables and a Pearson Chi-square test for categorical variables.

All other analyses were done on the per-protocol sample (PP, *n*=65). To test the PDAS' sensitivity to change following ECT in the two populations, baseline and endpoint scores were compared with paired samples t-tests. Furthermore, the proportions of participants who responded and remitted according to their pre-post PDAS total scores were compared with a Pearson chi-square test.

To determine whether the PDAS total score and/or the dichotomous measure (presence/absence of psychotic symptoms) are reliable predictors of response and remission after ECT, logistic regression models were fitted. In a first set of models, we entered response as a binary outcome variable, where patients with a reduction of 50% or more on the MADRS were coded as positive responders and those not achieving these rates as negative responders. In a second set of models, we entered remission as the dependent variable, where individuals with a MADRS score ≤ 10 were coded as positive and those with higher scores as negative. In the univariable analysis, the independent variable was either the PDAS (continuous variable) or the presence/absence of psychotic symptoms (binary variable). In the multivariable analysis, age, episode duration, and treatment resistance were added as covariates (74,120). In order to obtain a model with contributing covariates only, the initial model was simplified by stepwise backward elimination.

To test whether patients with PD had responded faster to ECT than patients without psychotic symptoms, we compared the times to response of these two groups by means of a Cox proportional hazard model. As the two groups differed significantly in these two variables, age and baseline depression severity were entered as covariates. A hazard ratio with 95% confidence intervals was calculated.

# Results

## Characteristics of the two patient populations

After screening, 33 patients with PD and 40 patients with non-psychotic MDD who were prescribed ECT were found eligible to be included in the study. The baseline sociodemographic and clinical characteristics of the participants stratified by subtype are shown in Table 5-1.

*Table 5-1. Differences in the demographic and clinical variables of the participants with major depression with and without psychotic features as tested by ANOVA or chi-square analyses before the start of the ECT course*

| | Depression with psychotic symptoms | Depression without psychotic symptoms | F or $X^2$ | P |
|---|---|---|---|---|
| N | 33 | 40 | | |
| Age, mean (SD) | 64.61 (12.64) | 53.98 (15.44) | F= 10.06 | 0.0022 |
| Sex, female % (N) | 75.8 (25) | 77.5 (31) | $X^2$= 0.03 | 0.8608 |
| Bipolar % (N) | 12.1 (4) | 22.5 (9) | $X^2$= 1.33 | 0.2487 |
| CORE-defined melancholia, % (N) | 93.9 (31) | 37.5 (15) | $X^2$= 24.71 | <.0001 |
| Episode duration (months), mean (SD) | 12.06 (17.92) | 16.08 (18.21) | F= 0.83 | 0.3649 |
| Treatment resistant*, % (N) | 57.1 (16) | 73.5 (25) | $X^2$= 1.84 | 0.1913 |
| HDRS17, mean (SD) | 28.61 (5.17) | 21.60 (4.54) | F= 37.17 | <0.0001 |
| MADRS, mean (SD) | 37.06 (6.20) | 29.33 (6.46) | F= 26.89 | <0.0001 |
| PDAS, mean (SD) | 23.09 (4.83) | 14.68 (2.83) | F= 85.82 | <0.0001 |
| PDAS (depression subscale), mean (SD) | 16.70 (3.30) | 12.88 (2.08) | F= 36.25 | <0.0001 |
| PDAS (psychosis subscale), mean (SD) | 6.39 (2.36) | 1.80 (1.59) | F= 98.07 | <0.0001 |
| PDAS severity, % (N)<br>Mild<br>Moderate<br>Severe | <br>3.03 (1)<br>54.55 (18)<br>42.42 (14) | <br>65.00 (26)<br>35.00 (14)<br>0 (0) | $X^2$=37.32 | <0.0001 |
| MoCA, mean (SD) | 20.03 (6.08) | 23.78 (3.62) | F = 10.64 | 0.0017 |
| Number of ECT sessions, mean (SD) - range | 10.91 (5.23), 2-25 | 11.41 (5.74), 4-27 | F = 0.11 | 0.7467 |

*CORE, Scale assessing psychomotor functioning, patients with a score ≥ 8 were classified as melancholic; * Patients were considered to be treatment resistant when they had had >2 failed antidepressant treatments; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; PDAS = Psychotic Depression Assessment Scale; MoCA = Montreal Cognitive Assessment.*

The patients with PD were older than those without psychotic symptoms and almost all of them met the criteria for CORE-defined melancholic depression, while they were, on average, also more severely depressed according to all symptom scales. Cognitive functioning (as assessed with the MoCA or Montreal Cognitive Assessment (111,112)) was better in the patients without psychotic symptoms but this could be attributable to their younger age. Episode durations were shorter in the PD group but not significantly so.

Eight patients could not complete the ECT course because of ECT-induced side effects (N=5) or for reasons not related to the ECT (*n*=3). Accordingly, the intention-to-treat (ITT) sample comprised 73 patients and the per-protocol (PP) sample 65 (31 patients with PD, 34 without psychotic symptoms), of whom 74% showed a positive response and 62% had achieved remission according to the MADRS. Of patients with PD, 90% responded and 81% remitted. Response and remission rates were considerably lower in patients without psychotic symptoms compared to those with psychotic symptoms (59% and 44%, respectively).

## Prediction of response/remission based on psychotic symptoms

The univariable logistic regression analysis on the PP sample (*n*=65) showed that the presence of psychotic symptoms was significantly associated with treatment response (MADRS decrease of > 50%, *OR*=6.53 (*CI* 1.66-25.78), *p*<0.01, *AUC*=0.70) and remission (MADRS score ≤ 10, *OR*=5.28 (CI 1.72-16.16), *p*<0.01, AUC=0.69). Similarly, a lower PDAS total score was associated with nonresponse (*unit OR* = the odds ratio per unit change of the predictor = 0.87 (*CI* 0.77-0.98), *p*=0.01, AUC=0.71) and nonremission (*unit OR* = 0.89 (*CI* 0.80-0.98), *p*=0.01, *AUC*=0.68). This shows that higher baseline PDAS total scores as well as the confirmation of the presence of psychotic symptoms equally contribute to the prediction of response and remission.

The results of the multivariable regression analyses can be found in Table 5-2. Only covariates that actually contributed to the predictive model were retained in these final models.

*Table 5-2. Results of the logistic regression analyses with MADRS response and remission as the primary outcome variables and age, treatment resistance, and episode duration as covariates in the per-protocol sample (N=65).*

| Dichotomous model | | | | | | PDAS model | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR(95% CI)* | P-value | $\lambda^2$ | Prob> $\lambda^2$ | AUC | | OR(95% CI)* | P-value | $\lambda^2$ | Prob> $\lambda^2$ | AUC |
| Outcome = MADRS response | | | 22.26 | <.0001 | 0.83 | Outcome = MADRS response | | | 22.13 | <.0001 | 0.85 |
| Psychotic symptoms [NO] | 3.16 (0.70-14.35) | 0.1356 | | | | PDAS | 0.90 (0.78-1.04) | 0.1513 | | | |
| Age | 0.92 (0.87-0.97) | 0.0016 | | | | Age | 0.91 (0.87-0.96) | 0.0008 | | | |
| Outcome = MADRS remission | | | 27.13 | <.0001 | 0.86 | Outcome = MADRS remission | | | 25.09 | <.001 | 0.84 |
| Psychotic symptoms [NO] | 4.48 (1.09-18.49) | 0.0380 | | | | PDAS | 0.93 (0.80-1.03) | 0.1197 | | | |
| Age | 0.93 (0.89-0.98) | 0.0070 | | | | Age | 0.93 (0.88-0.97) | 0.0007 | | | |
| Treatment resistance [NO] | 0.15 (0.03-0.78) | 0.0242 | | | | Treatment resistance [NO] | 0.17 (0.04-0.84) | 0.0173 | | | |

*In the dichotomous model, the presence of psychotic symptoms was used as a dichotomous variable. In the PDAS model, the PDAS score was used to objectify the predictor psychotic symptoms. *Please note, this is the unit OR of nonresponder/nonremitter versus responder/remitter; PDAS = Psychotic Depression Assessment Scale.*

Compared to a response prediction model with 'age' only (*AUC*: 0.81), adding either the dichotomous or the continuous predictor 'psychotic symptoms' did not result in clinically meaningful improvement (*AUC*: 0.83 and 0.85, respectively). Addition of the two predictors to the remission analyses (*AUC* 'age' only: 0.74) seemed slightly more contributive (*AUC* of 0.86 and 0.84, respectively). Overall, we found no clear difference in adequacy between the various models. Episode duration was the only covariate that was not withheld in any of the prediction models. Higher age, the presence of psychotic symptoms, and the absence of treatment resistance all three coincided with a beneficial effect of ECT.

## PDAS responsiveness

We used the PP data to analyze the responsiveness of the PDAS. As can be seen in Table 5-3, the PDAS total scores as well as its two subscale scores decreased significantly during ECT in all patients and in both subgroups (with and without psychotic symptoms).

*Table 5-3. Results of the paired samples t-tests of the differences in the PDAS total and subscale scores before and after ECT for the whole per-protocol sample and those with and without psychotic features.*

| | Baseline score | Endpoint score | t | P |
|---|---|---|---|---|
| Per-protocol sample (N=65) | | | | |
| Total PDAS (mean ± SD) | 18.80 (5.86) | 5.66 (3.85) | 16.52 | <.0001 |
| PDAS Depression subscale (mean ± SD) | 14.75 (3.38) | 4.62 (2.86) | 18.74 | <.0001 |
| PDAS Psychosis subscale (mean ± SD) | 4.05 (3.12) | 1.05 (1.34) | 8.55 | <.0001 |
| Depression with psychotic symptoms (N=31) | | | | |
| Total PDAS (mean ± SD) | 23.29 (4.92) | 5.65 (3.89) | 17.49 | <0.0001 |
| PDAS Depression subscale (mean ± SD) | 16.74 (3.40) | 4.35 (2.60) | 17.04 | <0.0001 |
| PDAS Psychosis subscale (mean ± SD) | 6.55 (2.34) | 1.29 (1.60) | 12.45 | <0.0001 |
| Depression without psychotic symptoms (N=34) | | | | |
| Total PDAS (mean ± SD) | 14.71 (2.91) | 5.68 (3.87) | 13.79 | <.0001 |
| PDAS Depression subscale (mean ± SD) | 12.94 (2.13) | 4.85 (3.09) | 13.12 | <.0001 |
| PDAS Psychosis subscale (mean ± SD) | 1.76 (1.63) | 0.82 (1.03) | 4.76 | <.0001 |

*PDAS = Psychotic Depression Assessment Scale*

The PDAS scores indicated more severe symptoms at baseline than after the ECT course; this pre-post difference (-13.1, 95% *CI* [-14.7, -11.6]) was significant ($t(64)$= -16.5, $p$<.0001) and represented a large effect: $r$=0.90.

At the endpoint of the study, 81.5% ($n$=53) of the PP sample had responded to ECT and 63.9% ($n$=46) was in remission according to the PDAS.

## Speed of response to ECT

For our Cox proportional hazard model testing the time to response (MADRS decrease >50%) in the patients with PD and those without psychotic symptoms we only entered the data recorded for the first eight weeks of treatment (Figure 5-1) in the PP sample.

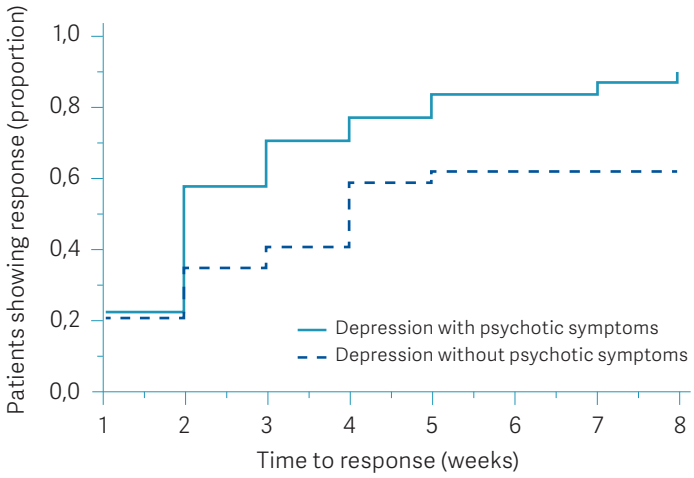


*Figure 5-1. Time-to-event analysis of the times to response (>50% MADRS reduction) for the per-protocol patients with (n=31) and without (n=34) psychotic symptoms. MADRS = Montgomery-Asberg Depression Rating Scale.*

The dependent variable thus was response within 8 weeks of treatment. As the two patient groups differed significantly in age and baseline depression severity, we accounted for these two covariates in the model. With a hazard ratio of 1.3 (95% *CI* 0.6-2.7, NS) in favour of those with psychotic symptoms, the model did not indicate a significant difference in the times to response between the two groups after controlling for age and baseline depression severity. The unadjusted hazard ratio was 1.9 (95% *CI* 1.1-3.4, $p$=0.029) for psychotic symptoms *v.* no psychotic symptoms.

# Discussion

The results of our study on the effectiveness of ECT in patients with a major depression with and without psychotic features show that, although the PDAS indeed is a sensitive measure of ECT outcome with higher scores predicting better response, the mere ascertainment of the presence of psychotic symptoms predicted ECT response and remission equally well. Age was an essential contributor in the prediction models tested, with older

patients being most likely to respond better and achieve remission. We found a significant difference in the speed of response in favor of patients with concomitant psychotic symptoms, that however lost its significance after correction for age and depression severity.

Unlike we hypothesized, we found no advantage of the PDAS over the dichotomous predictor 'presence/absence of psychotic symptoms'. This could be explained by a ceiling effect. Given that ECT was extremely effective in patients with PD (90% responders; 81% remitters), it is unlikely that the PDAS could do even better. One could also argue that the PDAS total score does not only reflect the severity of psychotic symptoms as it also quantifies depressive symptoms. Still, the depression subscale does include items on guilt, anxiety, and hopelessness, for instance, which are not seldom related to the content of patients' delusions; these seemed to be clinically relevant indicators, justifying the use of the scale's total score in our analyses. Although theoretically the PDAS makes a clear distinction between symptoms of depression and psychosis, in practice this distinction appears less apparent.

As psychotic symptoms are not always recognized by the clinician (130), we opted for classifying patients based on the clinical judgment of a clinician and a researcher that was not only based on their own observation but also on observations of nurses during hospitalisation and briefing from the family or referring doctor. The use of a systematic interview that evaluates the presence of psychotic symptoms, such as the Delusion Assessment Scale (131) could be valuable for future research to increase the reliability of correctly classifying patients as psychotically depressed.

The predictive effect of psychotic symptoms was also clouded by the covariates tested. As patients suffering from depression with psychotic features tend to be older and more severely depressed than patients without psychotic symptoms, both factors known to predict better ECT response, it is difficult to tell which of the variables is the better predictor. In our meta-analysis of ECT-response predictors, age was found to be a significant covariate in analyses including 'psychotic symptoms' as the independent variable, with higher odds ratios for PD versus patients without psychotic symptoms in cohorts with an older average age (120). In more recent studies, the predictive effect of age even seemed to be mediated by, amongst others, the presence of psychotic symptoms (132,133), suggesting that depression characteristics rather than age itself is associated with ECT outcome. Unfortunately, we were unable to create age categories to further explore this interrelation in the present study because of the limited sample sizes. Studies with larger cohorts did identify psychotic symptoms as an independent predictor, even after controlling for age and depression severity (75,80).

It is remarkable that episode duration played no significant role in the prediction models considering that this factor was one of the strongest predictors when used as a categorical variable in another recent ECT-predictor study of ours (123). Here, we found the prediction models we created with elements of the Maudsley Staging Method as a measure of treatment resistance to be adequate but less successful (AUC of 0.77 for response prediction) than the best prediction model in our current investigations using age, presence of psy-

chotic symptoms and treatment resistance (AUC=0.86 for remission prediction) as predictors of ECT outcome. Studies attempting to predict ECT response based on structural (70) or functional MRI data (71) seem to outperform prediction models based on clinical features. A prediction model based on results of structural imaging had a 100% sensitivity rate, with 78.3% specificity (70). The subgenual cingulate gyrus volume was most contributive in this small sample (n=23). With fMRI, a resting state network centered in the dorsomedial prefrontal cortex was identified that predicted treatment outcome with 84% sensitivity and 85% specificity (n=45) (71). New research that would focus on a combination of clinical and biological predictors may then be valuable. Besides pertinent baseline variables, the quality of the induced convulsions (based on wave amplitude and hemispheric brain wave synchronicity, amongst others) should be considered as clinically adequate seizures appear to coincide with better ECT outcomes (60).

To our knowledge, we are the first to have used the PDAS in a depressed population receiving ECT, with results showing that its total score is responsive to change. Earlier, the PDAS was found to be a sensitive measure of drug treatment response in psychotic depression (82) as well as a clinically valid, scalable, and responsive index of PD severity in older adults (134). In our ECT study the significant differences between baseline and endpoint PDAS total scores adequately reflected response in the whole sample and the two subgroups, showing 63.9% of the PP sample to be in remission, as was confirmed by the MADRS post-ECT scores. This remission rate is comparable to the rates reported in other studies (80,135).

Patients with PD responded to ECT faster than patients without psychotic symptoms (HR=1.9). The finding that, after adjusting for covariates such as age and baseline depression severity, patients with PD responded equally fast to ECT as those without psychotic symptoms is in contrast to the findings of several other studies (80,122). Potential explanations are a lack of power as a consequence of the limited sample sizes of our two subgroups or a clouding of the actual difference by adjusting for these covariates. One could also criticize selection of these covariates. Although age differed significantly between the two subgroups, the value of age as a predictor became subject of debate recently (132) and others factors such as bipolar status could be a valuable alternative. Although there is no clear difference in ECT outcome between patients with uni- and bipolar depression (74), several studies found a faster clinical improvement for patients with bipolar depression (136,137). Although others found no advantage, the role of polarity for speed of response to ECT could be worth further exploring in future studies (138).

## Strengths and limitations

This is the first study to measure depression severity with the PDAS before and after ECT and to explore the scale's predictive capacity and performance. The strongest prediction model we found (incorporating presence of psychotic symptoms as predictor, age and treatment resistance as covariates) has a sensitivity of 94.9% and specificity of 55.7%,

which is rather good for a prediction model exclusively based on clinical characteristics. However, because our samples were relatively small and there were significant differences between the patients with PD and those without psychotic symptoms (in age, presence of CORE-defined melancholia, depression severity and cognitive functioning) with a probable influence on their ECT outcomes, our results should be interpreted with caution. Replication of our findings in larger samples of comparably aged patients with psychotic and non-psychotic depression would be of great value.

An important limitation of this study is the beforementioned ceiling effect of the PDAS. As there were only a few patients with PD not responding (n=3) or remitting (n=6), it was very difficult for the PDAS to outperform the dichotomized predictor. The fact that practically all testing in this study was done by the same investigator (LVD) precludes inter-rater variability but can be considered a limitation in that it may have led to confirmation bias. Independent rating of the different scales would have been preferable but was not feasible within our wider research program.

## Clinical implications

ECT should be considered in depressed patients with psychotic symptoms and/or high PDAS scores. The PDAS is responsive to ECT-induced change and, also given its brevity (11 items), may be conveniently used to monitor treatment response in patients with psychotic depression undergoing ECT especially since general depression scales such as the HDRS of MADRS only capture a fraction of the psychotic symptoms in this population (82).

6

# ECT: THE ROLE OF PSYCHOMOTOR FUNCTIONING


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## 6.1. Distinguishing subgroups

Published as: Van Diermen L, Schrijvers D, Cools O, Birkenhäger TK, Fransen E, Sabbe BGC. Distinguishing subgroups based on psychomotor functioning among patients with major depressive disorder. Neuropsychobiology. 2018;76(4):199–208.

Original Paper

Neuropsychobiology

Neuropsychobiology
DOI: 10.1159/000490072

Received: March 19, 2018
Accepted after revision: May 15, 2018
Published online: July 4, 2018

# Distinguishing Subgroups Based on Psychomotor Functioning among Patients with Major Depressive Disorder

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**Keywords**
Psychomotor functioning · Major depressive disorder · Retardation · Agitation

**Abstract**
***Background:*** Retardation and agitation are symptoms of major depressive disorder (MDD), and their presence could play a role in determining clinically meaningful depressive subtypes such as nonmelancholic depression (NMD) and melancholic depression (MD). In this project, we explored whether three depression subgroups (NMD, MD with psychotic symptoms, and MD without psychotic symptoms) could be distinguished based on objective measures of psychomotor functioning. ***Methods:*** Sixty-nine patients with MDD underwent extensive clinical and psychomotor testing prior to treatment with electroconvulsive therapy. Psychomotor functioning was assessed subjectively using the Core Assessment of Psychomotor Change (CORE) and objectively by means of both 24-h actigraphy and performance on a fine motor drawing task. ***Results:*** The daytime activity levels measured by actigraphy were significantly lower ($F$ = 7.1, $p$ = 0.0004) in MD patients both with and without psychotic symptoms than in those with NMD. No objective psychomotor variable was able to distinguish between melancholic patients with and those without psychotic symptoms. ***Conclusions:*** The depression subtypes NMD, MD with psychotic symptoms, and MD without psychotic symptoms are not marked by increasing psychomotor retardation, possibly because psychomotor disturbance in MD with psychotic symptoms often consists of agitation rather than retardation, or a mixture of the two. However, psychomotor functioning as measured by actigraphy can be used to distinguish between NMD patients and MD patients. 

### Introduction

Psychomotor retardation and agitation are core symptoms of major depressive disorder (MDD) [1]. Parker describes a hierarchical model for distinguishing depression subtypes by the presence of three specific features [2]. A depressed mood is presumed to be present across all three



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subtypes and can therefore not provide any distinction. The distinction between nonmelancholic depression (NMD) and melancholic depression (MD) is marked by the presence of psychomotor disturbance (PMD) in melancholia [2–4]. PMD appears to be more prominent in the depressive subtype with psychotic symptoms than in patients who do not have psychotic symptoms [3, 5]. This last class is, however, distinguished by the presence of psychotic symptoms. To summarize, PMD and psychotic symptoms construct the hierarchical model, and members of the residual NMD class lack both features [6]. Underlying this, each subtype is assumed to be characterized by disruptions in the three relevant neurotransmitter systems (serotonin, noradrenaline, and dopamine), but their relative contributions vary. NMD seems to be largely serotonergically driven, whereas the melancholic and psychotic subtypes of depression additionally have contributions from the noradrenergic and dopaminergic systems, respectively [6].

Depression with psychotic features is known as a rather prevalent condition, with approximately 35% of severely depressed inpatients meeting the diagnostic criteria [7]. The lifetime prevalence varies between 0.35 and 1%, with higher rates in older age [8]. The hierarchical model we use to distinguish depression subtypes implies that patients with psychotic symptoms also have psychomotor symptoms or melancholia [6]. Although most of the depressed patients with psychotic features indeed belong to the melancholic subtype, a small group of depressed patients with psychotic symptoms does not present with melancholic features. Although the prevalence of psychosis is higher among melancholic patients (51.1%) than among nonmelancholic patients (17.7%), psychotic nonmelancholics definitely exist [9].

Despite being core symptoms of MDD, psychomotor symptoms are difficult to measure and their clinical observation is rater dependent and therefore subjective. Moreover, an exact definition of psychomotor functioning is lacking, given the complex involvement of numerous cognitive and psychomotor processes [10, 11]. This could explain why, to date, no studies have focused on the direct comparison of psychomotor functioning between the three subtypes mentioned above. The Core Assessment of Psychomotor Change (CORE) is a rating scale developed to assess psychomotor symptoms in a uniform and standardized way in patients with MDD. This scale provides a global impression of psychomotor functioning (in three different domains – retardation, agitation, and noninteractiveness) and was designed to distinguish between NMD and MD [3, 12]. However, the CORE instrument provides rather a rough estimate of psychomotor functioning and relies on the subjective judgment of the investigator.

Several other methods have been developed with the aim of ensuring more objective measurements of psychomotor functioning [10] able to detect abnormalities that escape the clinical eye. Such objective measurements could improve classification into depressive subtypes, assist in monitoring the evolution of a depressive episode, and play a role in treatment selection [13]. Many of the objective measurement methods that have been developed focus on the domains of gross and fine motor activity [10]. Gross motor activity refers to movement of the entire body that enables general movement and balance. Fine motor skills, on the other hand, are involved in fine movements such as writing and drawing. Previous research has applied drawing tasks in depressed subjects to reveal substantial fine motor retardation in patients with MDD [14–18]. Several studies have measured gross motor activity in psychiatric disorders by means of wrist actimetry [19, 20] and found lower gross psychomotor activity in depressed patients than in healthy controls [21–24]. Melancholic patients have also been found to be less active during wakefulness than nonmelancholic patients [21, 24].

Besides the various processes that are involved in psychomotor functioning, several other factors must be taken into account when studying psychomotor functioning in depressive subtypes. First of all, some authors claim that differences in PMD can be attributed to variations in symptom severity, rather than being distinguishing features of depression subtypes in themselves [25, 26]. Others do not agree, however [27, 28]. The second factor is age. Cognitive and psychomotor retardation often occur in the process of normal aging [13, 29], and it has been suggested that aging and depression have an additive effect on psychomotor performance [16]. Age should therefore be taken into account in the analysis of a depressed sample of subjects of different ages. The final factor that is believed to have an influence on psychomotor performance in depressed populations is pharmacotherapy. Psychotropic drugs can contribute to improvements in psychomotor and cognitive performance in the long term, mostly due to clinical recovery. On the other hand, certain drugs such as benzodiazepines have been found to impair psychomotor performance [10, 13].

Although motor retardation is considered to be one of the key elements of the melancholic subtype of depression [30], it remains unclear whether differences in objective psychomotor performance can indeed distinguish

between NMD and MD or distinguish MD patients with psychotic symptoms from those with no psychotic symptoms [10] irrespective of a clinician-rated instrument. The goal of this project was to evaluate the different domains of psychomotor performance in these three depression subgroups in order to assess whether it is one of these specific domains that can be held responsible for the division into diagnostic subgroups. We expected to find a difference in objective psychomotor functioning between the three subtypes, hypothesizing that, as we compared NMD patients to MD patients without psychotic symptoms and then to MD patients with psychotic symptoms, the daytime gross motor activity level would decrease and the time needed to complete fine motor tasks would increase. Additionally, differences in diurnal variation of activity levels between the subgroups will be assessed, with the expectation that the biggest differences in activity levels will be found between MD and NMD patients in the morning hours [31].

## Subjects and Methods

*Study Population*

We included 69 patients (52 women, 17 men; mean age of 57.9 [±15.1] years) with MDD or depressive episodes in bipolar disorder according to the DSM-IV-TR. The diagnosis was required to have been confirmed using the MINI diagnostic interview version 6.0 [32], and the patients had to have scored ≥17 on the Hamilton Depression Rating Scale – 17 items (HDRS17) at the time of inclusion. Patients with a history of substance abuse (<6 months ago) or primary psychotic or schizoaffective disorders were excluded.

The study was part of a project designed to investigate electroconvulsive therapy (ECT) response predictors that was being carried out at the University Psychiatric Hospital in Duffel (Belgium). The large majority of patients were severely depressed, awaiting treatment with ECT. Most of them had been hospitalized (91%).

In addition, a local database of healthy controls was used to create an age-matched healthy control group (36 women, 15 men; mean age of 55.2 [±15.9] years), collected during previous similar psychomotor studies by our group, applying exactly the same fine psychomotor measurement methods [18, 33, 34].

*Treatment*

During the study, most patients were being treated with antidepressants that were adequately dosed. Of the 69 patients, 52% were on tricyclic antidepressant monotherapy, 17% were undergoing selective serotonin reuptake inhibitor monotherapy, and 6% were being treated with other antidepressants. Five patients were not treated with antidepressants and 12 used a combination of antidepressants. Before the start of treatment with ECT, the current depressive episode was treated with 1 or 2 adequately dosed antidepressants in 29% of the patients, with 3 or 4 in 43% of the patients, with 5 or 6 in 20% of the patients, and with 7–10 antidepressants in 8% of the patients. Antipsychotics were being administered to 81% of the patients, and 28% of the patients were receiving mood stabilizers (mainly lithium) as an add-on therapy. In addition, 71% of the patients were being treated with benzodiazepines (at a dose of 8.5 mg diazepam equivalent on average). Treatment resistance among the patients was assessed using the Maudsley Staging Method [35]: 6% had mild treatment resistance, 80% had moderate resistance, and 14% were severely treatment-resistant. A history of other treatment methods for the current episode (besides ECT; $n = 2$) was not systematically assessed. Hospitalized patients were subjected to therapy programs on the wards.

*Clinical Assessment*

Mood

Depression severity was assessed with the HDRS17 [36]. Given the high prevalence of psychotic symptoms in this sample of depressive subjects awaiting treatment with ECT and the cooccurrence of psychotic symptoms with psychomotor symptoms in depression [2], we used the Psychotic Depression Assessment Scale (PDAS) to quantify the severity of the patients' psychotic symptoms. The PDAS is a rating scale which covers both the psychotic and depressive domains of depression with psychotic symptoms and is a sensitive measure of treatment response in this type of depression [37, 38].

Psychomotor Functioning

Psychomotor functioning was assessed as part of a larger test battery with assessment of mood and cognitive functioning. The patients had therefore been observed for about 1 h before psychomotor functioning was assessed by the main researcher, a Doctor of Medicine trained in psychiatry. For patients on two of the participating wards (approx. 10% of the measurements), psychomotor functioning was assessed by the psychomotor therapists of these wards that were trained to rate the CORE. All assessments were conducted in the week prior to ECT. Gross motor functioning was assessed within 2–3 days of the CORE ratings and fine motor measures.

*Clinician Rating.* The CORE is used to measure observable psychomotor functioning, the cardinal feature of melancholia [12]. It was developed as a diagnostic tool with the aim of classifying melancholic and nonmelancholic subtypes of depression [3, 4]. During assessment, 18 observable clinical features related to psychomotor functioning are scored on a 4-point scale based on severity, ranging from 0 (absence of the symptom) to 3 (severe). The CORE generates scores in three psychomotor categories: retardation, agitation, and noninteractiveness. A cutoff of 8 is used to define MD. The validity of the Dutch version of the CORE as a measure of PMD has been confirmed [39].

*Gross Motor Performance.* Gross motor performance was measured by means of the MotionWatch 8 (CamNtech Inc, Cambridge, UK), which registers the movement of the limb to which it is attached and can be used to quantify the intensity and duration of physical activity. Earlier studies support the use of accelerometry tools as an objective measure of gross psychomotor functioning [40]. During our study, the MotionWatch was worn around the wrist of the patient's nondominant arm for 24 consecutive hours [41]. Activity counts were stored in 2-s intervals. Analyses were performed using the most recent version of the MotionWare software. Approximate wake-up and bed times were set so that the software could calculate daytime and nighttime activity levels (DAL and NAL).

*Fine Motor Performance*. We used a digital drawing task to measure fine motor performance. In this line copying task (LCT), the patients were asked to copy straight lines that had one of four possible orientations (vertical, horizontal, or oblique in both directions). For a full description of the setup used for this task, we refer to previous papers by our group [16, 18]. The use of a graphic tablet (Wacom Intuos Pro) and a pressure-sensitive pen connected to a laptop allowed us to calculate variables such as initiation time and movement time (IT and MT). The IT mainly reflects the cognitive component of the performance and is defined as the time between the presentation of the stimulus and the beginning of the first drawing movement. The MT reflects the motor component and is defined as the time between the beginning of the first drawing movement and the end of the last drawing movement. Motor retardation affects both cognitive and motor processes, as reflected in increases in both IT and MT [13]. Not all patients were able to execute the drawing tasks, as some were too agitated or too severely depressed to be able to follow the instructions adequately ($n = 14$). Two patients had no baseline measurement of fine motor functioning because of planning issues, and 3 measurements could not be used because of technical problems at the time of testing.

*Definition of Subgroups*

The patients were divided into NMD and MD subgroups based on their CORE scores, as this instrument was designed to make this distinction [5, 12, 42]. Several other studies have compared nonmelancholic with melancholic patients based on this cutoff [4, 9, 43, 44]. Patients who scored <8 points formed the NMD group, while those who scored ≥8 were classified as MD patients. The latter group was then divided into patients with and those without psychotic symptoms based on the presence of delusions and hallucinations.

*Statistical Analysis*

In order to compare psychomotor functioning between the three subgroups of depression, we conducted one-way analysis of covariance (ANCOVA) using JMP 13, taking age into account as a covariate. The outcome variables were log transformed to obtain normality in residuals and homoscedasticity. As there were four main outcome variables (DAL, NAL, LCT IT, and LCT MT), we considered the ANCOVA to be significant at a Bonferroni-corrected $p$ value of 0.0125. If a significant difference between groups was found, Tukey's HSD multiple comparisons were performed to identify which groups differed from one another. As the effect size, partial $\eta^2$ or the proportion of variance explained by the subgroups that could not be explained by age was calculated for the objective motor measures. Based on the results of the above analyses, a ROC analysis was conducted to determine the sensitivity and specificity of daytime activity levels in separating MD from NMD.

Partial Pearson correlations were also conducted on the log-transformed data in SPSS 23.0, controlling for age, in order to explore correlations between psychomotor functioning and symptom severity. The symptom severity scores were diminished with the psychomotor item scores (rendering an HDRS15 score and a PDAS10 score, excluding retardation and agitation from the HDRS and retardation alone from the PDAS).

In the drawing tasks, only extreme outliers (lines drawn much more slowly or quickly than other lines drawn by the same patient) were removed from the data before calculation of the average IT and MT for each patient. The interquantile range was multiplied by 3, and values further beyond the 10 and 90% quantiles than 3 times the interquantile range were removed.

**Table 1.** Demographic and clinical characteristics of the patient sample ($n = 69$) and healthy controls ($n = 51$)

| | Patients with MDD ($n = 69$) | Controls ($n = 51$) |
|---|---|---|
| Age, years | 57.9±15.1 | 55.2±15.9 |
| Female, % ($n$) | 75.4 (52) | 70.6 (36) |
| Episode duration, months | 14.9±18.4 | |
| Psychotic symptoms, % ($n$) | 45.0 (31) | |
| Melancholic symptoms, % ($n$) | 62.3 (43) | |
| Bipolar, % ($n$) | 18.8 (13) | |
| HDRS17 score | 24.2±6.0 | |
| PDAS score | 18.3±5.7 | |
| Depressive symptoms | 14.5±3.3 | |
| Psychotic symptoms | 3.8±3.0 | |
| CORE score | 10.3±7.9 | |
| Retardation | 5.3±4.2 | |
| Agitation | 2.3±2.7 | |
| Noninteractiveness | 2.7±3.4 | |
| MotionWatch ($n = 67$) | | |
| DAL, counts per 2 s | 4.0±2.4 | |
| DAL, counts per hour | 7,250±4,325 | |
| NAL, counts per 2 s | 0.4±0.6 | |
| Drawing task ($n = 50$) | | |
| LCT IT, s | 1.1±0.5 | 0.9±0.2*** |
| LCT MT, s | 0.6±0.4 | 0.4±0.2*** |

Values are presented as means ± SD unless specified otherwise. The age-matched controls significantly differed from the patients according to the $t$ test (*** $p < 0.001$). MDD, major depressive disorder; DAL, daytime activity level; NAL, nighttime activity level; LCT, line copying task; IT, initiation time; MT, movement time.

## Results

The demographic and clinical characteristics of the entire sample are shown in Table 1. Patients were significantly slower than controls in IT and MT on the task of fine motor performance, the LCT ($p < 0.001$). As we did not have a control sample of patients that wore a MotionWatch for 24 h, we compared the activity levels found in our study to activity levels found in other studies. The average daytime activity level measured by the MotionWatch was 7,280 (±4,300) counts per hour in our sample. This is a low activity level compared with other studies that assessed psychomotor functioning in a somewhat

**Table 2.** Clinical and psychomotor functioning in the three depression subgroups: results of the ANCOVA analyses of log-transformed outcome variables accounting for age

| | NMD | MD no psy | MD psy | Age-controlled | | | |
|---|---|---|---|---|---|---|---|
| | | | | *F* | *p* value | Tukey's HSD | Partial $\eta^2$ |
| Age, years | 50.0±14.4 | 58.4±16.0 | 64.3±12.9 | | | | |
| HDRS17 score | 19.3±2.8 | 24.5±4.7 | 29.0±4.6 | 26.5 | <0.0001 | MD psy > MD no psy > ND | |
| PDAS total score | 13.6±2.4 | 16.2±2.9 | 23.1±4.9 | 30.4 | <0.0001 | MD psy > MD no psy > ND | |
| CORE total score | 3.4±1.9 | 11.9±4.9 | 15.8±7.9 | 45.5 | <0.0001 | MD psy and MD no psy > ND | |
| CORE NI score | 0.4±0.6 | 2.8±2.7 | 4.7±4.0 | 17.8 | <0.0001 | MD psy and MD no psy > ND | |
| CORE AG score | 1.0±1.2 | 2.3±1.8 | 3.6±3.5 | 7.3 | 0.0003 | MD psy > ND | |
| CORE RET score | 2.0±1.7 | 6.8±3.4 | 7.5±4.4 | 17.1 | <0.0001 | MD psy and MD no psy > ND | |
| MW DAL, counts/2 s | 5.6±2.5 | 2.8±1.0 | 3.3±2.2 | 7.7 | 0.0002 | ND > MD no psy and MD psy | 0.1813 |
| MW NAL, counts/2 s | 0.3±0.2 | 0.3±0.3 | 0.4±0.8 | 0.1 | 0.9324 | | 0.0047 |
| LCT IT, s | 0.9±0.2 | 1.4±0.7 | 1.2±0.4 | 8.6 | <0.0001 | | 0.0928 |
| LCT MT, s | 0.4±0.3 | 0.7±0.4 | 0.8±0.6 | 6.6 | 0.0009 | | 0.0862 |

Values are presented as means ± SD. NMD, nonmelancholic depression; MD no psy, melancholic depression without psychotic symptoms; MD psy, melancholic depression with psychotic symptoms; NI, noninteractiveness subscale; AG, agitation subscale; RET, retardation subscale; MW, MotionWatch; DAL, daytime activity level; NAL, nighttime activity level; LCT, line copying task; IT, initiation time; MT, motion time.

younger population (45.0 years) with depressive symptoms (12,417 ± 6,285 counts per hour). Compared to the controls (41.0 years), the difference is even larger, with a daytime activity level of 19,599 (±7,050) counts per hour [45]. The depressed adults in another ECT population had an average activity level of 10,140 counts per hour, but they were somewhat younger than the patients in our sample (47.9 years) [46]. These results indicate a substantial reduction in gross motor activity in our sample.

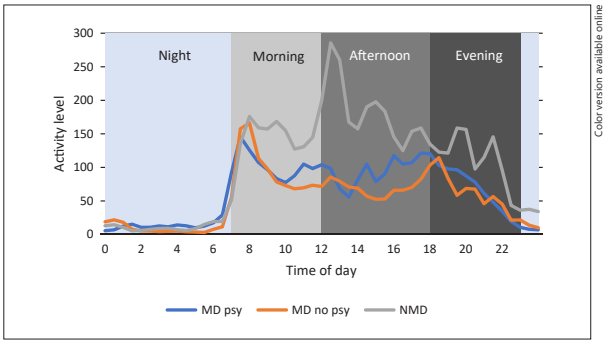
*Distinguishing Subgroups Based on Psychomotor Functioning*

In the final analyses, we distinguished between the subgroups NMD, MD with no psychotic symptoms, and MD with psychotic symptoms, as described in the Subjects and Methods section. When we divided the patients into these subgroups, we found that 2 patients did not fit the model: psychotic symptoms were present, but there were no melancholic symptoms. We identified 24 NMD patients, 14 MD patients with no psychotic symptoms, and 29 MD patients with psychotic symptoms. The hierarchical model for distinguishing subtypes of depression [2] was tested by comparing psychomotor functioning between these three subgroups (Table 2).

On average, the patients with MD and psychotic symptoms were older than the group of patients with NMD. The mean depression severity score as measured by the HDRS17 was lowest among NMD patients and highest among MD patients with psychotic symptoms. Because the CORE was used to distinguish between melancholic and nonmelancholic patients, the difference in CORE scores between these groups is logical. The average CORE score of the MD patients with psychotic symptoms was not significantly higher than the average score of the MD patients with no psychotic symptoms after correction for multiple comparisons.

The objective measures of psychomotor functioning revealed significantly lower daytime activity levels, as measured by the MotionWatch, in the MD groups (Table 2). Daytime activity was lowest in the MD group without psychotic symptoms. Daytime activity levels can play a role in distinguishing MD from NMD with an AUC of 0.82 in ROC analysis. According to our analyses, a daytime activity level of 3.35 counts per 2 s was the best cutoff point, with a sensitivity of 72% and specificity of 91%. With this cutoff, there were 2 false positives (classified melancholic, while they were not) and 12 false negatives (melancholic according to the CORE, but not according to activity levels). It is possible that these false negatives were mainly patients with agitation that were also classified as melancholic according to the CORE.

Patients with MD performed the copying tasks more slowly than those with NMD. However, this difference was not significant after correction for age and multiple comparisons. The raw data show that the patients with MD but no psychotic symptoms performed the cognitive




Color version available online

**Fig. 1.** Activity scores (number of movements per minute) by time of day. NMD, nonmelancholic depression; MD no psy, melancholic depression without psychotic symptoms; MD psy, melancholic depression with psychotic symptoms.

component of the LCT most slowly, while those with MD and psychotic symptoms performed the motor component of the task most slowly.

*Differences in Diurnal Variation between the Subgroups*

Besides comparing overall daytime activity levels as measured by the MotionWatch, we also examined activity levels by time of day to explore differences in diurnal variation between the subgroups (Fig. 1).

All three groups exhibited a peak in activity levels at wake-up time. The activity levels of the NMD group subsequently remained high, while the MD groups' daytime activity levels appeared lower. The difference between the MD group with and that without psychotic symptoms was unclear. We divided daytime activity levels into three periods: morning (from 7 a.m. to 12 noon), afternoon (from 12 noon to 6 p.m.), and evening (from 6 p.m. to 11 p.m.) (Table 3).

Activity levels in the afternoon and evening were significantly higher in the NMD group than in the two MD groups. The differences between the three subgroups were not found to be significant in the morning.

*Associations with Clinical Symptoms and the Effect of Psychotropic Drugs*

Severity of depression, as measured by the HDRS15, was found to correlate with CORE total and subscores (Table 4), as were PDAS10 scores. The two symptom scales did not correlate with activity levels measured by the MotionWatch, nor with measures of fine motor performance.

When we examined the effect of psychotropic drugs, no significant difference in objective measures of PMD was found between patients who were taking benzodiazepines and those who were not. There was also no significant difference between patients that used no antidepressants, those on monotherapy, and those on a combination of antidepressants ($p > 0.05$).

## Discussion

The current study was designed to determine whether three depression subgroups (NMD, MD with no psychotic symptoms, and MD with psychotic symptoms) could be distinguished based on objective measures of psychomotor functioning. The major strength of this study is its application of a combination of objective psychomotor measurement methods in a large sample of severely depressed patients. Measuring gross motor activity with actigraphy enabled us to distinguish between MD and NMD patients. This difference in activity level was most obvious in the afternoon and evening. After measuring fine motor activity using an LCT, we found no clear difference between the three subgroups. The fact that there was no clear correlation between objective PMD and depressive symptom severity indicates that it is the depression subtype rather than the severity of the depression that determines the level of psychomotor dysfunction. These findings are in line with the results of Razavi et al. [47]. Overall, however, no objective psychomotor measure was able to distinguish between all three subgroups clearly.

**Table 3.** Daytime activity scores by part of day: results of the ANCOVA analyses of log-transformed outcome variables accounting for age

| | NMD | MD no psy | MD psy | Age-corrected | | | |
|---|---|---|---|---|---|---|---|
| | | | | *F* | *p* value | Tukey HSD | Partial $\eta^2$ |
| MW morning | 5.0±2.4 | 3.3±1.4 | 3.3±1.9 | 3.5 | 0.0211 | | 0.0816 |
| MW afternoon | 6.2±3.6 | 1.3±0.7 | 3.0±2.4 | 11.1 | <0.0001 | NMD > MD no psy and MD psy | 0.2604 |
| MW evening | 3.9±1.6 | 2.1±1.4 | 2.2±1.6 | 8.9 | <0.0001 | NMD > MD no psy and MD psy | 0.1733 |

MW scores are given in counts per 2 s (mean ± SD). NMD, nonmelancholic depression; MD no psy, melancholic depression without psychotic symptoms; MD psy, melancholic depression with psychotic symptoms; MW, MotionWatch.

**Table 4.** Age-corrected partial Pearson correlations between psychomotor and clinical symptoms on log-transformed outcome variables

| | HDRS15 | PDAS10 |
|---|---|---|
| CORE_TOT | 0.505*** | 0.614*** |
| CORE_NI | 0.372** | 0.527*** |
| CORE_AG | 0.473*** | 0.377** |
| CORE_RET | 0.288* | 0.427*** |
| MW DAL | –0.087 | –0.210 |
| LCT IT | –0.184 | –0.227 |
| LCT MT | –0.108 | 0.014 |

HDRS15 = HDRS 17 excluding items 8 (retardation) and 9 (agitation). PDAS10 = PDAS excluding item 6 (retardation). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. NI, noninteractiveness subscale; AG, agitation subscale; RET, retardation subscale; MW, MotionWatch; DAL, daytime activity level; LCT, line copying task; IT, initiation time; MT, motion time.

The MotionWatch's ability to distinguish the NMD group from the two MD groups is consistent with findings from two smaller studies [21, 24]. A similar study also found lower activity levels [48] in a unipolar depressed group with motor retardation than in a group with no retardation. When we examined daytime activity levels per part of the day, we found that the morning activity levels were not significantly different between the three subgroups. However, a comparison of both groups of MD patients with the NMD group revealed a significant difference in morning activity levels, with MD patients exhibiting less activity than NMD patients. This is to be expected, as patients with melancholic symptoms often feel worse in morning. Because most of the patients were hospitalized, it is also likely that the wards' therapy programs had an influence on these results. The only other study that described activity levels by time of day before ECT [46] did not distinguish between subgroups and had a rather limited sample size ($n = 15$).

Although activity levels in the morning and evening were similar in the two groups of MD patients, those with psychotic symptoms showed higher afternoon activity levels than those without psychotic symptoms. This could be a consequence of increased agitation in the MD subgroup with psychotic symptoms – an increase which was not reflected in significantly higher CORE agitation subscale scores in the group with psychotic symptoms, however.

Copying tasks may also be able to distinguish subgroups, according to a study that compared fine motor functioning in melancholic and nonmelancholic patients [17]. The authors found a difference in both IT and MT on the LCT. In the current project, differences between the three subgroups were present but less convincing. After correction for age and multiple testing, they did not attain the level of statistical significance. The fact that we found no significant difference between those with NMD and those with MD could be explained by the large number of MD patients that were unable to complete the drawing task. More differences could have been revealed if the patients with the most severe retardation or agitation had been able to complete the task. When we compared the patients who completed the drawing task with those who did not, we found that the latter group were on average more severely depressed (mean HDRS17 score of 28 vs. 23) and had higher total CORE scores (17 vs. 8).

In contrast to our initial hypothesis, we found that objective measurements did not reveal larger PMDs in MD patients with psychotic symptoms. While the difference was not significant, those with psychotic symptoms even seemed to be somewhat more active and have shorter ITs on the LCT than MD patients who did not have psychot-

ic symptoms. A possible explanation is that the patients with psychotic symptoms showed more agitation, on average, than the patients who did not have psychotic symptoms according to their CORE agitation subscale scores, though this difference in agitation level was not significant. With regard to the influence of this factor on the patients' performance on the drawing task, it may be impatience, rather than acceleration, which is manifested as a reduction in IT compared to MD patients without psychotic symptoms. Most studies which compare patients with psychotic depression to patients with no psychotic symptoms show significantly higher rates of psychomotor agitation in the first group [49–51]. Others find no significant difference, however [52, 53].

Differences in underlying brain functioning could explain the lower activity levels found in the melancholic patients compared to the nonmelancholic patients. Earlier studies identified white matter microstructure alterations in the medial forebrain bundle in patients with MD [24] which could play a role in motor functioning. Extensive neurobiological comparisons of melancholic and nonmelancholic patients are scarce, however.

*Limitations*

The CORE was rated by the same person who instructed the patients during the instrumental assessments. Although a clear protocol was in place for instruction in these tasks, it would have been better if the assessments had been carried out by separate researchers. Because our patient population mainly consists of severely depressed or treatment-resistant hospitalized patients awaiting treatment with ECT, the potential for generalizing results to the broader population of depressed patients is limited. The fact that our model had no place for NMD with psychotic symptoms can also be considered a limitation of our study. The unequal distribution of patients over the three subgroups limits the strength of our findings. Other limitations of this study are consequences of its naturalistic design, which involved patients being treated with a variety of different combinations of psychotropic drugs that may have an influence on psychomotor functioning. We have no indication that the use of psychotropic drugs in our sample differs from their use in other severely depressed patients, however, and the influence of psychotropic drugs appears to be limited, as we found no significant difference in objective PMD between patients who were/were not being treated with benzodiazepines and those that were not treated with antidepressants, those on monotherapy, and those who were treated with a combination of antidepressants.

Our patients wore the MotionWatch for 24 consecutive hours, but patients diagnosed with MDD may exhibit different activity patterns on different days. We chose to monitor 24 h in order to ensure compliance and also for practical reasons, as the availability of the watches was limited. In future projects, it would be useful to apply a somewhat longer measurement period of 3 days so that activity levels can be averaged.

The fact that we divided our groups into nonmelancholic and melancholic patients based on their CORE scores could also be considered a limitation. Melancholia arguably entails more than observable PMD, but this definition was chosen because PMD is considered to be one of the key features of melancholia [12]. Grouping based on a different method that does not rely entirely on psychomotor functioning would, however, have been a valuable addition. An earlier study, which defined melancholia according to the DSM-IV major depressive episode specifier [54], found that 10 of their melancholic patients obtained CORE scores <8 and 22 patients scored ≥8. Using observable PMD as a classifier may have meant that a number of patients were classified as nonmelancholic according to the CORE, while a diagnostic melancholia specifier would have classified them as melancholic.

*Suggestions for Future Research*

Future projects could benefit from considering other means of measuring PMD in order to limit dropout among the most severely depressed patients and capture agitation more effectively. It would also be worth investigating measurements of activity levels over longer periods of time (>24 h) in outpatient settings, where ward activation programs cannot interfere with the results. Studies with larger sample sizes evenly distributed over the three subgroups could also enable researchers to distinguish between patients who predominantly exhibit retardation, agitation, or a combination of the two.

## Conclusions

To conclude, psychomotor functioning as measured by actigraphy can be used to distinguish between nonmelancholic depressed patients and those with melancholic symptoms. This study found no significant differences in objective psychomotor performance between MD patients with and those without psychotic symptoms, perhaps because PMD in those with psychotic symptoms often consists of both agitation and retardation, rather than retardation alone.

## Statement of Ethics

The study was approved by the Ethics Committee of Antwerp University Hospital (project No. 15/10/93) and carried out in accordance with the latest version of the Declaration of Helsinki. All subjects provided written informed consent before the study procedures were performed.

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# 6.2. Correlation between psychomotor domains

Published as: van Diermen L, Walther S, Cools O, Fransen E, Birkenhäger TK, Sabbe BCG, et al. Observer-rated retardation but not agitation corresponds to objective motor measures in depression. Acta Neuropsychiatr [Internet]. 2018;1–6. Available from: https://www.cambridge.org/core/product/identifier/S0924270818000212/type/journal_article

*Acta Neuropsychiatrica*

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**Short Communication**

**Cite this article:** van Diermen L, Walther S, Cools O, Fransen E, Birkenhäger TK, Sabbe BCG, Schrijvers D. (2018) Observer-rated retardation but not agitation corresponds to objective motor measures in depression. *Acta Neuropsychiatrica* page 1 of 6 doi: 10.1017/neu.2018.21

Received: 23 March 2018
Revised: 22 May 2018
Accepted: 29 May 2018

**Key words:**
depression; neuropsychology; psychiatric disorders

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## Observer-rated retardation but not agitation corresponds to objective motor measures in depression

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**Abstract**

*Objective:* To explore the correlations between observer ratings and instrumental parameters across domains of psychomotor functioning in depression. *Method:* In total, 73 patients with major depressive disorder underwent extensive psychomotor and clinical testing. Psychomotor functioning was assessed with (i) an observer-rated scale (the CORE measure) and also objectively with (ii) 24-h actigraphy, and (iii) a fine motor drawing task. *Results:* Observer ratings of retardation correlated with instrumental assessments of fine and gross motor functioning. In contrast, observer ratings of agitation did not correlate with observer ratings of retardation or with the instrumental measures. These associations were partly influenced by age and, to a lesser extent, by depression severity. *Conclusion:* Psychomotor disturbance is a complex concept with different manifestations in depressed patients. Although observer ratings of retardation correspond well with instrumental measures of the motor domains, objective measurement of agitation and other aspects of psychomotor disturbance require further research.

### Significant outcomes

- Observer-rated retardation correlated with an instrumental assessment of motor functioning.
- Agitation did not correlate with objectively measured motor functioning.
- Associations found were partly influenced by age and depression severity.

### Limitations

- Not all aspects of psychomotor functioning were captured by our measurement methods.
- Due to the complexity of the task, there was 23% dropout on the task of fine motor functioning.
- Our sample was heterogeneous, and we did not control for all factors with a potential influence on psychomotor functioning.

### Introduction

According to the Diagnostic and Statistical Manual of Mental disorders 5th edition (DSM-5), psychomotor retardation and agitation are symptoms of major depressive disorders (MDD) and have significant diagnostic and therapeutic implications (1,2). Although psychomotor disturbance (PMD) in depression may include psychomotor retardation and agitation, their defining features remain unclear, including the motor and cognitive domains. Therefore, the combined application of psychomotor rating scales, instruments and experimental tasks covering motor and cognitive domains could help to clarify this issue (2).

Observer-based rating scales have been developed to quantify PMD. For example, the CORE measure of psychomotor functioning provides a global impression of psychomotor functioning in the domains retardation, agitation and non-interactiveness; the CORE was designed to distinguish between non-melancholic and melancholic depression (3,4). However, all clinical rating scales require training and are prone to observer bias. Therefore, in-depth objective instrumental testing is recommended to explore the various domains of PMD (1,2).

The three domains that have received the most attention are speech, and gross and fine motor activity (2). Actigraphy allows continuous objective quantification of spontaneous gross motor activity (5). Similarly, computerised drawing tasks can assess cognitive and motor components of fine motor activity (6). However, reports of assessments across all psychomotor domains are scarce (2,7).

This study aimed to explore the association between observer ratings of psychomotor retardation and agitation, and objective measures of gross and fine motor functioning, in currently depressed subjects. We hypothesised that gross and fine motor functioning would be related (to varying extents) to expert observer ratings of psychomotor retardation and agitation.

## Material and methods

### Study population

This study included 73 patients (56 women, 17 men) with an MDD or a depressive episode in bipolar disorder (according to the DSM-IV-TR) recruited from the inpatient and outpatient department of Duffel Psychiatric Hospital (Belgium); their mean age was 58.8 (±15.1) years, and the (average) duration of a depressive episode was 14.3 (±18.1) months. These patients were awaiting treatment with electroconvulsive therapy (ECT) and are part of the PROTECT cohort (8). Diagnoses were confirmed by the MINI diagnostic interview version 6.0 and, at inclusion, patients had to score ≥ 17 on the Hamilton Depression Rating Scale-17 items (HDRS17) (9). Excluded were patients with a history of substance abuse (<6 months previously), or a primary psychotic or schizoaffective disorder.

All patients provided written informed consent before the study procedures were performed. The study protocol was in accordance with the Declaration of Helsinki and was approved by the local Medical Ethics committee.

### Treatment

Most patients were treated with antidepressants: 37 were on tricyclic antidepressant monotherapy, 12 on selective serotonin reuptake inhibitors monotherapy and four were treated with another antidepressant. Five patients were not treated with antidepressants, and 15 used a combination of antidepressants. Of all patients, 79% used antipsychotics for agitation or concurrent psychotic symptoms, 26% received add-on mood stabilisers (mainly lithium) and 73% were treated with benzodiazepines (at a dose of, on average, 8.4 mg diazepam equivalents). The study procedures were scheduled before ECT.

### Clinical assessment

#### Mood

The severity of the depressive disorder was assessed with the HDRS17 (9). To rule out double incorporation of psychomotor symptoms in our analyses, the depression severity score excluding the items on psychomotor functioning (8 – retardation and 9 – agitation) was calculated (HDRS15).

#### Psychomotor functioning

Psychomotor functioning was assessed as part of a larger test battery with an assessment of mood and cognitive functioning. Patients had therefore been observed for about 1 h before psychomotor functioning was assessed by the main researcher, an MD trained in psychiatry. For patients on two of the participating wards (~10% of measurements), psychomotor functioning was assessed by the psychomotor therapists of these wards that were trained to rate the CORE. All assessments were conducted in the week before ECT. Gross motor functioning was assessed within 2–3 days of the CORE ratings and fine motor measures.

*Clinician rated* The CORE measurement tool was used to assess observable psychomotor functioning (3,4). The clinician scores 18 observable clinical features on a 4-point scale based on severity ranging from 0 (absence of symptom) to 3 (severe). The CORE generates scores in three psychomotor categories: a central non-interactiveness scale capturing cognitive impairment, and two motoric scales capturing retardation and agitation. The Dutch version of the CORE has high inter-rater reliability and excellent validity (10).

*Gross motor functioning* Gross motor functioning was measured by means of the MotionWatch8 (MW) (CamNtech Ltd, Cambridge, UK) using accelerometry. Earlier studies support the use of accelerometry as an objective measure of spontaneous gross motor functioning (11) with reduced activity levels in depression (7,12–14).

Patients wore the actigraphy watch on the wrist of the non-dominant arm for 24 consecutive hours. Activity counts were stored in 2-s intervals. The approximated wake-up time and bedtime were set, and the software provided a daytime activity level (DAL) and nighttime activity level.

*Fine motor performance* Fine motor performance was measured with a digital Line Copying Task (LCT). On this task, significantly more psychomotor slowing has been demonstrated for melancholic versus non-melancholic depressive patients and patients with depression in general compared with controls (1,2,15,16). A full description of the set-up for this task is already published (17,18). In brief, patients sit at a table and are asked to copy lines presented on a computer screen. The use of a graphic tablet (WACOM Intuos Pro) and a pressure-sensitive pen, connected to a laptop, allows the calculation of variables such as initiation time (IT) and movement time (MT). IT mainly reflects the cognitive component of the performance and is defined as the time between the presentation of the stimulus and the start of the first drawing movement. MT reflects the motor component and is defined as the time from the start of the first drawing movement to the end of the last drawing movement.

The drawing tasks could not be performed by all patients as some of them were too agitated or severely depressed to follow instructions adequately ($N = 17$). Two patients had no baseline measurement of fine motor functioning because of planning issues, three measurements could not be used as a consequence of technical problems at the moment of testing.

### Statistical analysis

Statistical analyses were performed with SPSS 24 and JMP 13.

Descriptive statistics are reported as a mean ± standard deviation. The normal distribution of the variables allowed the use of Pearson's correlation. Partial correlation coefficients were calculated using multiple linear regression models accounting for either age alone, or age and depression severity; these two latter

variables are known to influence psychomotor performance (11,15,19). In case of missing data, patients were only excluded in the comparisons with missing data and not completely excluded from analyses. Because 21 comparisons were made, a Bonferroni-corrected $p$-value was calculated.

Differences in psychomotor functioning caused by potential confounders such as medication use, body mass index (BMI) (20) and smoking status (21) were assessed with analysis of variance (for medication use and smoking status) or correlational (for BMI) analyses.

Multiple regression models were calculated to further explore the relation between gross and fine motor functioning and the score on the CORE retardation subscale, including age, depression severity and smoking status as covariates. The relative contribution of the motor function to the prediction is expressed as the change in $R^2$ between a model including (i) solely age and depression severity, and a model including (ii) age, depression severity and motor function, as explanatory variables. Patients that had missing values in gross motor functioning or fine motor performance were excluded from the respective regression analyses.

## Results

Out of the 73 patients, 33 had psychotic symptoms, 46 had melancholic depression and 13 had bipolar depression. The average HDRS17 score was 24.8 (±6.0), the average HDRS15 score was 22.3 (±5.5). The total CORE score was 10.6 (±7.9), consisting of an average CORE subscale rating of 5.4 (±4.1, retardation), 2.4 (±2.8, agitation) and 2.8 (±3.4, non-interactiveness). On instrumental measures of gross psychomotor functioning, patients ($n = 71$) had a DAL of 3.9 (±2.4) counts per 2 s. Fine motor functioning could be tested in 51 patients; LCT IT was 1.1 (±0.5) s, and LCT MT was 0.6 (±0.4) s. In total, 50 patients had all three assessments.

Table 1 presents the correlation matrix. Strong correlations were found between the CORE total and its subscales, as well as between the cognitive and motor components of the LCT.

Observer ratings of psychomotor retardation and agitation correlated with the total CORE score, but not with each other. Similarly, objective instrumental measures of both gross and fine motor functioning correlated with CORE total scores, but not with each other. In addition, there was no correlation between the CORE agitation subscale and either of the objective measures of psychomotor performance. Correcting for age decreased the correlation coefficients, whereas adding depression severity to the partial correlation analysis slightly increased the strength of the correlation.

There was no significant difference in psychomotor functioning between patients that used no antidepressants, those that were on monotherapy and those that were treated with a combination of antidepressants, nor did psychomotor functioning correlate with BMI (all $p$-values >0.05). Smokers ($N = 22$), however, had significantly lower CORE total ($F = 5.78$, $p = 0.0188$) and retardation subscale ($F = 10.72$, $p = 0.0016$) scores than the non-smokers. They were also somewhat faster on the motor component of the drawing task (LCT MT, $F = 8.51$, $p = 0.0053$).

To test whether information on motor functioning could improve the prediction of the CORE retardation scores, multiple regression models were fitted with gross (MW DAL) and fine motor (LCT MT) functioning as explanatory variables, in addition to age, smoking status and depression severity scores (Table 2).

The regression model with the MW activity level explained 45% of the variance ($F = 1347$, $p < 0.0001$) in the CORE retardation rating, whereas the model with MT of the copying task explained 36% of the variance ($F = 6.33$, $p = 0.0004$). The fraction of the explained variance contributed by gross and fine motor functioning was 19% and 10%, respectively. This represents the additional accuracy in predicting the CORE retardation score contributed by the information on gross and fine motor functioning, in addition to the information on age, smoking status and depression severity.

## Discussion

The present study confirms the association between observer ratings of retardation and instrumental assessment of fine and gross motor functioning. However, observer ratings of agitation did not correlate with the instrumental measures; also, there was no clear correlation between fine and gross motor functioning. The associations were partly influenced by age and depression severity.

To our knowledge, this is the first study to directly compare three different measurement methods for psychomotor functioning in a relatively large, depressed patient population. Because a strict Bonferroni correction was used to correct for multiple comparisons, some relevant correlations may not be labelled as significant results.

Correlations between observer ratings of retardation and DALs were the most obvious. Correlations between the CORE retardation subscale and instrumental measures of fine motor functioning were also present; however, significance was lost after correction for age. Subtle cognitive and fine motor slowing might be a component of psychomotor functioning that is better detected by objective measurement than by observer-rated measurement. The more cognitive component genuinely escapes the clinician's eye. Therefore, the CORE retardation subscale might be a better reflection of gross than fine motor retardation. As some of the most severely depressed patients (often with high CORE scores) were unable to complete the drawing tasks because of the relative complexity, correlations with fine motor functioning have to be interpreted with care. The moderate to strong correlation between the CORE and DALs are in line with previous reports (11). Correlations between the CORE and results on the drawing tasks are similar to those between the scores on the Salpêtière Retardation Rating Scale and the results of drawing tasks found by Pier et al. (16). However, neither of these latter studies corrected for the effect of age or depression severity.

Moreover, worth discussing is the fact that observer-rated agitation does not correlate with either of the instrumental measures. This result is in contrast with the findings of Attu et al. (11) who reported correlations between CORE agitation and activity levels in the same direction as the correlation with CORE retardation, indicating that slower patients often experience retardation combined with periods of agitation. We suggest that the concept of CORE-defined agitation is a construct that is not adequately captured by actigraphy (as used here). Although being restless and moving around is an activity that is normally captured by the MW, agitation often appears alongside retardation, thereby compensating for the moments of increased activity with overall diminished activity levels. Besides that, agitation frequently appears more episodic and is not always present at the moment of observation, thereby impeding registration of this symptom. Moreover, since we monitored activity levels for only

**Table 1.** Pearson correlations between the psychomotor symptoms

| | CORE total score | CORE NI | CORE AG | CORE RET | MW DAL | LCT IT | LCT MT |
|---|---|---|---|---|---|---|---|
| CORE total score | 1 | | | | | | |
| CORE NI | | | | | | | |
| Not corrected | 0.920* | 1 | | | | | |
| Age corrected | 0.910* | | | | | | |
| Age and HDRS15 corrected | 0.909* | | | | | | |
| CORE AG | | | | | | | |
| Not corrected | 0.476* | 0.306 | 1 | | | | |
| Age corrected | 0.381* | 0.204 | | | | | |
| Age and HDRS15 corrected | 0.209 | 0.071 | | | | | |
| CORE RET | | | | | | | |
| Not corrected | 0.829* | 0.725* | −0.020 | 1 | | | |
| Age corrected | 0.792* | 0.675* | −0.176 | | | | |
| Age and HDRS15 corrected | 0.801* | 0.659* | −0.323 | | | | |
| MW DAL | | | | | | | |
| Not corrected | *−0.458** | *−0.406** | *0.010* | *−0.546** | 1 | | |
| Age corrected | *−0.376** | *−0.331* | *0.120* | *−0.488** | | | |
| Age and HDRS15 corrected | *−0.398** | *−0.335* | *0.162* | *−0.490** | | | |
| LCT IT | | | | | | | |
| Not corrected | *0.427** | *0.369* | *−0.016* | *0.429** | *−0.293* | 1 | |
| Age corrected | *0.234* | *0.216* | *−0.228* | *0.285* | *−0.173* | | |
| Age and HDRS15 corrected | *0.385* | *0.307* | *−0.129* | *0.348* | *−0.187* | | |
| LCT MT | | | | | | | |
| Not corrected | *0.532** | *0.455** | *0.009* | *0.523** | *−0.315* | 0.769* | 1 |
| Age corrected | *0.385* | *0.332* | *−0.184* | *0.410* | *−0.205* | 0.693* | |
| Age and HDRS15 corrected | *0.503** | *0.396* | *−0.129* | *0.452** | *−0.213* | 0.685* | |

AG, agitation subscale; HDRS15, Hamilton Depression Rating Scale, excluding 2 items on psychomotor functioning; IT, initiation time; LCT, Line Copying Task; MT, movement time; MW DAL, MotionWatch daytime activity level; NI, non-interactiveness subscale; RET, retardation subscale.
Correlations of interest are presented in italics.
*$p < 0.00239$.

24 consecutive hours, a non-parametric circadian rhythm analysis could not be carried out. One might expect that the stability of the activity-rest patterns could be more informative about agitation than the DAL. Moreover, calculation of immobility parameters could have been valuable (22). Besides motor agitation, the CORE agitation items are facial anxiety and agitation, verbal stereotypy and stereotype movements. Thus, four of the five CORE agitation items are unlikely to be captured by actigraphy, which might explain why we found no correlation between the CORE agitation subscore and actigraphy.

Although in our analyses we have used the HDRS17 excluding two items on psychomotor functioning as a measure for depression severity, it could have been interesting to rate depression severity according to the melancholia subscale of the HDRS17 (the HDRS6) that has proven to be superior to the HDRS17 in terms of scalability in a recent review of literature (23). However, because retardation is considered to be the most severe symptom of the melancholia subscale (24) and we would exclude this item for calculation of an adapted score (HDRS5), we have chosen to use the full HDRS in our analyses after all. We can confirm a somewhat greater age-controlled correlation between the CORE and the HDRS5 subscale ($r = 0.497$, $p < 0.001$) than between the CORE and the HDRS15 ($r = 0.433$, $p < 0.001$), which is consistent with findings by Caldieraro et al. (25).

A remarkable finding was that smokers showed somewhat milder psychomotor symptoms than non-smokers. A possible explanation for this difference can be found in age, as the smokers were on average younger than the non-smokers, but even controlling for age the CORE retardation subscale and motor component of the drawing task differ significantly for smokers versus non-smokers. This could be a consequence of the positive effect of nicotine on motor abilities (26) or could be explained by another

**Table 2.** Regression model of gross motor functioning ($r^2 = 0.45$) and fine motor performance ($r^2 = 0.36$) model versus CORE retardation subscale

| | | 95% Confidence interval | | |
|---|---|---|---|---|
| | Point estimate | Lower limit | Upper limit | *p*-value |
| Gross motor functioning | | | | |
| Intercept | 2.644 | −2.039 | 7.327 | |
| MW DAL | −0.787 | −1.122 | −0.454 | <.0001 |
| HDRS15 | 0.124 | −0.023 | 0.271 | 0.0968 |
| Age | 0.045 | −0.012 | 0.102 | 0.1165 |
| Smoking (0) | 1.201 | 0.347 | 2.054 | 0.0065 |
| Fine motor performance | | | | |
| Intercept | −0.339 | −4.855 | 4.177 | |
| LCT MT | 3.252 | 1.208 | 5.296 | 0.0025 |
| HDRS15 | 0.143 | −0.020 | 0.306 | 0.0849 |
| Age | −0.008 | −0.0694 | 0.053 | 0.7889 |
| Smoking (0) | 0.675 | −0.173 | 1.523 | 0.1161 |

HDRS15, Hamilton Depression Rating Scale, excluding 2 items on psychomotor functioning; LCT MT, Line Copying Task movement time; MW DAL, MotionWatch daytime activity level.

factor in which both groups differ (that we have not registered), such as coffee consumption (27).

## Limitations

A limitation of the present study is the amount of dropout (23%) on the task of fine motor functioning due to the complexity of the task. Development of a simplified measure to assess fine motor functioning would be valuable for severely depressed patients, who frequently experience PMD. Because of the limited size of our sample, we did not control for all potential confounders. Although we have looked for differences between patients that did not use antidepressants and those that were on monotherapy or several antidepressants, the use of different combinations of psychotropics could have influenced psychomotor performance and was not accounted for in our analyses. The diagnostic heterogeneity (uni- as well as bipolar, melancholic as well as non-melancholic, both psychotic and non-psychotic depression) can be considered another limitation of this study, as well as the difference in therapy programmes on the wards that could have influenced the DALs that were measured. Besides that, there was a skewed gender distribution for which we have no explanation.

## Conclusion

This study involved two domains of psychomotor functioning which were correlated with a well-known scale to measure PMD. Correlations were found that confirm the concept of psychomotor retardation, in part explained by age. These analyses indicate that different measurement methods are required to capture the different aspects of psychomotor functioning. Actigraphy and measurement of fine motor functioning can make a valuable contribution when diagnosing psychomotor retardation.

## Suggestions for future research

For future research, we emphasise that actigraphy and drawing tasks do not capture all aspects of PMD, as defined by the CORE. Because of the complexity of the construct, a more extensive test battery would be beneficial. For example, speech and gait analysis could be of added value to obtain more objective information on these items of the CORE.

**Acknowledgements.** The authors thank Herman Moens and Inge van Deun for their help in the data collection process. The authors would also like to thank Wouter Hulstijn for his valuable comments on the preliminary manuscript.

**Authors' Contribution.** L.V.D., D.S. and T.B. designed the study and wrote the study protocol. L.V.D. was responsible for data collection and statistical analyses. S.W. and E.F. contributed to the process of these analyses. L.V.D. wrote the draft of the manuscript and integrated the comments of all other authors. They all contributed to and approved the final version of the manuscript.

**Financial Support.** This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

**Conflicts of Interest.** None.

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## 6.3. Predicting ECT response: the role of psychomotor symptoms

Submitted as: van Diermen L, Vanmarcke S, Walther S, Moens H, Veltman E, Fransen E, Sabbe B, van der Mast R, Birkenhäger T, Schrijvers D. Psychomotor disturbance predicts ECT outcome in depression.

# Psychomotor disturbance predicts ECT outcome in depression

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## Abstract

**Background**: Psychomotor symptoms are core features of melancholic depression. This study investigates whether psychomotor disturbance predicts the outcome of electroconvulsive therapy (ECT) and how the treatment modulates psychomotor disturbance.

**Methods**: In 73 adults suffering from major depressive disorder psychomotor functioning was evaluated before, during and after ECT using the observer-rated CORE measure and objective measures including accelerometry and a drawing task. Regression models were fitted to assess the predictive value of melancholic depression (CORE ≥ 8) and the psychomotor variables on ECT outcome, while effects on psychomotor functioning were evaluated through linear mixed models.

**Results**: Patients with CORE-defined melancholic depression (n=41) had a 4.9 times greater chance of reaching response than those (n=24) with non-melancholic depression (Chi-Square=7.5, P=0.006). At baseline, both higher total CORE scores (AUC=0.76; P=0.001) and needing more cognitive (AUC= 0.78; P=0.001) and motor time (AUC=0.76; P=0.003) on the drawing task corresponded to superior ECT outcomes, as did lower daytime activity levels (AUC=0.76) although not significantly so after Bonferroni correction for multiple testing. A greater CORE-score reduction in the first week of ECT also predicted higher ECT effectiveness. ECT reduced CORE-assessed psychomotor symptoms and improved activity levels only in those patients showing the severer baseline retardation.

**Conclusions**: Although the sample was relatively small and results may have been confounded by differences in age and depression severity between responders and non-responders, psychomotor symptoms clearly predicted beneficial outcome of ECT in patients with major depression, indicating that monitoring psychomotor deficits can help personalise treatment.


## Highlights

- Patients with CORE-defined melancholic depression have a 4.9 times greater chance of reaching response to ECT than depressed patients without melancholic symptoms.
- High baseline CORE scores and poor performance on a drawing task predict a better ECT outcome.
- A substantial reduction in CORE scores during the first week of ECT precedes a beneficial treatment response.

# Introduction

Psychomotor disturbance is a core symptom of major depressive disorder (MDD) (139) and according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the presence of marked psychomotor retardation or agitation is important in specifying a depressive episode as melancholic depression (Mel-D)(1). Some authors even argue that the mere presence of psychomotor symptoms can distinguish Mel-D from non-melancholic depression (NMD), with the former representing the more severe end of the depression continuum (9, 30,139). Another line of evidence suggests that melancholia should particularly be seen as a categorical entity based on distinct biological underpinnings, higher heritability, a distinctive pattern of symptoms, and a differential response to treatment modalities such as antidepressants and electroconvulsive therapy (ECT) (31,32,140–145).

ECT is a relevant treatment option for patients with Mel-D (146–148), with 60-80% treatment efficacy depending on the criteria used for the selection of patients and the definition of treatment outcome (43,149). Despite its effectiveness and safety, in general, ECT is only considered when patients have failed to respond to several pharmacological treatments (101). However, a delayed start of ECT is known to reduce the chances of a good response (74), underscoring the importance of identifying predictors of ECT response to promote targeted patient selection. Melancholia has long been considered to be a good clinical predictor of depression outcome in ECT (29), but meta-analyses on the predictive value of melancholic symptoms were inconclusive due to study heterogeneity (74,120). This could be explained by the fact that several studies did not explicitly investigate psychomotor disturbance since this is not a mandatory symptom of Mel-D (150).

Moreover, definitions of psychomotor symptoms as key features of Mel-D remain elusive (7) as they may encompass different domains of psychomotor and cognitive functioning. To aid the differentiation between Mel-D and NMD, the CORE assessment of psychomotor functioning was designed (32). Although, like other observer-rated instruments, the CORE is clinically useful (5), it still provides a rather rough estimate of psychomotor performance and depends on the judgment and training of the investigator. These disadvantages may be overcome by, alternatively or additionally, applying objective psychomotor assessment tools such as accelerometry and computer-based drawing tasks (7) that may be even more predictive of depression outcome after ECT.

Also, little is known about the effect of ECT on (the course of) psychomotor functioning in Mel-D. Although in common clinical practice it is assumed that psychomotor improvement precedes the improvement of other symptom clusters of depression in patients treated with ECT, a recent study nonetheless showed that all clusters gauged by the Montgomery-Åsberg Depression Rating Scale (MADRS) responded to ECT in depressed older patients as early as in the first week of ECT, where the mood symptom cluster improved fastest compared to the melancholic and suicidal symptom clusters (151). To our knowledge, no recent studies have specifically investigated the effect of ECT on (the course of) psychomotor symptoms.

Therefore, the present study investigates the predictive value of psychomotor disturbance in depressed patients receiving ECT using both the observer-rated CORE instrument and objective measures, hypothesising that the presence of psychomotor symptoms such as agitation or retardation as assessed with the CORE, low baseline activity levels and/or fine motor performance and the change in psychomotor functioning in the first week of ECT will predict a favourable outcome. We additionally investigate the effect of ECT on (the course of) psychomotor functions.

# Methods

## Study design

We used a single-site, prospective longitudinal design. The study was conducted in Belgium and registered at the online clinical database ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02562846). Patients were included between August, 2015 and August, 2017. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

## Study population

Patients with a major depressive episode in uni- or bipolar disorder according to the DSM 5 who were scheduled for ECT were included. Diagnoses were confirmed using the MINI diagnostic interview, version 6.0. (102). Eligible patients also needed to have a score of at least 17 on the Hamilton Depression Rating Scale - 17 items (HDRS17) – at the time of inclusion. Patients with a history of any substance abuse in the past six months or a primary psychotic or schizoaffective disorder and patients that had recently (<6 months) been treated with ECT were excluded.

This study is part of a larger research project on ECT-response predictors conducted in Duffel Psychiatric Hospital (Belgium)(123–125). Reasons for ECT referral were treatment resistance, presence of severe melancholic or psychotic symptoms and acute suicidality. The study was approved by the Ethics Committee of the University Hospital of Antwerp (project number 15/10/93). All participants provided written informed consent.

## Treatment

### Pharmacological

Before ECT, 7% of the patients did not use any antidepressant, while 74% were treated with antidepressant monotherapy (selective serotonin reuptake inhibitor (n=12), tricyclic antidepressant (n=38), serotonin noradrenaline reuptake inhibitor (n=1), mirtazapine (n=2)) and 19% with a combination of antidepressants. Seventy-nine percent of the patients

used additional antipsychotic medication for agitation or psychotic symptoms; 27% were on add-on mood stabilizers (mainly lithium) and up to 73% also used benzodiazepines (on average, 8.5(±5.9) mg diazepam equivalents/day). Patients continued their antidepressants and/or antipsychotics during the study period, with the drugs and doses preferably not being changed four weeks before and during the ECT course. When we examined the effect of psychotropic drugs on psychomotor functioning, no significant difference in objective measures of psychomotor disturbance was found between patients who were taking benzodiazepines and those that were not. The total CORE score was, however, higher in the patients using benzodiazepines (12.2 vs 6.6), F-ratio =7.9, P=0.0064. The scores on the CORE agitation subscale were the only outcomes that significantly differed between the patients using benzodiazepines and those that did not (2.9 vs 1.0, F-ratio=7.4, P=0.0084). Correlations between benzodiazepine dose and the movement component of the line-copying task (r= 0.32, p=0.03; for a description of the task, see *Objective measures*) and the CORE agitation subscale (r=0.25, p=0.04) were also found. There were no significant differences in psychomotor functioning between the patients that used no antidepressants, those on monotherapy and those on a combination of antidepressants, nor in the psychomotor functions of the patients that used antipsychotic medication and those that did not (p > 0.05).

### ECT

ECT was administered twice a week according to recent guidelines (101) using a brief-pulse (0.5ms) constant-current Thymatron IV system (Somatics LLC, USA). Electrodes were placed right unilaterally (RUL) or bilaterally when a fast antidepressant effect was needed (55). Prior to the first session, the stimulus dose was established by the age method for RUL electrode placement and the half-age method for bilateral electrode position (57). Etomidate was the anaesthetic of choice (0.15mg/kg) and propofol (1mg/kg) and ketamine (1-2mg/kg) were used when etomidate was not tolerated or when clinical response was lacking after the first 12 sessions. Succinylcholine (0.5mg/kg) was used as a muscle relaxant.

The endpoint of the ECT course was determined by the treating psychiatrist based on improvement of mood and side effects of the treatment. ECT was continued until the patient was in remission or showed no further improvement during the last three sessions.

## Clinical assessment

### Mood

Depression severity was assessed with the 17-item Hamilton Depression Rating Scale (HDRS17) (103) prior to study entry and the Montgomery-Åsberg Depression Rating Scale (MADRS) (106,152,153) was used to evaluate the course of the depressive symptoms during ECT (105). Treatment responders were defined as those patients that showed an end-of-treatment decrease of at least 50% on the MADRS and remitters as those that had an end-of-treatment MADRS score ≤10.

## Psychomotor assessment

### Clinician-rated assessment

The CORE was used to assess observable psychomotor performance and to define Mel-D (total CORE score ≥ 8) (8). We chose to use CORE-defined melancholia because a comprehensive study (n=489) found that DSM-defined melancholia did not identify the depressed patients more likely to respond to ECT (77). A training video was used as the gold standard for the rating process. The investigator rated 18 clinical features of each patient on a 4-point severity scale ranging from 0 (no symptoms) to 3 (severe symptoms) in three psychomotor categories: a central non-interactiveness scale capturing cognitive impairment and two motor scales capturing retardation and agitation. The Dutch version of the CORE has high inter-rater reliability and excellent validity (107).

## Objective measures

### Accelerometry-based activity monitoring

Gross motor functioning was monitored using the MotionWatch8 (MW) (CamNtech Ltd., Cambridge, UK) accelerometer. Earlier studies support the use of accelerometry as an objective and non-intrusive measure of spontaneous gross motor functioning (108) with reduced activity levels found in major depression (4,154–156). Patients wore the actigraph on the wrist of the nondominant arm for 24 consecutive hours. Activity counts were stored in 2-s intervals. The approximated wake-up time and bedtime were set and the software provided a daytime activity level (DAL) in movement counts per 2 seconds.

In the first 54 consecutive participants measurements were performed at baseline, 1, 2 and 3 weeks into the ECT course and after the last ECT session. For feasibility reasons, gross motor functioning was only recorded before and after the ECT course in the last 19 participants.

### Line-copying task

Fine motor performance was evaluated with a digital line-copying task (LCT). This task has demonstrated significantly more psychomotor slowing in patients with Mel-D than in those diagnosed with NMD and in patients with major depression in general as compared to healthy controls (5–7,13). In brief, patients are asked to copy lines presented on a computer screen on a digital tablet (WACOM Intuos Pro) using a pressure-sensitive pen that is connected to a laptop, allowing the calculation of variables such as initiation time (IT) and movement time (MT), where IT mainly reflects the cognitive component of the performance, defined as the time between the presentation of the stimulus and the start of the first drawing movement, and MT the motor component, defined as the time from the start of the first drawing movement to the end of the last drawing movement (14).

The patients practised the task once before the actual test to diminish learning effects in later measurements. The LCT was performed at baseline, 1, 2 and 3 weeks into the ECT course and after the last ECT session by the first 50 participants. For feasibility reasons, the last 23 participants completed the LCT before and after the ECT course only. Not all participants succeeded in completing the task at all time points and some were offered a lighter version of the protocol because they were either too agitated, retarded or in other ways too severely depressed to follow all instructions adequately (n=17).

In two patients no baseline fine motor measurements were made due to planning issues, while in another three measurements could not be used as a consequence of technical problems at the time of testing.

## Statistical analysis

Statistical analyses were performed with JMP 14.0. Extreme outliers on the objective psychomotor measures were identified and removed based upon the following decision rule: the interquartile range was multiplied by 3 and values beyond 3 times the interquartile range removed (LCT IT n=2, LCT MT n= 1) before calculating the average values and standard deviations.

Using simple logistic regression, we modelled the associations between the presence of melancholia, separate psychomotor variables and response and remission after treatment. Melancholia was defined as 'present' when CORE scores were ≥ 8. The psychomotor variables include the baseline and change values in the first week of treatment of the CORE total and subscale scores and DALs in terms of accelerometer outcomes and LCT ITs and MTs. Response/remission after treatment was scored as a decrease of >50%/score of 10 or lower on the MADRS. The regression models estimate the change in odds (for response/remission) per unit change in the psychomotor variables and test whether a change in the psychomotor variable is associated with a significant change in odds. The predictive power of the models was expressed using the area under the curve (AUC).

Each of the psychomotor factors with a significant association to the outcome in the simple logistic regression analyses were included separately in a multiple regression model in which the presence of psychotic symptoms and benzodiazepine dose served as covariates. This starting model was simplified by stepwise backward elimination.

We fitted linear mixed models to assess the effect of ECT on psychomotor functioning. To account for the non-independence between observations from the same individual, individual ID was entered as a random effect in the model. The moment of testing was entered as a fixed effect. The CORE total and subscale scores, DALs and LCT ITs and MTs were entered as outcome variables. When there was a significant change across time points, a post-hoc analysis was carried out with a Tukey HSD correction for multiple hypothesis testing.

The subgroup of patients with the most severe retardation was created by selecting 25% of those patients showing the lowest DALs (n=18), in which group we also evaluated the course of symptoms during ECT by fitting linear mixed models.

As we used seven different outcome variables, an additional Bonferroni correction was applied to the p-values of the fixed effect. Therefore, a result was considered significant if the p-value was lower than 0.0071.

# Results

## The patient population

In total, 73 patients (56 women, 17 men, 58.8(±15.1) years of age) participated in the study. The demographic and clinical details listed in Table 6-1 and show that our cohort is characterized by an uneven distribution of male and female patients and a long mean episode duration.

*Table 6-1 - Characteristics of the study population (n=73)*

| | |
|---|---|
| Age, years (mean ± SD) | 58.8 (±15.1) |
| Female n (%) | 56 (76.7) |
| Bipolar n (%) | 13 (17.8) |
| Psychotic features N (%) | 33 (45.2) |
| CORE-defined melancholia N (%) | 46 (63.0) |
| Episode duration in months<br>Mean ± SD<br>Median, range | <br>14.3 (±18.1)<br>6.5, 1-84 |
| Treatment resistant N (%) | 46 (67.6) |
| Length ECT course (mean ± SD) | 11.2 (±5.8) |
| Benzodiazepine use N (%) | 53 (72.6) |
| Diazepam equivalent dose benzodiazepine users (n=53) (mean+-SD) | 8.5(±5.9) |
| Responders to ECT N (%) | 54 (73.9) |
| Remitters after ECT N (%) | 41 (56.2) |

CORE-defined melancholia is a score of ≥ 8 on the CORE Assessment of Psychomotor Functioning (8); treatment resistance is defined as >2 failed antidepressant treatments; response = MADRS decrease ≥50%; remission = final MADRS score ≤10.

Five patients were unable to complete the course because of side effects induced by the ECT and three for reasons unrelated to the treatment. The intention-to-treat sample thus

comprised 73 and the completer sample 65 patients. In the completer sample, 74% had responded and 62% were remitted after ECT.

## Predictive value of melancholia and (change in) psychomotor functioning for ECT outcome

The patients with Mel-D (n=41 in the completer sample) had 4.9 times greater odds to achieve response than the patients with NMD (Chi-Square=7.5, p=0.0063). The odds ratio for reaching remission was 2.9 for melancholic compared to non-melancholic depression (Chi-Square=3.9, p=0.0472).

We fitted logistic regression models with each of the psychomotor variables as independent variables and response (Table 6-2) and remission (Data Supplement 6-1) as based on the MADRS as the outcome variables. The absolute change in psychomotor variables for the responders/non-responders and the remitters/non-remitters can be found in Data Supplement 6-2.

*Table 6-2 - Response-prediction values for the psychomotor variables investigated as computed by simple logistic regression analyses on the completer sample (N=65)*

| | Baseline value | | | Change first week ECT | | |
|---|---|---|---|---|---|---|
| | Unit OR (95% CI) | p-value | AUC | Unit OR (95% CI) | p-value | AUC |
| CORE Total score | 0.840 (0.740;0.953) | 0.0007 | 0.76 | 0.558 (0.386;0.806) | <.0001 | 0.84 |
| CORE Non-interactiveness | 0.777 (0.598;1.010) | 0.0224 | 0.68 | 0.715 (0.501;1.019) | 0.0328 | 0.64 |
| CORE Agitation | 0.686 (0.479;0.983) | 0.0109 | 0.74 | 0.368 (0.171;0.791) | 0.0003 | 0.75 |
| CORE Retardation | 0.796 (0.657;0.964) | 0.0077 | 0.70 | 0.579 (0.370;0.906) | 0.0057 | 0.68 |
| Daytime activity level | 1.311 (1.021;1.684) | 0.0249 | 0.76 | 0.740 (0.485;1.127) | 0.1374 | 0.64 |
| LCT Initiation Time | 0.007 (0.000;0.528) | 0.0010 | 0.78 | 0.083 (0.001;7.738) | 0.2442 | 0.58 |
| LCT Movement Time | 0.012 (0.000;0.868) | 0.0029 | 0.76 | 0.051 (0.000;9.019) | 0.2293 | 0.55 |

*Unit OR= unit odds ratio; CI = confidence interval; AUC = area under the curve; LCT = line-copying task. Bonferroni-corrected p-values < 0.0071 are considered statistically significant and displayed in blue.*

Several of the baseline psychomotor variables were associated with ECT response, with higher CORE total scores and longer ITs and MTs on the LCT corresponding to a better response. The baseline CORE subscale scores and DALs showed a nominally significant association with ECT response, but this effect was no longer significant after Bonferroni correction for multiple testing. As to change in the first week of treatment, larger reductions in the CORE total scores and more specifically in the scores on the agitation and retardation subscales were significantly associated with a beneficial final treatment outcome. These results were confirmed by the remission analyses (Data Supplement 6-1). With an AUC of 0.84 (P<0.0001) for the change in CORE total scores and trends towards significance for the changes in its subscale scores, change in the first week of treatment proved to be especially relevant.

Stepwise backward elimination of the multiple regression models including each of the psychomotor variables with a significant association to the outcomes in Table 6-2 and the presence of psychotic symptoms and benzodiazepine dose as covariates resulted in an improvement of the prediction models with the CORE total score (AUC 0.76 → 0.83 (+benzodiazepine dose)), baseline LCT IT (AUC 0.78→0.87 (+benzodiazepine dose)) and MT (AUC 0.76 → 0.89 (+benzodiazepine dose)) and change in CORE agitation (AUC 0.75 → 0.85 (+psychotic symptoms)) and retardation (AUC 0.68 → 0.81 (note that in the elimination process the psychomotor variable was removed and both covariates were included)) after one week of ECT. A more detailed description of the multiple regression models can be found in Data Supplement 6-3.

## The effect of ECT on mood and psychomotor functioning

At first sight, there is a clear improvement in mood and psychomotor functioning according to the CORE scale (Table 6-3, Figure 6-1). No obvious change is seen in the more objective measures of gross and fine motor functioning. The course of psychomotor symptoms during ECT could be masked by heterogeneity in the expression of psychomotor symptoms such as agitation and retardation. In the quartile of patients with the lowest DALs (n=18), a significant increase in activity levels was seen during the ECT course using mixed model analyses (from 1.54(±0.61) at baseline to 2.41(±1.19) counts per 2s at the end of treatment, F(54.2)=4.8, p=0.0021, Data Supplement 6-4). As a substantial proportion of the patients with the lowest activity levels had not been able to complete all line-copying items, we did not perform mixed model analyses for this task.

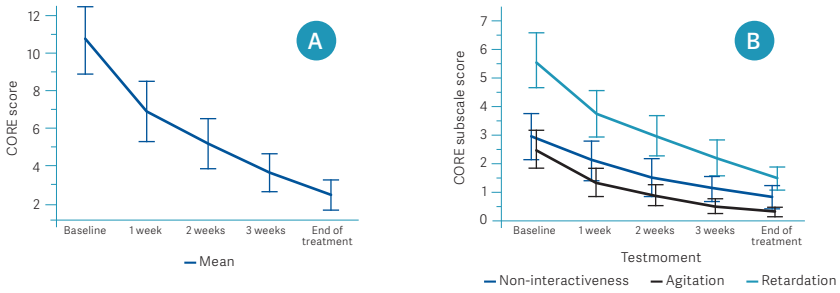
*Table 6-3 - Course of mood and psychomotor symptoms during ECT (N=73) as analysed by linear mixed models.*

| | Baseline | After 1 week | After 2 weeks | After 3 weeks | End of Treatment | Effect of time |
|---|---|---|---|---|---|---|
| MADRS | 32.82(7.40)[a] | 23.14(9.11)[b] | 18.88(9.49)[c] | 15.94(9.56)[d] | 11.15(7.30)[e] | F(4,273.0)= 117.3; p=<.0001 |
| MW DAL, counts per 2s | 3.95(2.38) | 4.06(2.46) | 3.79(2.27) | 3.86(2.10) | 4.18(2.34) | F(4,207.6)= 1.1; p=.3758 |
| LCT IT, s | 1.13(0.46) | 1.09(0.41) | 1.18(1.11) | 1.23(0.81) | 1.09(0.44) | F(4,140.2)=1.1; p=.3574 |
| MT, s | 0.63(0.44) | 0.56(0.36) | 0.64(0.62) | 0.72(0.71) | 0.65(0.39) | F(4,143.7)=0.4; p=.8118 |
| CORE total score | 10.64(7.90)[a] | 6.85(6.55)[b] | 5.07(5.70)[c] | 3.53(3.97)[cd] | 2.35(3.33)[d] | F(4,265.1)=59.7; p<.0001 |
| Non-interactiveness | 2.82(3.43)[a] | 1.99(3.02)[b] | 1.44(2.80)[bc] | 1.04(1.66)[bc] | 0.75(1.75)[c] | F(4,264.6)=15.8; p<.0001 |
| Agitation | 2.38(2.79)[a] | 1.25(2.14)[b] | 0.80(1.46)[bc] | 0.44(0.96)[c] | 0.24(0.69)[c] | F(4,268.6)=30.1; p<.0001 |
| Retardation | 5.44(4.12)[a] | 3.61(3.46)[b] | 2.86(2.99)[bc] | 2.11(2.41)[c] | 1.37(1.62)[d] | F(4,265.0)=54.0; p<.0001 |

*Value(SD). MADRS = Montgomery-Asberg Depression Rating Scale; MW DAL = MotionWatch daytime activity level; LCT= line-copying task; IT = initiation time; MT = movement time. The 1, 2 and 3-week objective psychomotor measurements were exclusively obtained in the first 50 patients entering the study (LCT: n=29-34 patients; MW DAL: n=43-50).*

*[abcde] Values that do not share the same superscript on the same line are statistically significantly different after Tukey adjustment for multiple comparisons.*

*Figure 6-1 - Effect of electroconvulsive therapy (ECT) on psychomotor functioning*




*Evolution of psychomotor function during ECT as based on the CORE total (A) and subscale scores (B). Each error bar is constructed using a 95% confidence interval of the mean.*

# Discussion

Using an observer-rated instrument (CORE) and objective measures (accelerometry and line-copying task) we investigated whether psychomotor functioning predicts ECT outcome in depressed patients and found that, as hypothesized, psychomotor disturbance as well as the presence of CORE-defined melancholia predicted a favourable outcome, as did objectively measured retardation and change in psychomotor functioning in the first week of treatment. Our analysis of the effects of ECT on (the course of) psychomotor functioning

revealed that CORE scores had clearly improved and most evidently so in the first three weeks of treatment. Daytime activity levels (DALs) only significantly increased in the patients showing the lowest baseline levels.

Our study then confirms the effectiveness of ECT in depressed patients displaying psychomotor symptoms, while our analyses show that both observer-rated and objective, electronic measures can be used in outcome prediction models. Despite the fact that part of the most severely depressed patients could not complete all elements of the line-copying task, a slower performance clearly corresponded to a beneficial treatment outcome. The most accurate prediction model we obtained was the one that had LCT movement time and benzodiazepine dose as covariates. Where two recent meta-analyses remained inconclusive due to study heterogeneity (74,120), our findings add to the knowledge on the effectiveness of ECT in Mel-D compared to NMD, and are partly in line with the results of a study (n=81) that particularly found an association between the retardation subscale of the CORE and ECT response (78), with the distinction that the baseline presence of agitation seems to play a somewhat more prominent role in our sample (AUC agitation > AUC retardation). A recent study evaluating the effect of ECT on the psychomotor functioning of an elderly population found no differences between patients with Mel-D and those with NMD (133). Taken together, finding the presence of marked psychomotor disturbances in depression to be a marker of ECT response, we venture that screening and monitoring psychomotor performance can help personalize depression treatment.

Because of their potential effects on psychomotor performance (7) and treatment outcome, mostly in anxious depression, in our prediction analyses we restricted ourselves to two well-documented covariates, i.e. psychotic symptoms (120) and benzodiazepine dose (157). As they negatively influence ECT-induced seizure duration (158), benzodiazepines were withheld at least 12 hours before each session. However, we still found that benzodiazepine dose significantly improved the prediction models for several psychomotor variables, with higher doses corresponding to better response and remission rates (Data Supplement 6-2). Arguably, benzodiazepine use in-between treatments influences depression symptoms, diminishing anxiety levels and, above all, slowing down or speeding up psychomotor functioning (in case of agitation and catatonia, respectively).

Besides this observed interdependence, the predictive effect of psychomotor functioning might also have been confounded by differences in, amongst other parameters, the responders' and non-responders' ages and depression severity. As in other studies (26,120), age evidently correlated with all the psychomotor variables, with the average age of the responders being 63, while this was 44 for the non-responders (see Data Supplement 6-2). Since at baseline no substantiated response prediction could be made, we did not match patients for age or symptom severity. Because the predictive effect of age appears to be mediated by psychomotor functioning and psychotic symptoms (132,133), we chose not to add this variable to our multiple regression models and since depression severity correlated with CORE scores, it was also not included as a covariate. The number of failed antide-

pressant treatments, or treatment resistance, and episode duration, two other known predictors of ECT outcome (74), evidently correlated and their predictive effects seems to be related to depression severity. In clinical practice, patients with very severe depression are offered ECT relatively soon, while patients with less severe symptoms are usually treated longer with various antidepressants before ECT is suggested, prolonging episode duration.

Although we found a clear improvement in post-treatment CORE scores, we found no statistically or clinically significant improvement in any of the objective psychomotor variables. As, to our knowledge, there are no other studies reporting on a longitudinal evaluation of psychomotor functioning in relation to ECT, we can only compare our results to the course of psychomotor symptoms during antidepressant trials. Meta-analyses on the subject found a positive effect of the agents on psychomotor speed (159) and daytime activity levels (160). It needs to be noted here that our sample consisted of patients without clear psychomotor symptoms, for whom no change in daily functioning was to be expected, and patients with clear retardation, agitation or both. Since a patient who has alternating periods of retardation and agitation may show the same activity levels as a patient without psychomotor disturbance, this complicates the interpretation of these values and their change. Given that the least active quartile of our patients did show a significant increase in objectively measured DALs, ECT appears to positively affect objectively measured psychomotor symptoms only when severe retardation is present. As most of the patients in this subgroup were unable to complete all assessments with the line-copying task, the effects of ECT on fine motor performance remain unclear. Overall, the psychomotor cluster is poorly understood and would benefit from novel assessment methods (161). The acute negative influence of ECT on cognitive functioning (89,90) should also be taken into account as depression-related psychomotor slowing might show subtle improvements that are masked by the transient negative ECT-induced cognitive effects. As such cognitive side effects usually resolve within two weeks after the last treatment (89), a follow-up measurement after one month could have been valuable in our study.

## Strengths and limitations

We used an extensive test battery to quantify different aspects of psychomotor functioning in depression in search of the best variables for our prediction models of ECT outcome. As far as we know this is the first study to use objective, instrument-based psychomotor measures in this context and to directly compare the outcomes of observer-rated and these electronic measures. Also novel is that, rather than looking at early changes in depression severity (122,162), we considered early changes in psychomotor functioning as a potential ECT outcome predictor.

Our study was limited in that the sample size was relatively small, which especially hampered the more complex fine-motor task as several patients were not able to finish the line-copying task because of the severity of their depressive symptoms, resulting in non-random dropout. The patients incapable of completing all LCT assessments were on

average more severely depressed (MADRS score of 39.6 vs 30.8) and showed more psychomotor symptoms (total CORE score of 19.7 vs 7.9). Therefore, there is an underrepresentation of the most severely depressed patients in our LCT analyses, which is why the results of this task should be interpreted with caution.

To conclude, we found that both CORE-defined melancholic depression and symptoms of psychomotor disturbance predict a good ECT response and remission. Particularly patients with high CORE total scores and poor fine-motor performance appear to benefit most from ECT, while a substantial reduction in CORE scores during the first week of ECT is an argument to continue the treatment as it predicted response as well as remission. The results obtained underscore the relevance of closer focus on psychomotor functioning in depression as the presence and severity of disturbances in this domain may guide treatment choices.

# Data Supplements

*Data Supplement 6-1 - Remission prediction for all psychomotor variables as computed by simple logistic regression analyses on the completer sample (n=65)*

| | Baseline value | | | Change first week | | |
|---|---|---|---|---|---|---|
| | Unit OR (CI) | p-value | AUC | Unit OR (CI) | p-value | AUC |
| CORE Total score | 0.929 (0.861;1.003) | 0.0400 | 0.66 | 0.697 (0.555;0.875) | <.0001* | 0.81 |
| CORE Non-interactiveness | 0.885 (0.747;1.048) | 0.1300 | 0.60 | 0.605 (0.413;0.887) | 0.0013* | 0.68 |
| CORE Agitation | 0.908 (0.749;1.102) | 0.3053 | 0.65 | 0.750 (0.530;1.063) | 0.0784 | 0.68 |
| CORE Retardation | 0.876 (0.759;1.011) | 0.0503 | 0.65 | 0.651 (0.452;0.937) | 0.0098 | 0.66 |
| Daytime activity level | 1.154 (0.927;1.438) | 0.1908 | 0.64 | 0.770 (0.524;1.132) | 0.1575 | 0.62 |
| LCT Initiation Time | 0.212 (0.035;1.298) | 0.0515 | 0.71 | 0.214 (0.005;8.677) | 0.4001 | 0.58 |
| LCT Movement Time | 0.227 (0.038;1.352) | 0.0632 | 0.69 | 0.011 (<0.0001;2.452) | 0.0636 | 0.63 |

*Unit OR= unit odds ratio; CI = confidence interval; AUC = area under the curve; LCT = line-copying task. Bonferroni-corrected p-values < 0.0071 are considered to be statistically significant and displayed in blue.*

*Data Supplement 6-2 – Differences in age, depression severity, treatment and baseline raw psychomotor variables for the responders/non-responders and remitters/non-remitters (n=65)*

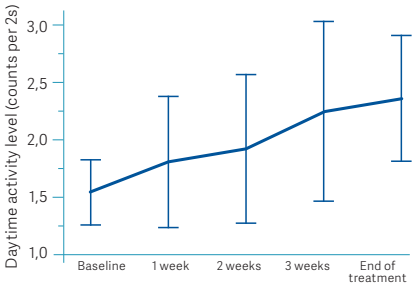
| | | MADRS Response | | MADRS Remission | |
|---|---|---|---|---|---|
| | | Nonresponders | Responders | Nonremitters | Remitters |
| Age | Mean | 44.41 | 63.31 | 49.76 | 63.75 |
| | SD | 17.12 | 11.64 | 16.80 | 12.15 |
| Baseline MADRS | Mean | 28.53 | 34.23 | 30.08 | 34.40 |
| | SD | 5.67 | 7.45 | 5.52 | 8.03 |
| CORE_Tot | Mean | 5.94 | 12.52 | 8.32 | 12.35 |
| | SD | 5.18 | 8.34 | 7.07 | 8.46 |
| CORE_NI | Mean | 1.41 | 3.40 | 2.08 | 3.38 |
| | SD | 2.29 | 3.75 | 2.91 | 3.80 |
| CORE_AG | Mean | 1.12 | 2.88 | 1.96 | 2.70 |
| | SD | 2.26 | 3.04 | 3.36 | 2.65 |
| CORE_RET | Mean | 3.41 | 6.25 | 4.28 | 6.28 |
| | SD | 2.29 | 4.48 | 3.51 | 4.45 |
| MW_DAL | Mean | 5.09 | 3.51 | 4.41 | 3.60 |
| | SD | 1.82 | 2.44 | 2.06 | 2.55 |
| LCT_IT | Mean | 0.85 | 1.23 | 0.98 | 1.23 |
| | SD | 0.17 | 0.51 | 0.37 | 0.51 |
| LCT_MT | Mean | 0.38 | 0.72 | 0.48 | 0.72 |
| | SD | 0.17 | 0.49 | 0.36 | 0.49 |
| Change CORE_tot WK1 | Mean | 0.82 | 4.85 | 1.60 | 5.18 |
| | SD | 1.63 | 4.11 | 3.06 | 3.98 |
| Change CORE_NI WK1 | Mean | -0.06 | 1.20 | -0.16 | 1.53 |
| | SD | 1.09 | 2.54 | 1.65 | 2.45 |
| Change CORE_AG WK1 | Mean | 0.06 | 1.54 | 0.68 | 1.45 |
| | SD | 0.97 | 1.86 | 2.12 | 1.48 |
| Change CORE_RET WK1 | Mean | 0.82 | 2.11 | 1.08 | 2.21 |
| | SD | 1.47 | 1.82 | 1.53 | 1.86 |
| Change MWDAL WK1 | Mean | -0.66 | 0.26 | -0.42 | 0.35 |
| | SD | 2.52 | 1.45 | 2.10 | 1.51 |
| Change LCT_IT WK1 | Mean | -0.04 | 0.05 | -0.01 | 0.05 |
| | SD | 0.12 | 0.24 | 0.22 | 0.21 |
| Change LCT_MT WK1 | Mean | -0.06 | 0.02 | -0.07 | 0.04 |
| | SD | 0.13 | 0.20 | 0.11 | 0.21 |
| Length ECT course | Mean | 13.76 | 10.38 | 13.20 | 10.05 |
| | Sd | 5.97 | 5.45 | 6.26 | 5.11 |
| Diazepam-equivalent dose | Mean | 6.43 | 8.87 | 6.99 | 9.22 |
| (benzodiazepine users only. n=47) | SD | 4.50 | 6.25 | 4.22 | 6.65 |

*Data Supplement 6-3 - Results of the stepwise backward logistic regression analyses with MADRS response as the primary outcome variable, a psychomotor variable as predictor and the presence of psychotic symptoms and benzodiazepine dose as covariates in the completer sample (n=65).*

| | | OR(95% CI)* | P-value | $\lambda^2$ | Prob> $\lambda^2$ | AUC |
|---|---|---|---|---|---|---|
| | **Baseline scores** | | | | | |
| Model 1 | Total CORE score | 0.87 (0.77-0.99) | 0.0317 | 18.27 | 0.0001 | 0.83 |
| | Benzodiazepine dose | 0.84 (0.72-0.98) | 0.0279 | | | |
| Model 2 | LCT Initiation Time | 0.02 (0.00-1.39) | 0.0707 | 18.31 | 0.0001 | 0.87 |
| | Benzodiazepine dose | 0.76 (0.59-0.97) | 0.0279 | | | |
| Model 3 | LCT Movement Time | 0.01 (0.00-0.29) | 0.0389 | 32.40 | <.0001 | 0.89 |
| | Benzodiazepine dose | 0.73 (0.57-0.94) | 0.0137 | | | |
| | **Change in the first week** | | | | | |
| Model 4 | Change CORE Agitation | 0.30 (0.12-0.73) | 0.0078 | 21.42 | <.0001 | 0.85 |
| | Psychotic symptoms [NO] | 8.66 (1.62-46.26) | 0.0116 | | | |
| Model 5** | Change CORE Retardation | removed | removed | 17.87 | 0.0002 | 0.81 |
| | Benzodiazepine dose | 0.83 (0.71-0.97) | 0.0170 | | | |
| | Psychotic symptoms [NO] | 4.78 (1.13-20.20) | 0.0334 | | | |

*AUC = area under the curve; LCT = line-copying task. *Please note, this is the unit OR (odds ratio) of the nonresponders versus the responders. ** The change in CORE retardation no longer significantly contributes to the prediction model after addition of the covariates.*

*Data Supplement 6-4 – Graph visualizing the course of the daytime activity levels during ECT in the quartile of patients with the lowest activity levels at baseline (n=18) as assessed with linear mixed models.*




| | Baseline | After 1 week | After 2 weeks | After 3 weeks | End of Treatment | Effect of time |
|---|---|---|---|---|---|---|
| | n=18 | n=13 | n=13 | n=12 | n=18 | |
| MW DAL, counts per 2s | 1.54(0.61)[a] | 1.82(1.02)[ab] | 1.94(1.16)[ab] | 2.29(1.32)[b] | 2.41(1.19)[b] | F(4,54.2)=4.8; p=.0021 |

*Value(SD). MW DAL = MotionWatch daytime activity level.*

*[ab] Values that do not share the same superscript are statistically significantly different after Tukey adjustment for multiple comparisons.*

7

# EXPLORING INTERDEPENDENCE BETWEEN PREDICTORS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Manuscript in preparation for publication:
Exploring interdependence between predictors of ECT outcome in depression.

## 7.1. Conceptual considerations

Evaluating the results of this research project, we can conclude that several clinical variables are associated with ECT outcome. At the same time, they often explained overlapping parts of the variance in outcome. Consequently, we wonder how these predictors are related to each other and to ECT outcome. In our own sample, the patients with psychotic depression (PD) were older and had more severe symptoms of depression compared to patients without psychotic symptoms. Also, they had somewhat shorter episode durations, while treatment resistance was less frequent (Chapter 5). Psychotic symptoms were almost in all cases accompanied by melancholic symptoms.

There has been much debate about the relevance of age as a factor in depression treatment, especially in relation to treatment response. In general, PD seems to be relatively prevalent in old age (163,164) and is often characterized by severe depressive symptoms (34), with ECT being considered one of the first treatment options for this population (165–167). Antidepressants seem to be less efficacious in late-life MDD (168) and we indeed found ECT to be more effective in elderly patients (Chapter 3). It is hypothesized that, rather than being a consequence of aging per se, the latter favourable response ensue from clinical factors that distinguish older from younger patients (169). In two large studies, responders were not only older but also more likely to have melancholic features, shorter episode durations and less likely to have been pharmacotherapy-resistant before starting ECT (170,171) compared to nonresponders. Furthermore, ECT responders more often suffered from psychotic depression (171). It seems reasonable to suggest that the symptom profile or depression severity is responsible for the reported differences in treatment efficacy and that the fact that older age is associated with better treatment outcome is simply a consequence of the fact that psychomotor and psychotic symptoms are more prevalent in older patients, as was recently confirmed by Heijnen *et al* (2019)(132). Their study shows that psychomotor retardation and psychotic features are strong predictors of ECT efficacy, that explain the association between age and ECT outcome.

As proposed by Parker *et al* (2000) (172) in their hierarchical model of depression, both psychomotor and psychotic symptoms can be considered markers of depression severity. Although depression severity as measured by a depression severity scale is often higher in patients with either one or both of these symptoms, this does not necessarily apply to individual patients. For example, patients with psychotic depression may be denying the presence of several of the most common depressive symptoms, generating an artificially low score on the depression severity scale. From our analyses (Chapter 5 and Chapter 6, Section 6.3), both the presence of observable psychomotor disturbance and the presence of psychotic symptoms appeared closely related to ECT outcome. Patients with observable psychomotor symptoms (CORE ≥ 8) were 4.9 times more likely to respond to treatment than

patients without such symptoms, while patients with psychotic symptoms were 6.5 times more likely to respond than patients without these symptoms.

The presence of psychomotor symptoms typifies a depressive disorder as being melancholic. The presence of psychotic symptoms defines a subtype of melancholic depression (30,173). Psychomotor symptoms are often more pronounced in patients with psychotic symptoms (173,174). Other factors that have been linked to ECT outcome (age, episode duration and resistance to antidepressant treatment) may then have their predictive effects mediated by these distinguishing elements of melancholia. As mentioned above, the prevalence of melancholic depression tends to be higher in old age and very severely depressed patients are treated with ECT relatively soon, while patients with moderate depression are usually treated with several antidepressants prior to considering ECT, prolonging episode duration. We therefore chose to extend the model proposed by Heijnen *et al* (2019) (132) by taking into account all the clinical predictors that have been relevant in past research and exploratively using more precise evaluation tools to assess the two key elements, i.e. psychomotor and psychotic symptoms, in our new model. In this conceptual model as visualized in Figure *7-1*, we suggest that ECT outcome is related to the presence of melancholia in which patients present with retardation, agitation or psychotic symptoms or a combination of the beforementioned symptoms, and that the other factors that have been linked to ECT outcome are indirect predictors whose predictive effects are mediated by the presence of melancholia.

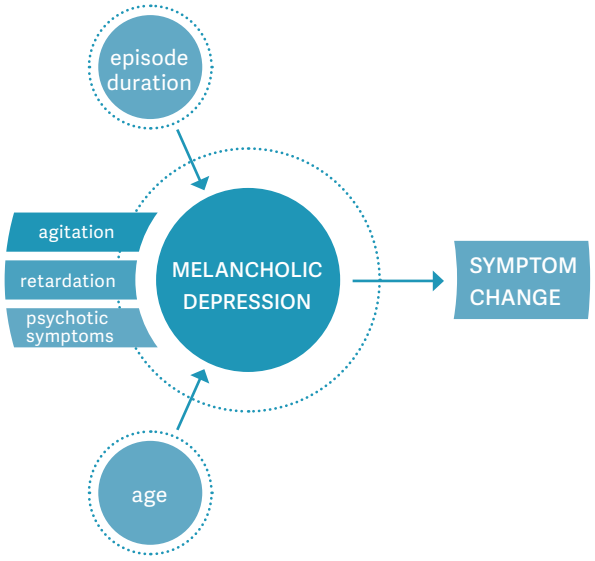


*Figure 7-1 - Predicting ECT outcome in depression: Conceptual model of predictor interdependence*

## 7.2. Methodology

For the in- and exclusion criteria and other methodological considerations of this study, we refer to the Methods section of Chapter 2.

### 7.2.1. Variables used in path-model

The outcome measure used was the decrease of the MADRS-score during treatment with ECT (either absolute or percentage). Age was used as a continuous variable. Episode duration was used as a continuous variable (in months) and coded as a dichotomous one (< 6 months (N=33) or > 6 months (N=35). Treatment resistance was also dichotomized based on if there were zero, one or two (N=22) versus more than two failed antidepressants (N=46) used in the current depressive episode. Psychotic symptoms were either classified as present or absent, but their severity was also assessed using the psychosis subscale of the Psychotic Depression Assessment Scale (PDAS). Psychomotor disturbance was assessed with the CORE assessment of psychomotor functioning and patients were classified as either melancholic or not melancholic based on a CORE cut-off of 8. Also, to get an indication of the content of the psychomotor symptoms present, the score on the CORE agitation and retardation subscale was used in the path-model.

### 7.2.2. Statistical analysis

First, Pearson or Spearman correlations were computed for variables coding for age and episode duration, treatment resistance, depressive symptomatology (i.e. psychotic features, psychomotor agitation, psychomotor retardation), and treatment outcome.

Next, to estimate the mediating role of depression symptomatology in the relationship between age / episode duration and ECT treatment effect, we constructed a path model and estimated the size and direction of all direct and indirect paths using structural equation modelling. For this purpose, we used the presence of psychotic symptoms and severity of agitation and retardation to describe depressive symptomatology to create a latent variable: melancholic depression.

Finally, by means of sensitivity analysis, we re-estimated our path model using the dichotomized variable for episode duration instead of a continuous variable, treatment resistance instead of episode duration, a dichotomous variable to code for the presence or absence of melancholia instead of two continuous variables coding for agitation and retardation, the PDAS psychosis subscale score to code for the severity of psychotic symptoms instead of the presence/absence of psychotic symptoms, and the percentage instead of absolute change in MADRS score, separately.

We used the following categories in our interpretation of the strength of the path coefficients: weak (<.2), moderate (0.2–0.5) or strong (>.5) (175). Since our model included both continuous and dichotomous variables, SEM analyses were conducted using robust weighted least squares estimation (176). The path analysis was conducted using MPlus, version 7.4 (177).

## 7.3. Results

Correlations between the variables used in the path-model can be found in Table 7-1.

| | MADRS symptom change (abs) | MADRS symptom change (perc) | Psychotic features (yes/no) | Psychotic features (PDAS - psychosis subscale score) | CORE-defined melancholic features (yes/no) | CORE retardation subscale score | CORE agitation subscale score | Age | Episode duration (months) | Episode duration (6 month split) | Therapy resistance (2 treatment split) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MADRS symptom change (abs) | 1.00 | | | | | | | | | | |
| MADRS symptom change (perc) | .85 (.07)*** | 1.00 | | | | | | | | | |
| Psychotic features (yes/no) | .58 (.10)*** | .39 (.11)** | 1.00 | | | | | | | | |
| Psychotic features (PDAS - psychosis subscale score) | .51 (.10)*** | .27 (.12)* | .77 (.08)*** | 1.00 | | | | | | | |
| CORE-defined melancholic features (yes/no) | .52 (.10)*** | .19 (.12) | .58 (.10)*** | .66 (.09) *** | 1.00 | | | | | | |
| CORE retardation subscale score | .42 (.11)*** | .26 (.12)* | .43 (.11)*** | .59 (.10)** | .67 (.09)*** | 1.00 | | | | | |
| CORE agitation subscale score | .36 (.11)** | .19 (.11) | .39 (.11)** | .44 (.11)*** | .45 (.11)*** | -.02 (.12) | 1.00 | | | | |
| Age | .43 (.11)*** | .44 (.11)*** | .34 (.11)** | .36 (.11)** | .40 (.11)** | .40 (.11)*** | .33 (.11)** | 1.00 | | | |
| Episode duration (months) | -.32 (.11)** | -.29 (.11)* | -.16 (.12) | -.04 (.12) | -.17 (.12) | -.35 (.11)** | .25 (.12)* | -.13 (.12) | 1.00 | | |
| Episode duration (6 month split) | -.34 .(12)** | -.32 (.12)** | -.18 (.12) | -.24 (.12)* | -.23 (.12) | -.33 (.12)** | -.04 (.12) | -.24 (.12) | .87 (.06)*** | 1.00 | |
| Therapy resistance (2 treatment split) | -.36 (.11)** | -.36 (.11)** | -.25 (.12)* | -.27 (.12)* | -.11 (.12) | -.25 (.12)* | -.04 (.12) | -.13 (.12) | .61 (.10)*** | .50 (.11)*** | 1.00 |
| M | 21.8 | 65.2 | Yes: 33/73 | 3.9 | Yes: 46/73 | 5.4 | 2.4 | 58.8 | 14.3 | <6: 33/68 | <2: 22/68 |
| SD | 10.3 | 24.3 | No: 40/73 | 3.0 | No: 27/73 | 4.1 | 2.8 | 15.1 | 18.1 | >6: 35/68 | >2: 46/68 |

*Table 7-1 - Correlations and standard errors of correlations, mean scores, and standard deviations of the variables in the path-model, including variables used for sensitivity analyses.*

The results of the path analysis can be found in Table 7-2 and Figure 7-2. The presence of melancholic depression was strongly associated with change in depressive symptoms. The association between age and the effect of ECT appears to be mediated by the presence of elements of melancholic depression. There is no direct association between age and the effect of ECT. Episode duration only had a direct association with ECT outcome. Sensitivity analyses supported the size and direction of the direct and indirect paths between episode duration and age and ECT outcome.

*Table 7-2 - Path model: Standardized direct and indirect effects of age, episode duration and clinical features of depression on symptom change in patients treated with ECT (N=73) resulting from SEM analysis. Significant effects are in bold script.*

| | Reduction in Depressive Symptoms | | |
|---|---|---|---|
| | Estimated | SE | p-value |
| Age | | | |
| *Direct effect* | -.14 | .19 | .479 |
| *Indirect effect* | | | |
| Age-Melancholic depression-Symptom change | **.53** | .18 | .004 |
| *Total effect* | **.39** | .09 | <.001 |
| Length of episode | | | |
| *Direct effect* | **-.38** | .08 | <.001 |
| *Indirect effect* | | | |
| Length of episode-Melancholic depression–Symptom change | .11 | .11 | .318 |
| *Total effect* | **-.27** | .08 | .001 |
| Melancholic depression | | | |
| *Direct effect* | **.84** | .17 | <.001 |

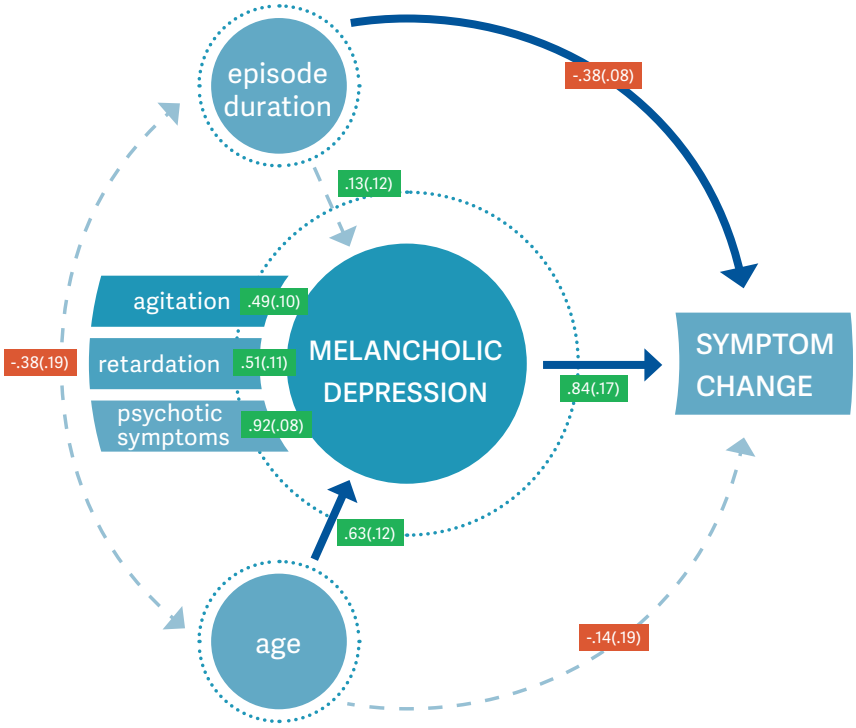


*Figure 7-2 - Path model of the relationship between age / episode duration, melancholic depression and the effect of ECT on depressive symptoms (N=73). Standardized coefficients and standard errors are reported. Significant paths ($p < 0.05$) are depicted as dark blue arrows; non-significant paths are depicted as light blue arrows. Negative associations are depicted in red, positive ones in green.*

## 7.4. Discussion

In this chapter we evaluated the interdependence of a selection of clinical predictors of ECT outcome. Although it is one of the best known predictors in the field of ECT, we found no direct predictive effect of age in our sample as it was rather indirect and mediated by the presence of symptoms of a melancholic depression, i.e. psychomotor retardation, agitation or psychotic symptoms. Episode duration, on the other hand, was directly associated with ECT response and its predictive effect was not mediated by the presence of melancholic depression.

We can only compare our model to the one recently proposed in a study conducted in The Netherlands (132). Differences between this model and ours are that we included an extra variable (episode duration) and that we grouped the psychomotor and psychotic variables

under one term: melancholic depression. In our sample, agitation significantly contributed to this concept, while its presence did not play a mediating role in the Dutch sample. An explanation could be that the measures we used were more sensitive in identifying the presence of retardation and agitation, given that Heijnen *et al* (2019) used HDRS item scores.

Opposed to what we expected, the association between episode duration and the effect of ECT was not mediated by the presence of melancholic depression. A longer episode duration can result from several factors, such as late help-seeking (178), inadequate treatment (179) or nonresponse to adequate treatment (128). The fact that a depressive disorder does not respond to a sequence of adequate medication trials might suggest that we are dealing with a treatment-resistant depression, although inadequate diagnostics (179), the presence of comorbidity (180) or other factors, such as familial, social, financial or employment issues, may have hampered recovery as well. When depressive symptoms persist, it is more likely that patients will encounter more of these additional problems, delaying or reducing the chance of recovery even further. Accordingly, we speculate that the association between episode duration and ECT response could also be mediated by factors that we did not evaluate in our present investigations. It would be interesting for future research to delineate the role of comorbidity here, with a focus on personality disorder (79, 85,181), where screening for its presence may, for example, be performed using the Standardized Assessment of Personality – Abbreviated Scale (SAPAS) (182,183). Samples should then be considerable in order to create a valid prediction model that can allow for all these variables.

The validity of our path was confirmed by the sensitivity analyses that were performed. The effects were comparable to those obtained when another outcome measure (percentage MADRS decrease instead of absolute decrease) was used. Unfortunately, dividing patients into two groups based on episode duration (more or less than 6 months) and using this more robust variable in our path model caused power problems, preventing the model from fitting all the data adequately. Although there were a few outliers in the continuous episode duration measure, the statistical model we used corrects for their presence. Because episode duration and treatment failure correlated strongly, they could not both be incorporated in our model. Replacing the one by the other did not substantially alter the associations found. Treatment failure was also directly associated with treatment outcome but had no indirect effects mediated by the presence of melancholic depression. Instead of the clinically relevant split-up between agitation and retardation, one could also use a dichotomous version of this variable to distinguish patients with and without melancholic depression. Sensitivity analyses using this rather robust dichotomous variable also did not clearly change the association found in the path models. The contribution of this variable to -melancholic depression- was comparable to that of psychotic symptoms. Using this container concept of psychomotor functioning makes the model somewhat less sensitive but somewhat more intuitive. In summary, the -shape- of the predictor used does not appear to influence the models created as sensitivity analyses showed that switching between continuous and dichotomous measures did not substantially alter the model.

To conclude, based on the results of our analysis of the interdependence of predictors (assumed to be) associated with treatment outcome, ECT can be said to be a very effective treatment option for patients suffering from melancholic depression, with the chance of a beneficial outcome being reduced in patients with longer episode durations. In this latter patient group, it would be of interest to first confirm the diagnosis of depression and, to look for comorbidity that may influence ECT outcome.

8

# THE EFFECT OF ECT ON COGNITIVE FUNCTIONING


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8.2. Evolution at an individual level 130
8.3. Discussion 134

Manuscript in preparation for publication: Short- and longer-term effects of ECT on cognitive functioning in patients with depression.

Besides the effects of ECT, we extensively evaluated cognitive functioning in our sample of depressed patients as cognitive impairment is a known side-effects of the treatment. Although efforts are made to limit the occurrence of such cognitive side effects (by using right unilateral electrode placement and limiting the number of treatments where possible), they can never be prevented completely. In this chapter we present the preliminary results on various cognitive functions following our ECT protocol.

As one would expect cognitive abilities to diminish with increasing age (184) and depression severity (91), we evaluated both factors in our sample using correlational analyses and indeed found a significant correlation between age and cognitive functioning and depression severity and cognitive functioning with higher age and higher depression severity corresponding to diminished global cognitive functioning (according to the Montreal Cognitive Assessment (MOCA)), working memory (Symbol Digit Substitution Task or SDST), and verbal memory and learning (Hopkins Verbal Learning Test – Revised (HVLT-R)). Higher age was also significantly associated with autobiographical memory problems, depression severity was not. Neither age nor depression severity correlated with subjective memory complaints.

## 8.1. Evolution of group means

In Table 8-1, the data on the course of mood and cognitive functioning can be found. Several of these variables are graphically displayed in Figure 8-1. We fitted linear mixed models to assess the effect of ECT on cognitive functioning. The subject ID was entered as a random effect and the moment of testing as a fixed effect. When a significant change over time points emerged, Tukey HSD analyses were used to assess which time points differed from each other (Table 8-1). Mood and MOCA ratings were collected for all patients. However, not all patients were able to complete the more extensive cognitive tests (HVLT-R, SDST, AMI (Autobiographical Memory Interview) and PRMQ (Prospective Retrospective Memory Questionnaire)) due to the severity of their depressive disorder (N=50 at baseline and end of treatment, N=46 at 3 months and n=41 at 6 months) that should be taken into account as selection bias. Dropout was most often due to refusal to further participate in the study.

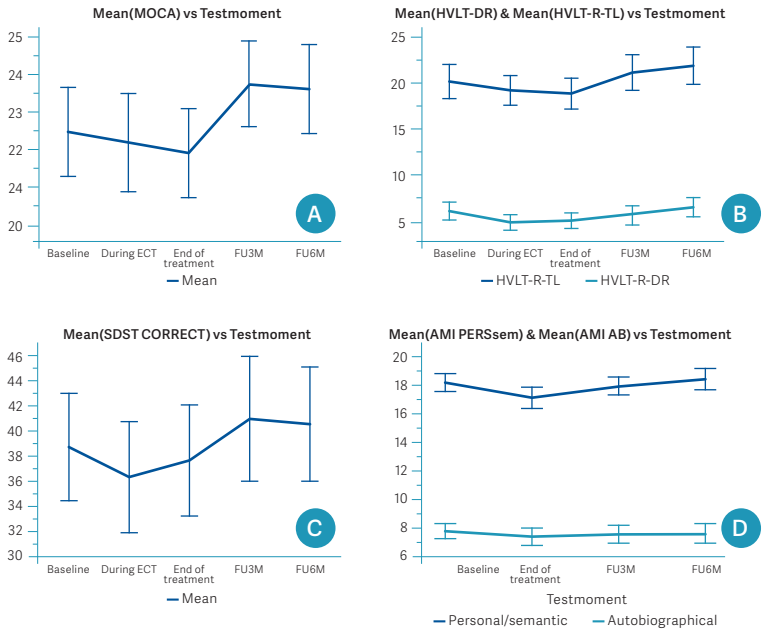
*Table 8-1 - Evolution of cognitive functioning during and after ECT in the completer sample (N=65) using linear mixed model analyses*

| | | Baseline | During* | End of treatment | FU3M | FU6M | Effect of time |
|---|---|---|---|---|---|---|---|
| | | N=65 | N=60 | N=65 | N=56 | N=51 | |
| HDRS | Mean | **24,91** | 16,75 | **7,95** | 9,19 | 9,33 | - |
| | Std Dev | **6,12** | 6,28 | **4,75** | 6,49 | 6,60 | - |
| MADRS | Mean | **32,74** | 23,30 | **10,35** | 12,23 | 13,74 | - |
| | Std Dev | **7,43** | 9,19 | **7,12** | 8,65 | 10,16 | - |
| MOCA | Mean | **22,45$^{ab}$** | 22,17$^{a}$ | **21,88$^{a}$** | 23,77$^{b}$ | 23,63$^{ab}$ | F(4,228.2)=4.3; p=0.0024 |
| | Std Dev | **4,91** | 5,24 | **4,91** | 4,44 | 4,36 | |
| HVLT-R-TL | Mean | **19,59$^{ab}$** | 18,66$^{a}$ | **18,31$^{a}$** | 20,57$^{b}$ | 21,27$^{b}$ | F(4,181)=5.6; p=0.0003 |
| | Std Dev | **6,59** | 5,59 | **5,94** | 6,42 | 6,32 | |
| HVLT-R-DR | Mean | **5,98$^{a}$** | 4,74$^{b}$ | **4,90b** | 5,52$^{ab}$ | 6,32$^{a}$ | F(4,179.4)=6.2, p=0.0001 |
| | Std Dev | **3,41** | 2,80 | **2,97** | 3,47 | 3,30 | |
| SDST (CORRECT #) | Mean | **38,41$^{a}$** | 35,85$^{b}$ | **37,29$^{ab}$** | 40,80$^{a}$ | 40,33$^{a}$ | F(4,180.2)=5.3, p=0.0004 |
| | Std Dev | **16,16** | 16,35 | **16,79** | 17,92 | 15,01 | |
| AMI part C - total score | Mean | **26,14$^{a}$** | . | **24,78b** | 25,75$^{ab}$ | 26,21$^{ab}$ | F(3,132.1)=3.1, p=0.0283 |
| | Std Dev | **3,74** | . | **4,12** | 3,47 | 3,81 | |
| AMI personal semantic | Mean | **18,39$^{a}$** | . | **17,41$^{b}$** | 18,20$^{ab}$ | 18,66$^{a}$ | F(3,131.6)=4.9, p=0.0029 |
| | Std Dev | **2,25** | . | **2,61** | 2,02 | 2,21 | |
| AMI autobiographical | Mean | **7,75** | . | **7,37** | 7,55 | 7,55 | F(3,132.3)=0.9, p=0.4380 |
| | Std Dev | **1,82** | . | **1,83** | 1,97 | 2,09 | |
| PRMQ total score | Mean | **33,31** | . | **33,15** | 32,55 | 33,16 | F(3,128.5)<0.1, p=0.9983 |
| | Std Dev | **12,68** | . | **9,36** | 10,73 | 13,72 | |
| PRMQ-prospective | Mean | **16,00** | . | **15,54** | 15,61 | 16,21 | F(3,128.3)=0.1, p=0.9442 |
| | Std Dev | **6,91** | . | **4,73** | 5,55 | 6,71 | |
| PRMQ-retrospective | Mean | **17,31** | . | **17,60** | 16,84 | 17,47 | F(3,129.0)=0.1, p=0.9379 |
| | Std Dev | **6,24** | . | **5,24** | 5,79 | 7,06 | |

*HDRS= Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MOCA = Montreal Cognitive Assessment; HVLT-R=Hopkins Verbal Learning Test – Revised; TL = total words learned; DR = delayed recall; SDST = Symbol Digit Substitution Task; AMI = Autobiographical Memory Interview; PRMQ = Prospective Retrospective Memory Questionnaire. * Measurement during ECT was performed after 1 week for MOCA and mood, after 2 weeks for the SDST and HVLT-R. $^{ab}$ Time points that do not share the same subscript are statistically significantly different after Tukey adjustment for multiple comparisons*

On average and despite an improvement in mood, we see a slight deterioration of cognitive functioning during ECT, which persists until the end of treatment, improving to levels (not significantly) above baseline at three and six months after the last treatment for most of the cognitive tests.

*Figure 8-1 - Evolution of cognitive functioning according to the MOCA (A), HVLT-R (B), SDST (C) and AMI (D) during and after ECT.*




## 8.1.1. Global cognitive functioning

Global cognitive functioning was gauged using three different versions of the MOCA to diminish learning effects. In our sample, the score at the 3-month follow-up was significantly better than the scores during ECT and at treatment completion. Compared to baseline, there was no worsening or improvement of global cognitive functioning at the group-mean level.

## 8.1.2. Verbal memory

For the assessment of verbal memory we used the HVLT-R, again using different versions, and made a distinction between total words learned (TL) and delayed recall (DR). TL was significantly higher at the 3 and 6-month follow-ups than it was during ECT and at the end of treatment (Figure *8-1* B). DR significantly deteriorated during ECT, with the deterioration persisting until the end of treatment. At six months, DR had significantly improved compared to the earlier assessments. Comparing baseline scores with those obtained six months after the acute treatment phase, we observed no significant differences in the group-mean performance on the HVLT-R.

### 8.1.3. Working memory

To assess working memory, we contrasted the correct number of digits reproduced on four different versions of the SDST. Performance scores significantly decreased during ECT but had improved to levels comparable to those recorded at baseline at both follow-up assessments (*Figure 8-1* C).

### 8.1.4. Retrograde memory

We used the last part of the AMI pertaining to recent events only, comparing a subscale score on personal/semantic memory and a subscale score more specifically reflecting autobiographical memory. The combined score was lower at treatment completion compared to baseline, which was mainly attributable to a deterioration in the score on the personal/semantic subscale. At the 6-month follow-up, the score had improved to levels comparable to the value obtained at baseline (*Figure 8-1* D).

### 8.1.5. Subjective cognitive functioning

Subjective memory problems were evaluated using the PRMQ. Neither the prospective nor the retrospective subscale scores changed significantly during and after ECT or follow-up.

Note that all the above analyses are preliminary and did not account for potential influencing of confounders such as age, baseline depression severity, presence/absence of melancholia or psychotic symptoms, electrode position, ECT treatment during the follow-up period or such other factors.

## 8.2. Evolution at an individual level

A recent study in patients with late-life depression pointed out that there are considerable differences in the effects of ECT on cognitive functioning at the individual level and further study is recommended to identify patients at high risk of cognitive side effects (185). We therefore also evaluated individual changes in cognitive functioning using the reliable change index (RCI) (186), which indicates whether a change in score is significantly greater than could be expected based on test-retest reliability. We used a 90% confidence-interval, meaning that RCI values of 1.645 or higher were considered statistically significantly different. RCIs were calculated according to Jacobson and Truax (187): RCI = (retest score - test score) / SE (standard error). The SE was calculated using the variance in baseline scores of a control sample and the reliability of the test extracted from papers on psychometric properties of the relevant cognitive tests (i.e. MOCA (188), SDST (189,190), HVLT-R (191), PRMQ (192)). No normative data for part C of the AMI were found. When the scores of the control group differed substantially from those of our clinical sample (which was the case for the

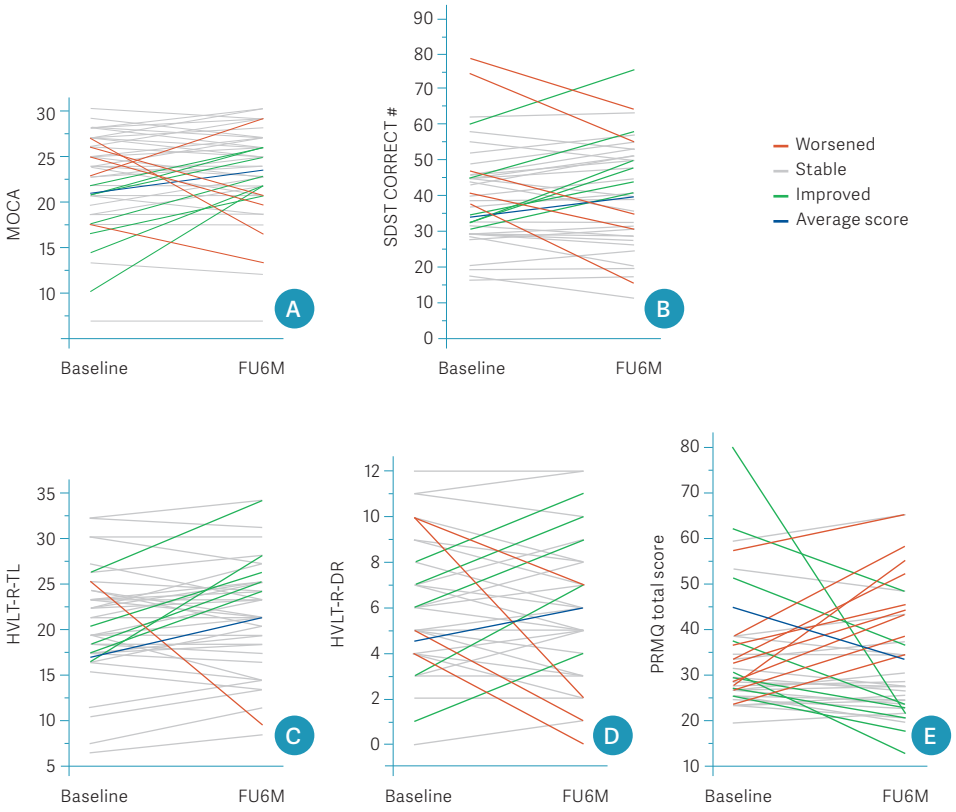
MOCA), we used the variance in baseline scores of our own sample. Results of the RCI analyses for each of the outcome variables at different time points can be found in Table 8-2 and the visualization of RCI analyses at the 6-month follow-up in Figure 8-2.

*Table 8-2 - Effect of ECT on cognitive functioning on an individual level.*

| | During | End of treatment | FU3M | FU6M |
|---|---|---|---|---|
| **MOCA** | | | | |
| Worsened | 13 | 17 | 3 | 4 |
| Stable | 41 | 40 | 44 | 38 |
| Improved | 6 | 8 | 9 | 9 |
| **SDST** | | | | |
| Worsened | 11 | 6 | 4 | 5 |
| Stable | 36 | 40 | 36 | 28 |
| Improved | 1 | 5 | 6 | 6 |
| **HVLT-R-TL** | | | | |
| Worsened | 10 | 11 | 3 | 1 |
| Stable | 36 | 36 | 38 | 35 |
| Improved | 1 | 4 | 5 | 5 |
| **HVLT-R-DR** | | | | |
| Worsened | 15 | 11 | 9 | 4 |
| Stable | 27 | 35 | 32 | 31 |
| Improved | 5 | 3 | 5 | 6 |
| **PRMQ_TOT** | | | | |
| Worsened | | 12 | 10 | 9 |
| Stable | | 26 | 27 | 20 |
| Improved | | 9 | 6 | 8 |

*Number of participants who worsened, remained stable or improved on the cognitive tasks compared to baseline according to the Reliable Change Index at the four time points.*

*Figure 8-2 - Effect of ECT on long-term cognitive functioning per-patient.*




*Patients with worsened (red), stable (grey) and improved (green) cognitive performance on the MOCA (A), SDST (B), HVLT-R (C and D) and PRMQ (E) based on the Reliable Change Index (between baseline and 6 months post-ECT). The average score is also displayed (blue).*

During ECT and at the end of treatment, we see a worsening of cognitive functioning in a substantial part of the patients on almost all of the cognitive (sub)tests. As can be seen in the Table 8-2 and its graphical representation, the scores of most of the patients are stable at six months compared to the baseline values. Thus, although we found no significant differences at the group-mean level between these time points, we did find differences at the individual level. Global cognitive functioning (as measured with the MOCA) had improved in about 20% of our patients (N=9), while 10% (N=4) performed significantly worse at six months compared to baseline. Looking at working memory (SDST), we see approximately 15% of the patients improving (N=6) and an equally great part deteriorating (N=5). The effect of ECT on verbal learning (HVLT-R) differs depending on the outcome measure used. In only

one patient (2%) the total number of words learned had dropped at the 6-month follow-up, while it had improved in 12% (N=5), with delayed recall being poorer in 10% (N=4) and improved in 15% (N=6). Eight patients report significantly more memory problems six months after ECT compared to baseline while another nine describe significantly less memory problems.

### 8.2.1. The deteriorators – Who are they?

As we deemed it clinically most relevant, we grouped patients whose performance had deteriorated at two or more time points on one or more of the cognitive (sub)tests (MOCA, SDST, HVLT-R TL and DR, N=27) and created a subgroup within this group whose performance was also poorer at at least one of the two follow-up assessments (N=13). The differences between the patient groups with and without clear worsening of cognitive functions can be found in Table 8-3.

*Table 8-3 - Differences between patients with and without clear cognitive decline during and after ECT*

| | | Worsening ≥ 2 time points | | | Worsening ≥ 2 time points (at least 1 at follow-up) | | |
|---|---|---|---|---|---|---|---|
| | | NO | YES | | NO | YES | |
| **N** | | **38** | **27** | | **52** | **13** | |
| Age | Mean | 62,79 | 52,15 | F-Ratio = 8.19; P=0.0057 | 59,65 | 53,23 | NS |
| | SD | 14,23 | 15,52 | | 14,89 | 17,81 | |
| HDRS_TOT | Mean | 26,13 | 23,19 | NS | 25,65 | 21,92 | F-Ratio = 4.06; P=0.0483 |
| | SD | 6,35 | 5,42 | | 6,23 | 4,72 | |
| MADRS | Mean | 33,95 | 31,04 | NS | 33,50 | 29,69 | NS |
| | SD | 7,33 | 7,36 | | 7,23 | 7,73 | |
| MOCA | Mean | 20,92 | 24,59 | F=10.07; P=0.0023 | 21,96 | 24,38 | NS |
| | SD | 5,27 | 3,42 | | 5,08 | 3,71 | |
| **Psychotic** | | | | | | | |
| No | | 17(26.2%) | 17(26.2%) | NS | 22(33.9%) | 12(18.5%)) | $X^2$ = 12.07; P=0.0012 |
| Yes | | 21(32.3%) | 10(15.4%) | | 30(46.2%) | 1(1.5%) | |
| **Melancholic** | | | | | | | |
| No | | 12(18.5%) | 12(18.5%) | NS | 15(23.1%) | 9(13.9%) | $X^2$ = 7.28; P=0.0070 |
| Yes | | 26(40.0%) | 15(23.0%) | | 37(56.9%) | 4(6.2%) | |

*HDRS= Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MOCA = Montreal Cognitive Assessment; NS = not significant.*

The patients experiencing a detrimental effect of ECT on their cognitive functioning are somewhat younger than those without such clear effects. Also, according to the HDRS, they are somewhat less severely depressed and showed better baseline cognitive functioning. Interestingly, the patients with melancholic depression (N=4/41) and those with psychotic symptoms (N=1/31) seldom showed clear cognitive impairment at follow-up as a consequence of the ECT.

### 8.2.2. Summary of the cognitive analysis results

Having conducted exploratory analyses of mean cognitive functioning during and after ECT, we see a negative effect on global cognitive functioning, working memory, verbal memory and personal semantic memory during the course and at treatment completion at the group level. However, at the 3 and the 6-month follow-up, all mean performance scores had returned to baseline values.

At the individual level, we found patients both improving and deteriorating on each test, with those experiencing memory problems often showing a somewhat higher baseline cognitive performance (MOCA), being relatively younger and less severely depressed than those not experiencing a clear worsening of their cognitive skills, while they seldom have melancholic or psychotic features.

## 8.3. Discussion

Our group means of cognitive functioning during and after a treatment course of ECT are in line with the findings of a meta-analysis on ECT-related objective cognitive performance, where acute anterograde amnesia was observed during and one week after ECT, with memory functions recovering in the follow-up period (89). We likewise found no evidence of persistent cognitive dysfunction at the group level but would like to nuance previous and our findings. As major depression has a known negative influence on cognitive functioning (91), one could argue that any baseline assessment will reflect only -depressed- cognitive abilities. Poor performance at follow up could then be considered to indicate persistent cognitive dysfunction, not compared to baseline but compared to predepression functioning. With mood improving, cognitive functioning is also expected to improve, whereas we saw a status quo in the longer term. Here,  and although a comparable study to ours in older patients found no such relationship, analyses separating responders from nonresponders could be valuable to clarify if this status-quo effect is a consequence of the heterogeneity in the change in mood (185). If we cannot show improvement in cognitive functioning in ECT responders, it is possible that the treatment has longer-lasting side effects that may be masked by improvements coinciding with improvements in mood. Another explanation could be that functional impairment after recovery from depression is a pre-existing vulnerability (193).

9

# GENERAL DISCUSSION

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# 9.1. Main findings

## 9.1.1. Clinical predictors of ECT outcome: contribution of the literature

In a comprehensive literature review and meta-analysis evaluating clinical predictors of response and remission to ECT in depression, we found evidence suggesting superior efficacy of ECT in patients with psychotic (and correspondingly more severe) depression and in older patients, whereas the data reported for melancholic symptoms were inconclusive (**Chapter 3**). However, effect sizes of our meta-analyses were small, suggesting that relying on clinical indicators for response prediction alone may be ill-advised and/or that in past studies the predictors were not applied optimally.

## 9.1.2. Clinical predictors of ECT outcome: results of our study

To find out how we can best use clinical predictors of ECT response, we conducted a longitudinal study. A thorough baseline evaluation and follow-up of 73 patients treated with ECT enabled us to assess the value of several of these predictors.

In **Chapter 4**, the focus is on the predictive value of treatment resistance, which factor we evaluated with an instrument called the Maudsley Staging Method (MSM). We opted for this instrument as we deemed it to have great potential for implementation in clinical practice because of its ease of use. On top of that, it comprises three elements (episode duration, prior antidepressant regimens, depression severity) that have been associated with a beneficial ECT outcome. All of the presumed associations with response to ECT, i.e. shorter episode duration, limited number of failed antidepressant treatments and more severe depressive symptoms, were confirmed in our sample. Shorter episode duration most consistently predicted a larger treatment effect in depressed patients. The number of failed antidepressants did not significantly improve the prediction models that already included data on episode duration because these variables correlated strongly ($r = 0.56$, $P < 0.001$). Depression severity did improve the accuracy of the prediction models tested. A composite score of episode duration and depression severity, the two strongest MSM factors, was constructed (adapted MSM) and compared to the predictive effect of the total original MSM score. The adapted MSM was indeed an improvement. To increase the accuracy of our ECT response prediction model even further, age was categorized and added as a third variable to the adapted MSM, with older age corresponding to a better ECT outcome. The most accurate prediction model including episode duration, depression severity and age as created with the MSM had an AUC of 0.77.

In **Chapter 5,** we compared the predictive capacity of the mere presence/absence of psychotic symptoms to the predictive capacity of the severity of symptoms of psychotic depression as gauged with the Psychotic Depression Assessment Scale (PDAS) and found the presence of psychotic symptoms and higher PDAS scores to be associated with better

treatment outcome. Contrary to our expectations, we found no advantage of the PDAS score over the mere presence/absence of psychotic symptoms although this may be attributable to a ceiling effect given the extremely high response and remission rates for the subgroup of patients with psychotic depression. Incorporating all relevant covariates (the presence of psychotic symptoms, higher age and greater depression severity) in the analyses, the best prediction model rendered an AUC of 0.87.

The focus in **Chapter 6** is on psychomotor symptoms. The presence of marked psychomotor retardation or agitation is an important feature of major depressive disorder and can play a role in specifying a depressive episode as melancholic depression (Mel-D)(1,172). Due to the heterogeneity in the studies we reviewed, it is not yet confirmed that the presence of Mel-D is a predictor of ECT outcome (Chapter 3). Looking for the most suitable instrument to use in models predicting ECT response (section 6.1, section 6.2), we employed several ways to measure psychomotor functioning and found significant differences in daytime activity levels (DALs) between patients with Mel-D (score ≥ 8 on the CORE assessment of psychomotor functioning) and those with non-melancholic depression (NMD). According to our analyses, a DAL of 3.35 counts per 2 seconds was the best cut-off point, with a sensitivity of 72% and specificity of 91%. Unlike what one would expect, the group difference in DALs was most obvious in the afternoon and evening and not in the morning. The results on a line-copying task (LCT) demonstrated that the performance of the patients with Mel-D was also slower than that of the patients with NMD, but these differences were not significant after correction for age and multiple comparisons.

Looking at the predictive effect of the psychomotor variables, we uncovered that patients with (CORE-defined) melancholic depression were 4.9 times more likely to respond to treatment with ECT than patients with NMD (section 6.3). The total CORE score also adequately predicted treatment response. In fact, all of the psychomotor variables (higher CORE scores, lower DALs, slow performance on the LCT) were associated with the response to ECT, albeit that some of these variables did not survive Bonferroni correction. Also, improvement in psychomotor functioning in the first week of treatment preceded a clinically beneficial treatment outcome. Particularly the change in CORE total score and its agitation and retardation subscale scores proved to be useful in this respect. Multivariate regression analyses with baseline fine motor performance (LCT movement time) and benzodiazepine dose as covariates produced the best prediction model (AUC 0.89).

### 9.1.3. Clinical predictors of ECT outcome: interdependence investigated

Looking back at the analyses of this project, we can conclude that several clinical variables were associated with ECT outcome. At the same time, they often explained overlapping parts of the variance in treatment response. Inspired by a recent study that showed that age has its predictive effect via other clinical variables such as psychomotor retardation and psychotic symptoms (132), in the study reported on in **Chapter 7** we evaluated the inter-

dependence between the different variables in our own sample.

Although it is one of the best known predictors in the field of ECT, we found no direct predictive effect of age in our sample; it rather was indirect and mediated by the presence of symptoms of melancholic depression: psychomotor retardation, agitation and psychotic symptoms. Episode duration and treatment resistance were directly associated with ECT outcome and their predictive effects were not mediated by the presence of melancholic depression.

ECT outcome then seems to be related to the presence of melancholic depression. Episode duration appeared more directly associated with ECT outcome, but its predictive effect may be mediated by other factors not accounted for in our model, such as the presence of a personality disorder.

### 9.1.4. Side-effects of ECT: do they persist?

Alongside the desired effects of ECT, we evaluated reported side effects of the treatment. These exploratory analyses presented in **Chapter 8** showed acute anterograde amnesia during and immediately after the ECT course but recovering memory function in the follow-up period (up to six months). Our results are in line with those reported in the current literature on the subject (89). No persistent objective cognitive dysfunction could be confirmed at the group (means) level. Looking at the course in individual patients using RCI analyses, however, we observed clear heterogeneity in the effect of ECT on their cognitive functioning, with some patients improving and others significantly deteriorating during treatment. The patients experiencing memory problems often had somewhat higher baseline cognitive abilities, were relatively younger and less severely depressed than the patients not showing a clear worsening in the cognitive functions assessed. Additionally, they seldom showed melancholic or psychotic features.

## 9.2. Discussion of the main findings

The results of our meta-analysis reported in **Chapter 3** differed slightly from those of a meta-analysis on the same subject performed three years earlier (74). Whereas we found a convincing predictive effect of the factors age and psychotic symptoms, in the earlier meta-analysis these predictors were only weakly associated with ECT outcome. Moreover, although we found a predictive effect of depression severity, Haq *et al* (74) concluded the evidence on this aspect to be inconclusive. This difference could be explained by the fact that in our meta-analysis we probably analysed a more homogeneous sample that facilitated detection of significant differences, as we retrieved unpublished data from 21 authors and separated studies that used response and remission as outcome measures. The two meta-analyses agreed that the evidence on the predictive capacity of melancholic symptoms was inconclusive because the number and size of datasets were too small and given heterogeneity between the studies.

### 9.2.1. How should we use clinical predictors of ECT response?

In our first paper on predictors of ECT outcome (**Chapter 4**), we focused on the complex concept of treatment resistance. As, up to now, there is no consensus on the exact definition of the concept (83,194), we chose the MSM since the method gauges a continuum of treatment resistance. We preferred this model over considering treatment resistance to be an all-or-nothing phenomenon. The MSM reflects the complexity of treatment-resistant depression without the disadvantages of hierarchical staging models such as the Thase and Rush model (195) that assumes that treatment prior to ECT follows a certain protocol sequence although in clinical practice treatment is always patient-specific (84).

The fact that with our study we found evidence supporting the effectiveness of ECT especially for the most severely depressed and urgent patients is not in agreement with the findings of the original MSM report (84) in which severer depressive symptoms significantly lowered patients' chances of remission. It is important to note here that the original study measured treatment outcome at discharge after administration of a variety of treatments while in our study we exclusively investigated the effect of ECT. Given that one of our inclusion criteria was a baseline HDRS score ≥ 17, our sample comprised a select group of more severely depressed and urgent patients and thus did not reflect the entire spectrum of depression severity. Furthermore, patients with a severe depressive disorder relatively often have psychotic symptoms, as was the case in our sample, who have been reported to show a remarkably good response to ECT (120). Depression severity as established with the adapted MSM we created was therefore the reverse of the original MSM, with lower scores reflecting lower treatment resistance and greater chances of a good ECT response. It is remarkable that treatment resistance as defined by our adapted MSM is determined by depression severity and episode duration, and that the number of failed antidepressant treatments (often used as a stand-alone indicator of treatment resistance) appear to be redundant when data on the other two aspects are available.

Another point worth discussing is the fact that within the clinical or research context it is often not feasible to reconstruct a patient's exact treatment history and episode duration. Since some of these relevant data are difficult to retrieve from the medical files, we often need to rely on the memory of the patient or family members. Here, the categories as used in the MSM increase the reliability of these recollected data, which benefits both researchers and clinical practitioners.

The adapted MSM we compiled can be efficiently used in clinical practice to explore a combination of variables related to ECT response. And although the total adapted MSM score gives an indication of the probability of a beneficial ECT outcome, we, of course, do not recommend to base patient-treatment matching exclusively on the outcomes of this instrument. As our series of investigations have shown, it remains important to also consider data on other aspects of depression, such as psychomotor functioning or the presence of a personality disorder, if available.

We were puzzled by the fact that we found no advantage of the PDAS total score over the dichotomous predictor 'presence/absence of psychotic symptoms' (**Chapter 5**), even though this lack may be explained by a ceiling effect given that ECT was extremely effective in patients with psychotic depression. One could also argue that the PDAS total score does not merely reflect the severity of psychotic symptoms as it also quantifies depressive symptoms. Still, the depression subscale does include items on guilt, anxiety and hopelessness, for instance, which are frequently related to the content of a patient's delusions; to us, these seemed to be clinically relevant indicators, justifying the use of the scale's total score for our analyses. Although, theoretically, the PDAS makes a clear distinction between symptoms of depression and psychosis, in practice this distinction was less apparent. We nevertheless consider the PDAS to have great potential for use in ECT research and clinical practice because the scale proved sensitive to ECT-induced change in patients with psychotic depression as well as those without psychotic symptoms. Its depression subscale has clinimetric properties superior to those of both the HDRS17 and the MADRS (196). Also, general depression scales such as the HDRS and the MADRS only capture a fraction of the psychotic symptoms in this patient population (82), another argument in favour of the PDAS. The fact that the predictive effect of psychotic symptoms was so convincing, stresses the importance of this symptom cluster, which is not always recognized in clinical practice (130).

Opting for a clinician-rated assessment of psychomotor functioning, the CORE, to distinguish between patients with Mel-D and NMD (**Chapter 6**) seemed reasonable (32) given the biological differences found between the CORE-based diagnoses of Mel-D and NMD (142). It has the advantage that it captures both retardation and agitation, while the objective measures we used in our study seemed to mainly capture retardation (section 6.2), which is in line with previous reports on the topic (13,108). We pose that minor cognitive and fine motor deficits are components that are better detected by objective, electronic tools than by observer-rated measurements. Subtle psychomotor impairments that could escape the clinician's eye can best be captured by a digitized task gauging specific elements of fine motor performance.

Agitation proved to be an aspect of psychomotor functioning that is much harder to capture with objective methods or instruments as it frequently is more episodic and not always present at the time of observation. Moreover, agitation often occurs alongside retardation, complicating its detection. As both retardation and agitation can be indicative of Mel-D, we underscore the need to look for both phenomena. Although we found the presence of both expressions of psychomotor disturbance to be associated with ECT outcome (section 6.3), we still recommend to make a distinction between patients displaying retardation alone and those with (superimposed or sole) agitation since the latter group presents diagnostical as well as clinical challenges (197). Are patients with agitated depression bipolar or unipolar? There is evidence in support of both hypotheses. According to some, agitated depression is a mixed state and patients should accordingly be classified as pseudo-unipolar (197–199). However, others claim that agitated depression is no more fre-

quently bipolar than retarded depression and pure agitated depression even less frequently bipolar than unipolar (200). Our clinical experience is in line with this last hypothesis. Irrespective of the underlying diagnosis, there seems to be consensus on the fact that agitated depression poses a greater suicide risk and that treatment for this group of patients asks for a special approach given that antidepressants alone could worsen the symptoms and increase agitation (199,201), supporting the arguments in favour of early consideration of ECT. Additionally, early adequate treatment of patients with agitated depression is of the greatest relevance because the clinical subtype is also known for its rather negative long-term prognosis (202,203).

Based on previous and our findings, we suggest using a combination of instruments to assess psychomotor functioning. Retardation can best be captured by the CORE retardation subscale, by actigraphy and drawing tasks. The CORE agitation subscale seems to best reflect its presence and severity. Still, as alluded to above, in view of its clinical and therapeutic significance and given its more episodic nature, the identification and quantification of agitation warrants more or prolonged attention.

Our psychomotor analyses (section 6.3) showed that electronic as well as observer-rated measures can be used in prediction models. The study also adds to the knowledge on the efficacy of ECT in Mel-D compared to NMD, where two recent meta-analyses remained inconclusive due to study heterogeneity (74) (**Chapter 3**). Our results partly coincide with those of a study (N=81) that particularly found an association between the CORE retardation subscale and ECT response (78), although the presence of agitation at baseline seemed to play a somewhat greater role in our sample. A recent study evaluating ECT outcome based on psychomotor functioning in an elderly population found no differences between patients with Mel-D and NMD (133), but this could be due to underpowering as only 19.4% of the population had an NMD diagnosis.

### 9.2.2. Understanding the interdependence of predictors

As confirmed by our path analyses (**Chapter 7**), it is not because patients are older that they respond better to ECT, it is because these older patients more often suffer from psychotic depression and CORE-defined melancholia than younger patients do. Comparing our model to the only other comparable model that was recently proposed in a Dutch study (132), we can note two differences: we included episode duration as an additional variable and clustered the psychomotor and psychotic variables under the term melancholic depression. In our patients, agitation significantly contributed to the notion of melancholic depression, while agitation did not mediate response in the sample of our Dutch colleagues, which may result from our use of more sensitive measures to identify the presence of retardation and agitation, where Heijnen et al (2019) used HDRS item scores only.

Refuting our hypothesis, the association between episode duration and ECT response was not mediated by melancholic depression but may be by other factors not investigated, such

as comorbidity or other personal and socioeconomic aspects impeding recovery, for instance relational, social, financial or employment problems, since patients with longer-term depression are more likely to also be faced with such additional issues, further reducing their chances of recovery. It would be informative if new research were to evaluate the mediating role of comorbidity, particularly the role of personality disorders, where the Standardized Assessment of Personality – Abbreviated Scale (SAPAS) (182,183) could be used to screen for their presence.

Sensitivity analyses confirmed that the associations in the path model we created were independent of the -shape- of the predictor used, given that replacing continuous by dichotomous versions of the variables did not substantially alter the model.

Based on the results presented in this doctoral thesis, we recommend treatment with ECT if factors inherent to melancholic depression, i.e. psychomotor retardation and/or agitation and psychotic symptoms are present since we found them to be key predictors of treatment outcome. Finding age to only have an indirect influence, we think it should not be given too much weight. Patients not responding (well) to ECT are often those coping with more chronic depressions with less severe symptoms and, sometimes, a personality disorder, which latter factor appears to have a negative impact on the outcome of all forms of depression treatment (85,204). Recent unpublished research (205) using the abovementioned SAPAS (182,183) to screen for personality disorders showed promising results. Using a cut-off score of 3 to indicate a likely underlying personality disorder, the authors found clear differences in the treatment outcomes of patients above and below this threshold, with the patients not meeting the SAPAS threshold having a 5.7 times larger odds of responding to ECT than those scoring above the cut-off limit (205). As we did not systematically assess the presence of personality disorders prior to initiating ECT in our naturalistic study, it is impossible to say anything meaningful about their potential role in our sample.

Our proposal to focus on the depressive disorder rather than on related factors is consistent with the EAS, the ECT appropriateness scale, proposed by Kellner *et al* (2012)(206), which gauges the severity, heritability (207) and episodic nature of the depression, all aspects related to a type of depression with a biological aetiology, although the approach we suggest is somewhat different in that we put the focus on identifying two factors related to depression severity, namely the presence of psychomotor disturbance and psychotic symptoms.

### 9.2.3. Why do patients with melancholic depression respond better to ECT?

In an extremely simplified interpretation of the neurotrophic hypothesis of depression, stress disrupts neuroplasticity, resulting in a dysfunctioning of several essential brain structures such as the hippocampus and amygdala. Dysfunctions in these structures hamper the control over the HPA-axis and higher cortisol levels limit BDNF expression

(62,208,209). Treatment of depression with antidepressants (210,211), lithium (212) or ECT (213) seems to have beneficial neurotrophic effects by increasing BDNF levels (64, 67,214), resulting in enhanced neuroplasticity (65) and restored control over the HPA-axis. The superior effect of ECT over other treatment methods (43) could be explained by the fact that ECT is a more potent stimulator of neuroplasticity (213), with increased cell proliferation (2.5- to 4-fold vs 1.5-fold) and a relatively abrupt start of this neurogenic process (3 days after a single seizure) compared to antidepressants (2-3 weeks) (215–217).

The stress-regulation system of patients with melancholic depression seems to be more severely disturbed than it is in patients without symptoms indicative of melancholic depression (73, 143,218), which, so it seems, 'leaves more room for improvement'. Patients without melancholic and psychotic symptoms often have the more reactive depressive disorders or are the more treatment resistant, showing a chronic course of symptoms sometimes complicated by the presence of a personality disorder. We then posit that melancholic depression is the purest biological expression of all depressive disorders and that patients suffering from the syndrome can be expected to optimally benefit from ECT, the most direct and powerful of treatments.

10

# CLINICAL IMPLICATIONS AND RESEARCH PERSPECTIVES

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## 10.1. Clinical implications

The identification of reliable predictors of ECT response can contribute to a more targeted patient selection, enhancing outcomes and remission rates and thereby limiting the burden of depression for both the patient and society. Since a more accurate patient-treatment matching lies in practical clinician- and patient-friendly assessment tools, we evaluated the predictive capacity of several easy-to-assess clinical variables. In view of the current need of budget cuts in health care and the severity of the pathology in the patient populations treated with ECT, low-cost and quick assessment strategies are preferred over expensive and more invasive testing.

This research project has shown that ECT response can to a rather large extent be predicted by a combination of easily assessed clinical variables. In patients with major depression, antidepressants will generally be considered the treatment of choice. When antidepressant regimens do not work (sufficiently) (165,166) and when a rapid response is required (76) or when a patient fulfils certain criteria as explained below, ECT may be suggested. Based on our results, we can expect positive results particularly in patients suffering from melancholic depression either with or without psychotic symptoms. Apart from being severely depressed, these patients present with psychomotor retardation or agitation (or both). Up to now, current treatment guidelines for psychotic depression (PD) are highly diverse, with some recommending antidepressant-antipsychotic combination therapy, others antidepressant monotherapy, while in some ECT is considered equally appropriate as a first-line treatment (119)). Based on our studies we would suggest to recommend ECT as a first-line treatment in all PD treatment guidelines. Additionally, we recommend screening patients for psychomotor disturbance, suggesting that in cases of observable psychomotor agitation and/or retardation ECT should also be considered as a first-line treatment option. When we do not consider ECT at an earlier stage in these cases, we consign severely depressed patients to less effective treatments and the risk of prolonged illness. Especially in patients with a relatively long episode duration and a high number of failed antidepressant treatments, we recommend a more expectant policy, where, while reconfirming the diagnosis, comorbidity with a potential influence on ECT outcome is carefully screened for, as well as other factors that could diminish ECT response, such as the patient's family, social, employment and financial status. If the diagnosis is established and no relevant comorbidity or other issues potentially affecting treatment outcome are found, there is no reason to withhold ECT from these patients. However, when one or more features indicative of melancholic depression are present, we propose not to let episode duration guide the treatment decision. Moreover, although the chances of a good response are likely to be lower in patients not fulfilling the criteria of melancholic depression, that is those without signs of psychomotor or psychotic symptoms, we do not discourage the use of ECT since in our trial, for instance, 20% of the patients with the longest episode duration and symptoms of moderate depression still reached remission following their ECT course. So, overall, ECT might be the best treatment option also for individuals suffering from persistent MDD especially when other guideline treatments have failed.

An accurate prediction of the efficacy of ECT for depression will facilitate the shared treatment-decision making process. For some patients it may prevent a detrimental delay in effective treatment and for others exposure to needless (cognitive) side effects. Because of its limited availability, ECT may at present not be used as frequently as it actually could (219,220). Besides reliable methods to arrive at a sound indication for ECT, this could be one of the hurdles impeding an optimal usage of the treatment. From a health-economical point-of-view, it seems reasonable to increase ECT availability and its usage as it is not only a clinically effective but also a cost-effective treatment (221).

To summarize, as we found ECT to be most effective in these patients, we propose that ECT should be considered as a first-line treatment when depressed patients have concurrent psychotic symptoms or a high CORE score (8 or higher) implying either the presence of retardation or agitation or both. Our recommendation is supported by our finding that these patients experience the least amount of cognitive side effects from the treatment.

## 10.2. Future research perspectives

In our meta-analysis we found and scrutinized many (often) small-scale studies reporting on (some of the) factors that are known to be relevant with respect to ECT efficacy. Larger studies that investigate all of the relevant predictors identified so far could be valuable to confirm the interdependence we found in our path model. It therefore remains pertinent to continue collecting simple, quantifiable clinical variables on a large scale to enable us to compare (combinations of) specific predictors in more homogeneous groups of patients. We recommend assessing the severity of psychomotor symptoms by means of the CORE, as this symptom cluster is still poorly understood and underinvestigated, while replication of our results on the predictive effect of psychomotor disturbance would be most valuable. As actigraphy and drawing tasks do not seem to capture all aspects of psychomotor disturbance as defined by the CORE, we look forward to the research domain criteria (RDoC – a research framework for investigating and understanding mental disorders) that will soon include a motor domain to provide a framework for studying motor dysfunction in mood disorders (161). Given its potential in specifying the diagnosis of depression, we think it is worth investigating the predictive capacity of psychomotor disturbance in other disorders as well, for instance in schizophrenia (222).

Besides these clinical predictors, we deem it useful to also screen for the presence of personality disorders (85) in future research, while, given that clinically adequate seizures appear to coincide with better ECT outcomes (60), the quality of the induced convulsions (based, among other factors, on wave amplitude and hemispheric brain wave synchronicity) also merits closer attention. New research focusing on a combination of clinical and biological predictors would also be valuable, where we see potential in structural (70) and functional MRI data (71) and the monitoring of cortisol (73) and inflammation, more specifically, IL-6 (223).

# SUMMARY

Finding the most effective treatment for major depressive disorder is one of the great challenges of the twenty-first century. Although ECT is one of the most effective treatments available, it is often not used until all other treatment options have failed. This is unfortunate, given the remarkably favourable outcomes reported for the most severely depressed patients. When we do not prescribe ECT sooner, this group of patients will unnecessarily be subjected to less effective treatments, increasing the risk of prolonged illness and suicide. In the studies reported in this dissertation, predictors of ECT outcome were evaluated to identify patients most prone to respond to ECT and to thus improve patient-treatment matching.

In a comprehensive review and meta-analysis of the literature assessing clinical predictors of ECT response in depression, we found superior efficacy of the procedure in patients with psychotic (and correspondingly more severe) depression and in older patients; the data on melancholic symptoms were insufficient and ambiguous (**Chapter 3**).

In the study presented in **Chapter 4**, the predictor treatment resistance was examined using the Maudsley Staging Method (MSM), which instrument would also be suitable for use in clinical practice because of its simplicity and clinician/patient-friendliness. Assessing three factors linked to good ECT response, we indeed found shorter episode duration to most consistently predict a larger effect of ECT, with fewer failed antidepressant treatments and more severe depressive symptoms also corresponding to better outcomes. Adapting the MSM, a composite score of episode duration and depression severity, the two strongest MSM variables, was computed and to increase the accuracy of our prediction model, age was categorized and added as a third variable, where older age was shown to correspond to a better ECT outcome. The adapted MSM significantly predicted ECT outcome.

The study reported in **Chapter 5** compared psychotic symptoms as a dichotomous predictor with the severity of psychotic depression as measured with the Psychotic Depression Assessment Scale (PDAS). The presence of psychotic symptoms and higher PDAS scores were both associated with superior ECT effects. Although the PDAS was responsive to change during and after ECT, surprisingly, its scores did not generate better results than the dichotomous variable, possibly due to a ceiling effect given the very high response and remission rates for the patients with psychotic depression. No significant differences were found in the speed of response between the patients with and those without psychotic symptoms.

Psychomotor retardation and/or agitation in major depressive disorder can be understood to indicate melancholic depression (Mel-D). Up to now, it could not be confirmed that Mel-D is a predictor of ECT response (**Chapter 3**). Testing ECT prediction models, we assessed specific gross and fine psychomotor functions with observer-rated and electronic instruments (**Chapter 6**). The CORE assessment of psychomotor functioning (score ≥ 8) revealed significant differences in daytime activity levels between patients with Mel-D and

those with non-melancholic depression (NMD). Interestingly, the differences were most pronounced in the afternoon and evening. Scrutiny of the predictive effects of the psychomotor variables analysed revealed that patients with (CORE-defined) Mel-D were 4.9 times more likely to respond to ECT than patients with NMD, with the CORE total score also adequately predicting ECT response. Analyses showed that all psychomotor variables were associated with the effect of ECT, with higher CORE total and subscale scores, lower activity levels and slow performance on the line-copying task (LCT) predicting a better response, although not all significantly so after Bonferroni correction. Furthermore, improvement in psychomotor functioning in the first week of treatment predicted a beneficial clinical outcome, where the change in CORE total score and its agitation and retardation subscale were most informative.

Despite their predictive capacities, several clinical variables appeared to explain overlapping parts of the variance in treatment outcome. Path analyses suggest that ECT response is mediated by melancholic depression, a type in which besides severe depressive symptoms either psychomotor disturbance or psychotic symptoms, or both, occur (**Chapter 7**). The association between age and ECT outcome is also mediated by the presence of melancholic depression and although episode duration and medication failure are both directly associated with ECT response, other variables that we have not accounted for may have played a role.

The exploratory analyses of potential side effects of ECT presented in **Chapter 8** showed acute anterograde amnesia during and after the treatment course, with memory functions being restored during the 6-month follow-up period. Group (means) analyses found no indications of persistent objectively measured cognitive dysfunction but RCI analyses did reveal clear heterogeneity in cognitive functioning at the patient-level , with some patients improving and others significantly deteriorating during treatment. The patients suffering from memory problems tended to have higher pretreatment cognitive scores and were overall younger, less severely depressed and seldom had melancholic or psychotic symptoms than those whose performance was not (markedly) impaired.

Wrapping up, we propose to recommend ECT as a first-line treatment for depressed patients concurrently presenting with psychotic symptoms and/or melancholic symptoms, reflecting either retardation or agitation, or both, since the findings presented in this dissertation showed ECT to be most effective in these subgroups, while cognitive side effects were the most moderate. We also suggest to confirm the diagnosis in patients with persistent symptoms and to look for any comorbidity or other relevant patient-specific factors that could potentially negatively affect ECT response.

# SAMENVATTING

Het vinden van de meest effectieve behandeling voor depressie is een van de grote uitdagingen van de 21e eeuw. Hoewel ECT een van de meest effectieve beschikbare behandelingen is, wordt het vaak niet gebruikt totdat alle andere behandelmogelijkheden ineffectief bleken. Dat is jammer, aangezien ECT spectaculaire resultaten kan hebben zeker voor de meest ernstig depressieve patiënten. Als we niet eerder ECT overwegen, stellen we ernstig depressieve patiënten bloot aan minder effectieve behandeling en het risico op langdurige ziekte en suïcide. In de studies beschreven in dit doctoraat werden voorspellers van ECT outcome geëvalueerd om patiënten te kunnen identificeren met grote kans op respons om zo patient-treatment matching te verbeteren.

In een uitgebreide literatuurstudie en meta-analyse over klinische voorspellers van outcome na ECT bij depressie, vonden we superieure effectiviteit van ECT bij patiënten met psychotische (en bijgevolg ernstigere) depressie en bij oudere patiënten, terwijl gegevens over het predictief effect van melancholie inconclusief waren (**hoofdstuk 3**).

In **hoofdstuk 4** evalueerden we therapieresistentie met de Maudsley Staging Method (MSM), geschikt voor gebruik in de klinische praktijk wegens zijn eenvoud en gebruiksvriendelijkheid. Bovendien bestaat het uit drie elementen die geassocieerd zijn met een gunstige ECT outcome, en alle veronderstelde associaties (kortere episodeduur, een beperkt aantal reeds gefaalde antidepressieve behandelingen en meer ernstige depressieve symptomen) werden bevestigd in onze studie. Kortere episodeduur was de meest consistente voorspeller van een gunstige outcome. Een samengestelde score van episodeduur en de ernst van de depressie, de twee sterkste MSM-factoren, werd geconstrueerd (aangepaste MSM) en om de nauwkeurigheid van ons predictiemodel te verhogen, werd de leeftijd van de patiënt gecategoriseerd en toegevoegd als een derde variabele aan de aangepaste MSM, waarbij hogere leeftijd overeenkwam met een betere behandeloutcome. De aangepaste MSM was een significante voorspeller van ECT outcome.

In **hoofdstuk 5** werd de voorspellende waarde van de aan- of afwezigheid van psychotische symptomen vergeleken met de voorspellende waarde van de ernst psychotische depressie gemeten met de Psychotic Depression Assesment Scale (PDAS). Aanwezigheid van psychotische symptomen en hogere PDAS-scores waren geassocieerd met een beter behandelresultaat. In tegenstelling tot wat we verwachtten, vonden we geen voordeel van de PDAS als voorspeller ten opzichte van de dichotome voorspeller, hoewel dit te maken kan hebben met een plafondeffect wegens de erg hoge respons- en remissiecijfers voor patiënten met psychotische depressie. We vonden geen significant verschil in -time to response- tussen patiënten met en zonder psychotische symptomen.

De aanwezigheid van uitgesproken psychomotorische retardatie of agitatie kan een onderscheid tussen melancholische (Mel-D) en niet-melancholische depressie (NMD). Tot nu toe kon nog niet worden bevestigd dat de aanwezigheid van Mel-D gepaard gaat met een gunstige ECT outcome (**hoofdstuk 3**). Bij het testen van ECT predictiemodellen evalueerden we specifiek grove en fijne motoriek met zowel als observatieschaal als meer

objectieve meetinstrumenten (**hoofdstuk 6**). Significante verschillen in activiteitsniveaus overdag werden gevonden tussen patiënten met Mel-D en NMD. In tegenstelling tot wat men zou verwachten, was het verschil in activiteitsniveaus overdag het meest duidelijkst in de middag en de avond. Patiënten met Mel-D hadden in onze sample een 4.9 keer grotere kans om goed te reageren op een behandeling met ECT dan patiënten met NMD, en ook de totale CORE-score voorspelde adequaat het effect van de behandeling. In feite waren alle onderzochte psychomotorische variabelen geassocieerd met de respons op behandeling met ECT (hogere CORE-totaal en subschaal-scores, lagere activiteitsniveaus overdag, trage prestaties op een lijnkopieertaak) hoewel een aantal van deze predictoren de Bonferroni-correctie niet overleefden. Verbetering van het psychomotorisch functioneren in de eerste behandelingsweek bleek bovendien een voorloper te zijn van een gunstige behandeloutcome, waarbij verandering in de totale CORE-score en de agitatie en retardatie-subschaal het meest waardevol bleken.

Hoewel de voorspellende waarde van verschillende klinische variabelen door onze analyses werd bevestigd, lijken ze vaak overlappende delen van de variantie in uitkomst te verklaren. Volgens pad-analyse (**hoofdstuk 7**) lijkt ECT-outcome bepaald te worden door de aanwezigheid van symptomen van een melancholische depressie waarbij psychomotorische symptomen en/of psychotische symptomen aanwezig zijn. De associatie tussen leeftijd en ECT-outcome wordt ook gemedieerd door de aanwezigheid van melancholische depressie en hoewel episodeduur en behandelfalen direct geassocieerd lijken te zijn met ECT-outcome, zouden andere variabelen waar we geen rekening mee hebben gehouden in onze analyses een rol kunnen hebben gespeeld.

De verkennende analyses naar neveneffecten van de behandeling (**hoofdstuk 8**) laten acute anterograde amnesie zien tijdens en vlak na de behandeling met ECT, maar herstellende geheugenfunctie in de 6 maanden durende follow-up periode. Kijkend naar groepsgemiddelden vonden we geen persistent objectief cognitief disfunctioneren, maar de RCI-analyses tonen een duidelijke heterogeniteit in cognitief functioneren op patiënt-niveau, waarbij een deel significant verbetert en anderen significant verslechteren tijdens de behandeling. De patiënten die geheugenproblemen ervaren, lijken wat hogere baseline cognitieve scores te hebben en waren jonger, minder ernstig depressief en hadden zelden melancholische of psychotische symptomen dan de patiënten zonder duidelijke geheugenproblemen.

Op basis van onze bevindingen stellen we voor om ECT te beschouwen als een eerstelijns behandeloptie voor patiënten met psychotische en/of melancholische symptomen, vertraging en/of agitatie, aangezien de bevindingen in dit proefschrift aantoonden dat ECT het meest effectief bleek te zijn in deze subgroepen, terwijl cognitieve bijwerkingen beperk waren. We stellen voor om de diagnose te bevestigen bij patiënten met langere episodeduur en om te zoeken naar eventuele comorbiditeit of andere relevante patiëntspecifieke factoren die mogelijk de ECT respons negatief kunnen beïnvloeden.

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# DANKWOORD

Zo, een punt er achter. Eerst en vooral wil ik het PZ Duffel en de Universiteit Antwerpen bedanken. Zij schonken mij het vertrouwen om een ambitieus project op poten te zetten en uit te voeren en gaven mij de tijd, het werkveld en de middelen die nodig waren om dit project niet tussen de soep en de patatten maar deftig uit te kunnen voeren. Bedankt!

De grootste berg dank spreek ik graag uit naar de deelnemers van het onderzoek, P01 tot P74. Bedankt om eerst al -ja- te zeggen op een vraag die niet evident is, bedankt om mijn wekelijks vragenvuur keer op keer te trotseren, bedankt om dit onderzoek er nog bij te pakken in een periode van je leven waarin dat echt niet evident is. En dat allemaal voor de wetenschap.. Bedankt om mij ontzettend veel te leren over depressie in al zijn verschillende verschijningsvormen, over verdriet, over herstel en ook om mij de gelegenheid te geven mijn skills mbt motiverende gespreksvoering te optimaliseren.

Ik zag de afgelopen jaren de ECT-dienst uitgroeien tot een geoliede machine waar patiënten met veel professionaliteit en empathie worden behandeld. De aanpak bestaat niet alleen uit aandacht voor bloeddruk en hartslag maar ook voor het verhaal van de individuele patiënt. Het ECT-team bestaat uit mensen met hart voor hen, wat aan de basis ligt van een geslaagde ECT-behandeling. Ik wil jullie bedanken namens de patiënten maar ook namens mezelf. Bedankt voor het werk wat jullie doen, om hen zo goed te behandelen en om mij op de hoogte te houden voor en op ECT-behandeldagen.

Het was ook een eer om te werken met Didier Schrijvers, mijn promotor. Bedankt Didier! Je hebt een erg belangrijke rol gespeeld in dit project. Ik zat boordevol plannen en je hebt doorheen de jaren heen met regelmaat even op de rem moeten trappen. Ik remde dan wel niet altijd maar het heeft me toch echt geholpen om een focus te vinden en behouden. Het was daarnaast erg zinvol om een promotor te hebben die ook nog heel bevlogen zijn klinisch werk uitvoert. Op die manier bleven de dingen die we onderzochten realistisch en verloren we de belasting van de deelnemers niet uit het oog. Bedankt Didier om mee te denken en om voor mij een zeer toegankelijke en betrokken promotor te zijn.

Naast Didier bedank ik ook graag de andere leden van de medische staf in het PZ en dan vooral Carmen en Yamina. Bedankt om aan mij te denken wanneer er ECT werd gestart en bedankt voor het vertrouwen dat ik kreeg om met jullie pt aan de slag te gaan. Ook promotor Bernard Sabbe wil ik graag nog eens extra bedanken, voor uw geduld met mij, om mij te overtuigen om tóch te kiezen voor psychiatrie en om voor de onderzoeksplannen waar ik mee rondliep een draagvlak te zoeken. Bedankt ook voor uw terecht kritische blik op de drafts van onze papers.

Ook wil ik graag landgenoot en promotor Tom Birkenhäger bedanken. Je expertise op vlak van wetenschappelijk onderzoek bij deze doelgroep hadden we echt niet kunnen missen. Ik apprecieer je nuchterheid en ook jij hield mij goed met beide benen op de grond. Dank je om al mijn drafts zo snel en grondig door te nemen. Als ik ergens in mijn hoofd niet uit ge-

raakte, wist je steeds op een heel respectvolle manier mee te denken waardoor geen enkel probleem onoplosbaar leek te zijn.

Naast promotoren bedank ik ook graag andere mensen die dit project haalbaar hebben gemaakt, dwz het personeel op de deelnemende afdelingen. De verpleegkundigen die bloednames hebben gedaan en de PMT-ers die me hebben geholpen met het verzamelen van de psychomotorische data. Herman en Inge, bedankt! Ook de collegae van SINAPS en degenen die het vroegere -torentje- nog hebben bewoond. Eline, bedankt om voor mij kapper te spelen en om vele zweetvoeten te trotseren voor die verrekte enkel-arm index. Ingrid, ook jij bent je roeping als kapster duidelijk mislopen. Niet alleen bedankt voor alle bloednames maar ook om lekker je aangename zelf te zijn en om met groot succes toch een beetje de moeder van het wetenschappelijk onderzoek te zijn de afgelopen jaren. Jeroen, heel erg bedankt voor het delen van je kennis en kunde in het VITO! Tom, ook aan jou heb ik erg veel gehad en wat was het leuk om samen twee ECT- symposia te organiseren. Ook de andere collegae en coördinatoren van SINAPS wil ik bedanken om gedurende het project mee te denken en om bij elke nieuwe inclusie mee enthousiast te zijn. Aan mijn lotgenoten nog een persoonlijk woordje van dank. Peter, Claudia en Livia, bedankt om me wegwijs te maken in de wondere wereld van wetenschappelijk onderzoek in Duffel. Kaat en Mirella, het was erg aangenaam om met jullie in hetzelfde wetenschappelijk schuitje te varen. Olivia, aan jouw werkethos kunnen we allemaal een voorbeeld nemen. Bedankt voor het creëren van een dynamische werkomgeving en om kritisch mee te denken met werkelijk alles wat passeerde. Dank voor je geloof in mijn onderzoek en in mij als mens. Bedankt ook om naast een collega een vriend te zijn waarmee ik after-work la chouffe kon gaan drinken, zodat we de wetenschappelijke wereld konden relativeren. Last but zeker not least in dit rijtje komt Seline, mijn absolute wetenschapsmakker. Wat heb ik veel aan jou gehad. Je kon zo goed meedenken met mijn wetenschappelijke en andere dilemma's, begreep mijn vreugde en frustraties, was een klankbord en een voorbeeld van wetenschappelijke integriteit ten top en nog veel meer. Je was de perfecte bureaugenoot. Ik heb veel bewondering voor jou en voor hoe je in het leven staat en hoop voor de wereld dat je wetenschapper blijft. Ik stel voor dat we elkaar wetenschappelijk maar vooral ook vriendschappelijk niet uit het oog verliezen.

Er is in onze onderzoeksgroep veel knowhow, maar ik ben erg dankbaar dat ook mensen van buiten onze onderzoeksgroep mee hebben willen denken over dit project. Ook deze mensen, die ik doorheen het traject heb opgezocht of ben tegengekomen, wil ik heel graag bedankt. Nathalie Franck (UZA), bedankt om me in de wondere wereld van de enkel-arm index wegwijs te maken, Frank Kooij (Centrum Medische Genetica, UA), bedankt voor het meedenken en bepalen van BDNF polymorfismen. De mannen van radiologie in het UZA wil ik ook heel graag bedanken om mij in korte tijd te leren hoe ik zelf hersenscans maak. Bedankt voor het vertrouwen dat ik kreeg om met zo'n indrukwekkend apparaat te werken en bedankt voor jullie flexibiliteit de planning van de scans Floris, Michel, Pim en Prof. Parizel! Erik Fransen (UA) en Kristof Vansteelandt (KUL), bedankt voor jullie statistisch significante hoeveelheid geduld en het meedenken over alle analyses.

Mijn woorden van dank gaan tot over de grens. Liesbeth van Rossum en Yolanda De Rijke (Erasmus MC, Rotterdam), bedankt om mee te denken over het bepalen van cortisol in haar en om voor ons de analyses te doen. Uit hetzelfde ziekenhuis verdient ook Astrid Kamperman een klein standbeeld. Astrid, jouw expertise was van onschatbare waarde bij het doen van onze meta-analyse en ook voor het slotstuk van mijn doctoraat speelde je een grote rol. Bedankt om met mij mee te denken over de samenhang tussen predictoren, bedankt om de laatste analyses onder tijdsdruk en met koorts tot een goed einde te brengen en bedankt om je nuchtere kritische zelf te zijn. Daar hou ik van. Philip Van Eijndhoven (Radboud UMC, Nijmegen), heel erg bedankt om samen met mij na te denken over de aanpak van de analyse van de hersenscans en om er voor te zorgen dat die grote bestanden met beelden werden herleid tot een overzichtelijke database met cijfertjes waar ik beter weg mee weet. Esmée Verwijk (Amsterdam UMC), ook jou wil ik graag bedanken. Voor je enthousiasme als het gaat om de cognitieve data van het project en om mee te denken over de analyses. Ik hoop dat we dit in de nabije toekomst nog in een wonderschone paper kunnen gieten. De laatste Nederlandse heldin die ik wil bedanken is Roos van der Mast (Leiden UMC). Hoewel we elkaar vanaf het begin met regelmaat tegenkwamen was je niet rechtstreeks bij mijn project betrokken. Bij de laatste papers speelde je wel een grote rol, bedankt om mijn teksten zo kritisch te lezen. Ik ben er van overtuigd dat dit de kwaliteit van mijn papers ontzettend ten goede is gekomen.

Ook de nog niet genoemde co-auteurs van de verschillende papers bedank ik graag voor het meedenken! Sebastian Walther (University of Bern), thanks for your valuable help on the psychomotor papers. Søren Ostergaard (Aarhus University Hospital), Eveline Veltman (Leiden UMC), Pieter Versyck, Simon Vanmarcke, Jan-Baptist Belge en Robin Baeten – bedankt voor de aangename samenwerking!

Beste juryleden, dear members of the jury. I would also like to explicitly thank you for the time invested in critically evaluating this dissertation. Your comments were valuable. Prof. Morrens, Menovsky en Engelborghs, bedankt om de voortgang van mijn doctoraat de afgelopen jaren op te volgen. Prof. Sienaert and Kellner, thanks a lot for your willingness to participate in the evaluation and the defense of this dissertation.

Niet geheel onbelangrijk zijn ook de mensen die er voor hebben gezorgd dat het doctoraat er qua taal en vorm uit ziet zoals u het nu voor u hebt. Hanneke, je herschreef de meeste van mijn papers. Ik dacht dat mijn Engels redelijk goed was, maar heb daar wel elke keer serieus aan getwijfeld als ik de documenten terugkreeg. Bedankt om ze zo grondig te proofreaden en bedankt om ook te proberen om mij wat grammaticale en andere principes bij te brengen in de kantlijn! Ervin, bedankt voor je steun bij de laatste loodjes en het onder handen nemen van mijn path-model. Rein, bedankt voor de nette brochure die je maakte voor mijn studie, ik ben er van overtuigd dat dit boekje mijn inclusies serieus heeft geholpen. Ook de lay-out van dit boek neem je op je. Op het moment dat ik dit schrijf weet ik nog niet wat je er van gaat maken, maar heb ik het volste vertrouwen dat ook een tweede danku zeker op zijn plaats is. Ook wil ik graag alle mensen bedanken die hebben gereageerd op de

oproep voor een kunstwerk voor de cover van mijn doctoraat. Er waren ontzettend veel inzendingen, de ene nog knapper dan de ander. Christian en Greet van De Loods, bedankt om dit mogelijk te maken en Luc, heel erg bedankt om een werkelijk adembenemend duplicaat te maken van het reeds verkochte kunstwerk waarop ik verliefd was geworden.

Dan gaan we nu even weg uit de professionele sferen, want ook naast de mensen rechtstreeks betrokken bij het project zijn er mensen die er aan hebben bijgedragen. Laat ik beginnen met pap en mam. Zonder jullie was dit alles niet mogelijk geweest. Mijn zorgend kantje heb ik duidelijk van jou mam. En mijn nuchterheid, praktische ingesteldheid en redelijk grenzeloos met werk kunnen bezig zijn lijkt eerder van jou te komen pappie. Deze eigenschappen vormen een perfecte bodem voor een klinisch gericht doctoraat, kan ik jullie vertellen. Bedankt om mij te hebben geleerd dat het belangrijk is om te doen wat je graag doet, want dat heb ik gedaan. Het deed me deugd dat jullie naar mijn eerste symposium zijn gekomen en dat jullie een poging hebben gedaan om mijn eerste paper te lezen.

Er zijn de afgelopen jaren veel mensen geweest die de voortgang van het project van dichtbij of iets verder weg hebben meegemaakt. Alle buren, bekenden, lieve vrienden, collegae en familieleden wil ik ontzettend hard bedanken om te (blijven) vragen aan hoeveel mensen ik al zat. Dat deed veel deugd. Eindelijk kan ik zeggen dat het AF is! Bedankt broer, schoonbroer en lieve zuster om jullie charmante nuchtere zelf te zijn. Lieve, dank je om te geloven in mij en mijn grootse plannen (de grote multicentrische van Diermen studie). Tine, bedankt voor je gezelschap doorheen het doctoraatstraject! De Duvel-club met Wilco en mijn loopmakker Charlotte draag ik ook een heel warm hart toe, hoe meer dokters in een vierkantshoeve hoe beter.

Vergeet ik dan nog iemand? O ja, mijn lief. Lies. Waar zal ik beginnen. Dankjewel voor je geduld met mij en met mijn project. Bedankt om een psychotisch depressieve patiënt te spelen. Bedankt om mij het gevoel te geven dat ik in een 5-sterren hotel woon. Dankjewel voor al je lieve briefjes in mijn brooddoos, voor de gênante foto's die je per post in Duffel liet aankomen. Bedankt voor je oprechte belangstelling in alles wat met de studie te maken had. Bedankt om op de kast naast mijn bureau de voortgang van alle papers nauwgezet bij te houden in procenten. Bedankt om boos te worden op mensen die mij niet netjes behandelen. Bedankt voor de diensten die je me bewees als word-consulente. Bedankt om naar de goede kant te swipen toen je mijn foto tegenkwam op Tinder. Bedankt ook om mijn vangnet te zijn. Bedankt voor mijn P70-feest. Dat gaf zo veel erkenning! Bedankt Lies, bedankt lief, bedankt om te zijn wie je bent en om mij te laten zijn wie ik ben. Liebedich!

Ten slotte nog een klein woordje voor Flo. Je kunt nu nog niet lezen maar ook jou wil ik bedanken en dan vooral om af en toe te slapen zodat mams haar doctoraat kon afmaken. Je bent een schatje.

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Op voldoende wijze.

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**Master na master in de specialistische geneeskunde - volwassenenpsychiatrie, Universiteit Antwerpen, Antwerpen**
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Begeleiden van studenten ter ondersteuning van docenten op terugkomdagen.

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## Cursussen

**Klinische electrocardiografie, Universiteit Antwerpen**
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**Organisatie Wetenschappelijke Symposia, PZ Duffel, Duffel**

24/03/2015 - To shock or not to shock.
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## Publicaties

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