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Can psychomotor disturbance predict ect outcome in depression?

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ABSTRACT

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. 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. 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 was associated with higher ECT effectiveness. ECT reduced CORE-assessed psychomotor symptoms and improved activity levels only in those patients showing the severer baseline retardation. Although the sample was relatively small, psychomotor symptoms were clearly associated with beneficial outcome of ECT in patients with major depression, indicating that monitoring psychomotor deficits can help personalise treatment.

1. Introduction

Psychomotor disturbance is a core symptom of major depressive disorder (MDD) (American Psychiatric Association, 2013; Parker et al., 2017) 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)(APA, 2013). 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 (Parker, 2007, 2000; Parker et al., 2017). Another line of evidence suggests that melancholia should particularly be seen as a categorical entity based on distinct biological underpinnings, a distinctive pattern of symptoms, and a differential response to treatment modalities (Caldieraro et al., 2013; Lamers et al., 2013, 2010; Parker et al., 2010; Parker and McCraw, 2017; Spanemberg et al., 2014; Veltman et al., 2017).

Electroconvulsive therapy (ECT) is a relevant treatment option for patients with Mel-D (Kellner et al., 2012; Lisanby, 2007; Perugi et al., 2012; Prudic et al., 2004; UK ECT Review Group, 2003). Despite its effectiveness and safety, in general, ECT is only considered when patients have failed to respond to several pharmacological treatments (van den Broek et al., 2010). However, a delayed start of ECT is known to reduce the chances of a good response (Haq et al., 2015), 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 ECT outcome in depression (Hickie et al., 1990), but meta-analyses on the predictive value of

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melancholic symptoms were inconclusive due to study heterogeneity (Haq et al., 2015; Van Diermen et al., 2018b). This could be explained by the fact that different definitions of Mel-D were used.

To aid the differentiation between Mel-D and NMD, the CORE assessment of psychomotor functioning was designed (Parker and McCraw, 2017). Although, like other observer-rated instruments, the CORE is clinically useful (Schrijvers et al., 2008), 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 (Bennabi et al., 2013) that may be even more sensitive to detection of psychomotor disturbance.

Also, little is known about the effect of ECT on (the course of) psychomotor functioning in MDD. 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 could not confirm this (Veltman et al., 2019b). The authors showed that all symptom clusters responded to ECT in depressed older patients as early as in the first week of ECT. The mood symptom cluster improved fastest compared to the melancholic and suicidal symptom clusters. 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. We use both the observer-rated CORE instrument and objective measures of psychomotor functioning, hypothesising that the presence of psychomotor disturbance will be associated with a favourable outcome. We additionally investigate the effect of ECT on (the course of) psychomotor functions.

2. Subjects and methods

2.1. 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 Helsinki Declaration. The study was approved by the Ethics Committee of the University Hospital of Antwerp (project number 15/10/93).

2.2. Study population

Patients with a major depressive episode in uni- or bipolar disorder according to the DSM-IV-TR who were scheduled for ECT were included. Diagnoses were confirmed using the MINI diagnostic interview, version 6.0. (Sheehan et al., 1998). Eligible patients also needed to have a score of at least 17 on the 17-item Hamilton Depression Rating Scale (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. All participants provided written informed consent.

This study is part of a larger research project on ECT-response predictors conducted in Duffel Psychiatric Hospital (Belgium)(van Diermen et al., 2018a, 2018b; Van Diermen et al., 2018a). Reasons for ECT referral were treatment resistance, presence of severe melancholic or psychotic symptoms and acute suicidality.

2.3. Clinical assessment

2.3.1. Mood

Depression severity was assessed with the 17-item Hamilton Depression Rating Scale (HDRS17) (Trajković et al., 2011) prior to study entry and the Montgomery-Åsberg Depression Rating Scale (MADRS) (Carmody et al., 2006; Hawley et al., 2002; Müller et al., 2003) was used to evaluate the course of the depressive symptoms during ECT (Montgomery and Asberg, 1979). The MADRS is a scale that is rather sensitive to change (Khan et al., 2002) and independent of the presence and severity of psychomotor functioning. 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.

2.3.2. Psychomotor assessment

2.3.2.1. Clinician-rated assessment. The CORE was used to assess observable psychomotor performance and to define Mel-D (total CORE score ≥ 8) (Parker and Hadzi-Pavlovic, 1996). 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 (Fink et al., 2007). 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 presence of catatonia was assessed with the Bush-Francis Catatonia Rating Scale (Bush et al., 1996).

2.3.2.2. Objective measures

2.3.2.2.1. 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 (Attu et al., 2012) with reduced activity levels found in major depression (Krane-Gartiser et al., 2015; Razavi et al., 2011; Sobin and Sackeim, 1997; Walther et al., 2012). 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 s.

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.

2.3.2.2.2. Line-copying task. Fine motor performance was evaluated with a digital line-copying task (LCT). 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). IT mainly reflects the cognitive component of the performance, defined as the time (in seconds) between the presentation of the stimulus and the start of the first drawing movement. MT is the motor component, defined as the time (in seconds) from the start of the first drawing movement to the end of the last drawing movement (Beheydt et al., 2015).

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 of this rather complex sequence of tasks (for each line: put pen in start circle, look at computer screen, draw line in box on paper, put pen in stop circle) 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.

2.4. Treatment

2.4.1. ECT

ECT was administered twice a week using a brief-pulse (0.5 m s) constant-current Thymatron IV system (Somatics LLC, Lake Bluff, Illinois, USA). Electrodes were placed right unilaterally (RUL) or bilaterally when a fast antidepressant effect was needed (Kolshus et al., 2017). 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 (Petrides and Fink, 1996). Etomidate was the anaesthetic of choice (0.15 mg/kg) and propofol (1 mg/kg) and ketamine (1–2 mg/kg) were used when etomidate was not tolerated or when clinical response was lacking after the first 12 sessions. Succinylcholine (0.5 mg/kg) was used as a muscle relaxant. Benzodiazepines and lithium were withheld at least 12 h before each session given the negative influence of benzodiazepines on seizure duration (Tang et al., 2017) and lithium on cognitive functioning (Porter et al., 2008).

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.

2.4.2. Pharmacological

Before ECT, seven percent of the patients did not use any antidepressant, while 74% were treated with antidepressant monotherapy (mainly selective serotonin reuptake inhibitors (n = 12) and tricyclic antidepressants (n = 38)) and 19% with a combination of antidepressants. Seventy-nine percent of the patients used additional antipsychotics 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 score on the CORE agitation subscale was the only subscale score that significantly differed between patients using benzodiazepines and those who did not (2.9 vs 1.0, F-ratio = 7.4, P = 0.0084). Significant correlations between benzodiazepine dose and the motor component of the line-copying task (r = 0.32, p = 0.03) 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).

2.5. 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 averages 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, but also DALs in terms of accelerometer outcomes and LCT ITs and MTs. Response/remission after treatment was defined 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 was included separately in a multiple regression model in which baseline depression severity (MADRS), 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.

3. Results

3.1. 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 are listed in Table 1 and show that our cohort is characterized by an uneven distribution of male and female patients and a long mean episode duration.

There were two patients with documented dementia and three with Parkinson's disease. Five patients were unable to complete the course

Table 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)
BFCRS-defined catatonia N (%)	10 (13.7)
Episode duration in months	
Mean ± SD	14.3 (± 18.1)
Median, range	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)

Table 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 red.

Table 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= < 0.0001
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 = 0.3758
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 = 0.3574
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 = 0.8118
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 < 0.0001
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 < 0.0001
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 < 0.0001
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 < 0.0001

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.

because of side effects induced by 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.

3.2. 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 2) and remission (Data Supplement 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 2.

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 1). With an AUC of 0.81 (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 the covariates (baseline depression severity (MADRS), presence of psychotic symptoms and benzodiazepine dose) and each of the psychomotor variables with a significant association to the outcomes in the simple logistic regression analyses and 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 3.

3.3. 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 3, Fig. 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 4). As a substantial proportion of the patients with the lowest activity levels had not been able to complete the line-copying task, we did not perform mixed model analyses for this task.

4. Discussion

Using an observer-rated instrument (CORE) and objective measures (accelerometry and line-copying task) we investigated whether

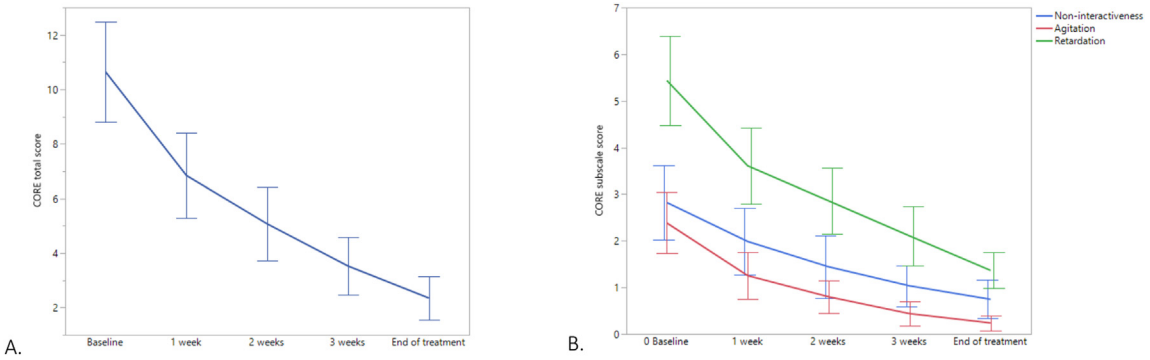

Fig. 1. Effect of electroconvulsive therapy (ECT) on psychomotor functioningEvolution of psychomotor function during ECT as based on the CORE total (A) and subscale scores (B). Each error bar is constructed using a 95% confidence interval of the mean.

psychomotor functioning was associated with ECT outcome in depressed patients and found that, as hypothesized, psychomotor disturbance as well as the presence of CORE-defined melancholia was associated with a favourable outcome, as was 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 the line-copying task, a slower performance clearly corresponded to a beneficial treatment outcome. The most accurate prediction model we obtained was the one based on LCT movement time, with benzodiazepine dose as covariate. Where two recent meta-analyses remained inconclusive due to study heterogeneity (Haq et al., 2015; Van Diermen et al., 2018b), 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 (Hickie et al., 1996). In our sampe however, baseline presence of agitation seems to play a somewhat more prominent role (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 (Veltman et al., 2019a). 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 personalise depression treatment.

Because of their potential effects on psychomotor performance (Bennabi et al., 2013) and treatment outcome we restricted ourselves to three well-documented covariates in our prediction analyses, i.e. depression severity (Van Diermen et al., 2018b), psychotic symptoms (Van Diermen et al., 2018b) and benzodiazepine dose (Benasi et al., 2018). Psychomotor symptoms and depression severity go hand in hand. Psychomotor symptoms can either be considered a marker of depression severity (the symptoms only appear at the most severe end of the depression spectrum) or as marker of a specific depression subtype (Parker, 2000). We decided also to control for depression severity to explore the influence of depression severity on the association found between psychomotor symptoms and ECT outcome. Since depression severity was not withheld in any of the multiple regression models, we now conclude that ECT outcome seems to be more closely related to the presence of these psychomotor symptoms than to simply the general severity of a depressive disorder. As they negatively influence ECT-induced seizure duration (Tang et al., 2017), benzodiazepines were withheld at least 12 h 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 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).

The predictive effect of psychomotor functioning might also have been confounded by differences in, amongst other parameters, the responders' and non-responders' ages Since at baseline no substantiated response prediction could be made, we could not match patients for age. Because the predictive effect of age appears to be mediated by psychomotor functioning and psychotic symptoms (Heijnen et al., 2019; Veltman et al., 2019a), we chose not to add this variable as a covariate to our multiple regression models.

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 (Rosenblat et al., 2015) and daytime activity levels (Burton et al., 2013). It needs to be noted here that our sample consisted of patients without clear psychomotor symptoms, for whom no change in psychomotor functioning was to be expected, as well as 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 results 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. The fact that we did not find this effect in the patients with less severe retardation could result from our study being underpowered to detect smaller effects.

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 (Walther et al., 2019). The acute negative influence of ECT on cognitive functioning (Ingram et al., 2008; Semkovska and McLoughlin, 2010) 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 (Semkovska

and McLoughlin, 2010), a follow-up measurement after one month could have been valuable in our study.

4.1. Strengths

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 (Lin et al., 2015; Spaans et al., 2016), we considered early changes in psychomotor functioning as a potential ECT outcome predictor.

4.2. Limitations

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 were associated with ECT outcome. 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 was associated with 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 could guide treatment choices.

Potential conflicts of interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.07.009.

CORE-defined melancholia is a score of ≥8 on the CORE Assessment of Psychomotor Functioning (Parker and Hadzi-Pavlovic, 1996); BFCRS = Bush-Francis Catatonia Rating Scale (Bush et al., 1996); treatment resistance is defined as > 2 failed antidepressant treatments; response = MADRS decrease ≥50%; remission = final MADRS score ≤10.

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