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Influence of age on ECT efficacy in depression and the mediating role of psychomotor retardation and psychotic features

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ABSTRACT

Objective: To investigate whether older age predicts a higher efficacy of electroconvulsive therapy (ECT) in severely depressed patients. Also, to analyze whether psychomotor disturbance and/or psychotic features might explain the potential higher efficacy of ECT in older age.

Method: A total of 96 patients with major depressive disorder treated with bilateral ECT were evaluated. The 17-item HAM-D and the MADRS were used to evaluate the efficacy of ECT and time to remission, respectively. Psychomotor disturbance was defined according the HAM-D.

Results: Middle-aged (MA; 50–70 years) and older-aged (OA; ≥70 years) patients had a non-significant larger symptom reduction compared with young-aged (YA; < 50 years) patients. Medium effect size was found in favor of MA ($d = 0.44$) and small effect size in favor of OA ($d = 0.30$), when compared to YA. Patients with psychotic features and patients with psychomotor retardation had a significantly larger symptom reduction ($p < 0.001$ and $p = 0.005$, respectively; $d = 0.88$ and $d = 0.66$, respectively). The association between age and ECT efficacy is mediated by psychomotor retardation ($p = 0.049$) and in lesser extent by psychotic features ($p = 0.071$).

Conclusion: The results show that psychomotor retardation and psychotic features are strong predictors of ECT efficacy and explain the association between age and ECT efficacy. Instead of focusing on the age of a patient, clinicians should focus on the presence of psychomotor disturbances and psychotic features of depression, when considering ECT treatment.

1. Introduction

Electroconvulsive therapy (ECT) is a highly effective treatment in severe major depression (UK ECT ReviewGroup, 2003). However, up to 30% of patients fail to achieve response (UK ECT ReviewGroup, 2003) and up to 45% of the patients do not achieve full remission (Kellner et al., 2010).

Few convincing clinical predictors of efficacy of ECT in major depression are known: The absence of medication resistance, the presence of delusions, previous ECT treatment and a shorter duration of the index episode (Heijnen et al., 2010; Birkenhager et al., 2003; Loo et al., 2011; Petrides et al., 2001; van Waarde et al., 2013; Haq et al., 2015; Medda et al., 2014). Further, marked psychomotor disturbance (agitation and/or retardation) might be a predictor for better ECT efficacy (Buchan et al., 1992; Hickie et al., 1996). Another relevant predictor of ECT efficacy might be older age as it is reported that ECT is more likely to be effective in older patients (Nordenskjold et al., 2012; O'Connor et al., 2001; Spashett et al., 2014; Tew et al., 1999). Apart from one study (Nordenskjold et al., 2012), all of the studies included patients with major depression exclusively. On the other hand, others failed to find an influence of older age on ECT efficacy (Birkenhager et al., 2010; Bloch et al., 2001; Damm et al., 2010). However, in two of these studies the population was a mixture of patients with major depression, schizophrenia and/or schizoaffective disorder (Bloch et al., 2001; Damm et al., 2010). Birkenhager et al. (2010) found no linear relationship between age and ECT efficacy. Two meta-analyses of clinical predictors found an association between older age and higher ECT response rates (van Diermen et al., 2018; Haq et al., 2015). However, this association was weak and heterogeneity between studies was substantial.

Therefore, it is important to investigate whether older age is a predictor of efficacy of ECT. Specific symptoms such as the presence of psychotic features and marked psychomotor disturbance might be more common in elderly patients (Brodaty et al., 1997; O'Connor et al., 2001). Psychotic features in major depression are a convincing predictor for higher ECT efficacy (Birkenhager et al., 2003; Loo et al., 2011; Petrides et al., 2001) and the same might apply to marked

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psychomotor disturbance (Buchan et al., 1992; Hickie et al., 1996). Therefore, the hypothesized higher efficacy of ECT in older depressed patients might be partly explained by the presence of one or both of these symptoms.

1.1. Aims of the study

The primary aim of the present study is to test the hypothesis that older age predicts higher ECT efficacy and a shorter time to remission in severely depressed patients.

Next, it is important to identify possible underlying mechanisms, like specific depressive symptoms. Therefore, the secondary aim is to analyze whether psychomotor disturbance and/or psychotic features mediate the relationship between age and ECT efficacy.

2. Methods

2.1. Patients

The PROSPECT cohort is a prospective study of depressed patients treated with ECT at the Department of Psychiatry of the Erasmus Medical Center from January 2006 up to date. Patients are included in the PROSPECT cohort if they meet the DSM-IV criteria (American Psychiatric Association, 1994) for major depressive disorder (MDD) with or without psychotic features and have a score of ≥17 on the 17-item Hamilton Rating Scale for Depression (HAM-D) (Bech et al., 1986). Diagnoses are based on clinical observations during a routine drug-free period. A diagnosis of mood congruent psychotic depression is made solely when the patient shows definite mood-congruent delusions.

A subset of adult PROSPECT patients (18 years and older) was selected for the current analyses. We excluded all patients with alcohol or drug dependence, a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, psychotic disorder not otherwise specified, obsessive-compulsive disorder, dementia, and other neurological disorders. To avoid electrode placement acting as a confounding factor, only patients treated with bilateral ECT were selected. Although a recent randomized trial found no difference in efficacy between high dose-unilateral and bitemporal ECT in MDD (Semkovska et al., 2016), generally, bilateral ECT is considered more effective than right unilateral ECT (UK ECT ReviewGroup, 2003). To avoid bias, of patients receiving more than one ECT course during this period, only the first treatment course was included in the sample.

The study was conducted in accordance with the latest version of the Declaration of Helsinki and informed consent of the participants was obtained after the nature of the procedures had been fully explained. Since all data were obtained as part of standard psychiatric care, medical ethical review was not deemed necessary.

For the purpose of our analyses, patients were divided into three age groups to investigate the impact of age: young-aged (YA) patients: < 50 years, middle-aged (MA) patients: ≥ 50 and < 70 years, and old aged (OA) patients: ≥ 70 years. **Since a recent meta-analysis showed a curvelinear relationship between age and ECT efficacy (**van Diermen et al., 2018**), this categorization allows us explore non-linear relationships. We suppose a decreased efficacy of ECT in patients < 50 years.** This categorization was chosen because it can be considered as clinically relevant categories corresponding to a younger age group, a middle age group and an older age group. HAM-D items were used as indicator of the presence of unique symptoms. A score of 2, 3 or 4 on the HAM-D items 8 (psychomotor retardation) or 9 (psychomotor agitation), was classified as the presence of the symptom. A score of 0–1 on item 8 represents normal speech and thought or slight retardation and a score of 2–4 stands for at least obvious retardation at interview. A score of 0–1 on item 9 represents no agitation or fidgetiness and score of 2–4 stands for at least obvious restlessness (playing with hands, hair, moving about).

2.2. Electroconvulsive therapy

Patients were withdrawn from all psychotropic medication at least five days prior to the first ECT treatment and the majority of patients were maintained medication-free during the course of ECT. Because several patients participated in a study involving nortriptyline, 16 patients were treated with nortriptyline during the course of ECT. Approximately 3 patients in the YA group (23%), 9 patients in the MA group (18%) and 4 patients in the OA group (12%) received nortriptyline during ECT. In case of severe agitation, incidental use of haloperidol was allowed, whereas the use of benzodiazepines during ECT was not allowed.

All patients were treated with bilateral ECT. ECT was administered twice weekly with a brief-pulse constant current apparatus (Thymatron, Somatics, IL, USA). Seizure threshold, defined as the stimulus dosage that elicited a seizure of at least 25 s according to the cuff method, was determined during the first session with empirical stimulus titration. If the starting stimulus dose failed to elicit a seizure of at least 25 s, stimulus charge was increased according to the titration schedule and the patient was restimulated after 30 s. For the second treatment, the stimulus dosage was set at 1.5 times the seizure threshold. During the course of ECT, stimulus dosage settings were adjusted upward to maintain seizure duration of at least 25 s as measured with the cuff method.

Anesthesia was achieved after premedication with 0.2 mg glycopyrrolate, with intravenous administration of etomidate (0.2 mg/kg), alfentanil (7–10 μg/kg) and succinylcholine (0.5–1.0 mg/kg). During the procedure, patients were ventilated by mask until the resumption of spontaneous respiration. Physiological monitoring included pulse oximetry, non-invasive blood pressure measurement, electrocardiogram and electroencephalogram. The number of ECT treatments was determined by clinical observation; a minimum of 10 bilateral treatments was required before evaluation as a non-responder. ECT was continued until patients were either asymptomatic or had not shown any further improvement as measured by the HAM-D over the course of three consecutive treatments.

2.3. Evaluation of treatment outcome

The 17-item HAM-D was used to evaluate the severity of MDD and was routinely performed 1–3 days prior to ECT and 1–3 days after treatment termination to evaluate the efficacy of ECT. High inter-rater reliability and internal consistency have been shown for this scale (Miller et al., 1985). Since the Montgomery Asberg depression rating scale (MADRS) (Montgomery and Asberg, 1979) is more sensitive to detect small changes over time (Carmody et al., 2006), the MADRS was performed weekly during ECT treatment to evaluate the time to remission. The MADRS was also performed 1–3 days prior to ECT 1–3 days after ECT. The primary outcome criteria for efficacy are mean reduction (continuous) in HAM-D scores per group and proportion of patients in remission (dichotomous) as measured by the HAM-D. The secondary outcome criterion is time to remission as measured by the MADRS. Remission was defined as a HAM-D score of ≤. 7 or a MADRS score of ≤9.

Response was defined as a reduction of ≥50% on the HAM-D score, relative to the baseline HAM-D score.

2.4. Statistical analysis

Differences with regards to socio-demographic, clinical, and outcome variables between subgroups of patients were tested with T-tests or ANOVA test for continuous variables, and Pearson's Chi-square and Fisher's Exact test (FET) for categorical variables. In case of a 2 × 3 contingency table, we employed the Freeman-Halton extension (Freeman and Halton, 1951) of the Fisher's Exact test.

Effect sizes were calculated to estimate the magnitude of the effect.

Cohen's *d* was calculated with respect to continuous outcomes (reduction of HAM-D scores) while a Relative Risk (RR) was calculated with respect to dichotomized outcomes (proportion of patients in remission). A Cohen's *d* of 0.2–0.3 and a RR of 2 (or 0.50) is seen as a small effect; a Cohen's *d* around 0.5 and a RR of 3 (or 0.33) as a medium effect; and a Cohen's *d* of 0.8 and RR of 4 (or 0.25) and higher, as a large effect (Cohen, 1988).

To analyze the impact of age and clinical features on time-to-remission, survival analyses were conducted using the Kaplan-Meier method (Kaplan and Meier, 1958; Kleinbaum and Klein, 2012). Log-rank tests were used to test whether the survival curves for the age groups were equivalent. Analyses were conducted using SPSS version 21.0. Finally, we estimated the mediating effects of psychomotor agitation, retardation and psychotic symptoms in the relationship between age (three age groups) and reduction of depressive symptoms. The size and significance of all direct and indirect paths between age and symptom reduction were estimated using structural equation modelling. Robust weighted least squares estimation was used to allow the inclusion of continuous and dichotomous variables into the model (Yuan and Bentler, 2000). Path analysis was conducted using MPlus version 7.4 (Muthén and Muthén, 2015).

3. Results

3.1. Patient characteristics

Of the 190 patients receiving ECT treatment between 2006 and 2015, 85 were excluded because they fulfilled one or more exclusion criteria, 6 patients dropped out because they refused further ECT treatment or patients were transferred to another department, and 3 patients dropped out because a reliable HAM-D and MADRS score was not obtainable due to severity of the depression with catatonic features and/or mutism. Finally, 96 patients (67% female) were included for analysis; mean age was 63.9 (SD 12.3, range 33–96) years (Fig. 1). Of these patients, 57 (59%) suffered from depression with psychotic features, 29% had an episode duration > 1 year, and the mean baseline HAM-D-score was 28.8 (SD 6.4).

Table 1 presents the clinical characteristics for the total patient sample and for the three age groups separately: YA: < 50 years (n = 13), MA: ≥50 and < 70 years (n = 50), and OA: ≥70 years (n = 33). In the MA group, 63% had pharmacotherapy failure, significantly less than in the YA and OA group; in the OA group, 42% of the patients were previously treated with ECT, significantly more than in the YA and MA group; in the YA group, 23% of the patients had psychotic features, significantly less than in the OA and MA group; and none of the patients in the YA group had psychomotor retardation, while more than half of the MA and OA patients showed psychomotor retardation. No differences between the age groups were found for sex, episode duration > 1 year, the presence of psychomotor agitation, number of ECT treatments, and baseline HAM-D score.

The mean reduction in HAM-D score was 21.3 (SD 9.0) points. Response was obtained in 82 (85%) patients, and 67 (70%) patients met the criteria for remission. The mean number of ECT sessions was 15.0 (SD 4.8). The average ECT charge was 219.6 mC for the YA group, 302.4 mC for the MA group and 386.4 mC for the OA group.

3.2. Effect of age on efficacy of ECT

There was no significant difference in HAM-D reduction between the three age groups. However, best treatment effect was observed in the MA group. YA showed worst effect. Difference (non-significant) between the MA and YA group was medium sized and difference between the OA and YA group was small sized. Further, the proportion of patients in remission was larger in the MA and OA group than in the YA

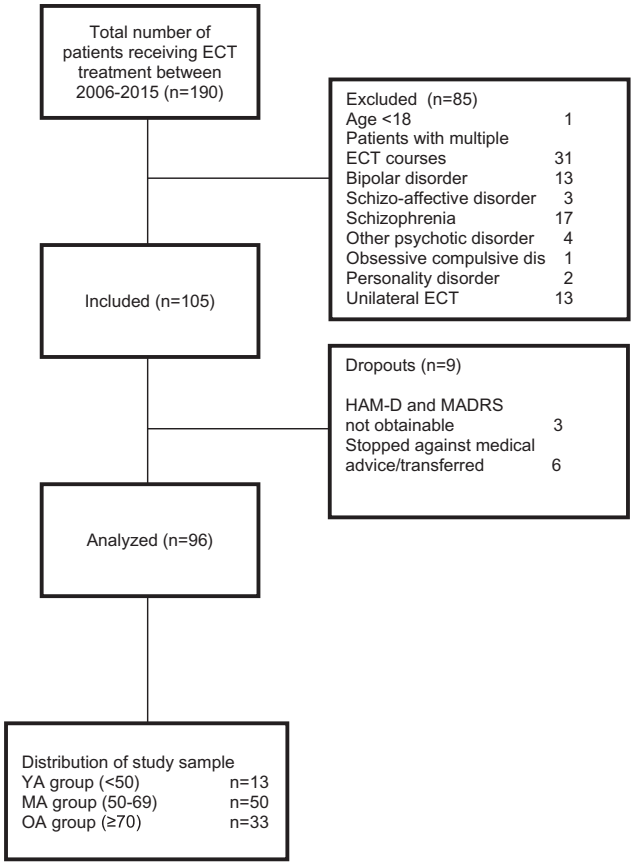

Fig. 1. Study flow diagram.

Table 1
Clinical characteristics of the study sample (n = 96).

	< 50 years: young age (n = 13)	50–69 years: middle Age (n = 50)	≥70 years: old age (n = 33)	Total (n = 97)	Test
Female, n (%)	8 (62)	31(62)	25 (76)	64(67)	$X^2(2) = 1.87$; p = 0.39
Treatment history					
Episode duration > 1 year, n (%)	6 (46)	13 (26)	9 (27)	28 (29)	$X^2(2) = 2.12$; p = 0.35
Pharmacotherapy failure[a], n (%)	12 (92)	31(63)	29 (88)	72(76)	$X^2(2) = 8.75$; p = 0.013
Previous ECT treatment, n (%)	1 (8)	4(8)	14 (42)	19(20)	FET $X^2 = 14.67$; p < 0.001
Phenomenology					
Psychotic features, n (%)	3 (23)	33(66)	21 (64)	57(59)	FET $X^2 = 7.94$; p = 0.020
Psychomotor retardation[b], n (%)	0 (0)	25(64)	19 (61)	44(54)	FET $X^2 = 14.97$; p < 0.001
Psychomotor agitation[b], n (%)	4 (40)	17(44)	8 (26)	29(36)	FET $X^2(2) = 2.48$; p = 0.30
Current treatment					
Mean number of ECTs (SD)	15.9 (4.1)	14.0(4.9)	15.5 (5.0)	14.7(4.8)	F(2) = 1.42; p = 0.25
Mean baseline HAMD score (SD)	27.5 (4.8)	29.5(7.0)	28.1 (6.3)	28.8(6.4)	F(2) = 0.66; p = 0.52

Notes: [a] Missing N = 1; [b] Missing N = 16.

group; however, this difference was not significant. RRs suggest a small effect between the YA and MA group and between the YA and OA group (Table 2).

3.3. Effect of age on time to remission

The average time to remission was 9.1 weeks in the YA group, 7.4 weeks in the MA group, and 7.8 weeks in the OA group. There was no significant difference in time to remission when comparing the three age groups. Pairwise comparisons showed a trend to significance in favor of the MA group over the YA group (Table 2).

3.4. Effect of symptomatology on efficacy of ECT

The efficacy of ECT, as measured by the mean reduction in HAM-D score, was significantly superior in patients with psychotic features compared to patients without psychotic features; a large effect size was found. However, there was no significant difference in the rate of patients attaining remission between patients with or without psychotic features; the RR suggests a small effect.

The mean reduction in HAM-D score was significantly larger in patients with psychomotor retardation compared to patients without psychomotor retardation, with a medium effect size. There was a trend to a significantly higher rate of patients attaining remission among inpatients with psychomotor retardation, compared with patients without retardation; the RR suggests a small effect.

Small, non-significant differences were found in mean reduction in HAM-D score and remission rate between patients with and without psychomotor agitation (Table 2).

3.5. Effect of symptomatology on time to remission

Survival analyses support these findings. That is, remission was achieved approximately one week earlier in patients with psychotic features and psychomotor retardation, and 3–4 days earlier in patients without psychomotor agitation. However, none of these effects reached significance (Table 2).

3.6. Mediating effects of symptomatology

Table 3 and Fig. 2 show the results of the path analysis. In line with earlier analysis the path analysis reports no significant association between age and reduction of depressive symptoms (total effect of age), significant direct relationships between psychomotor retardation and psychotic symptoms on symptom reduction, and no significant relationship between psychomotor agitation and symptom reduction. Regarding the indirect paths, we found a significant mediating pathway through psychomotor retardation. Psychotic symptoms showed a trend towards mediation. Both indirect paths were positive, meaning that older age was associated with more psychotic symptoms and psychomotor retardation, resulting in larger depressive symptom reduction. With regards to psychomotor agitation, we found a negative non-significant association. Overall, we found a trend (p = 0.058) towards mediation of the association between age and symptom reduction by clinical features. The direction of the remaining direct path between age and symptom reduction conversed to negative (older age relates to less symptom reduction), but was not significant.

4. Discussion

4.1. Effect of age on the efficacy of ECT

We failed to find a significant difference when examining the primary outcome criteria. However, medium sized differences in favor of the middle aged (MA) group and small sized differences in favor of the old aged (OA) group when compared with the young aged (YA) group suggest a correlation between older age and higher ECT efficacy.

The reduction in HAM-D scores was 3–4 points larger in the OA and MA group when compared with the YA group, which is a clinically relevant difference. No differences were found between the groups for baseline HAM-D scores. No significant difference was found according to the secondary outcome criterion. However, the MA and OA group achieved remission almost 1,5 to 2 weeks earlier than the YA group.

The differences between the YA group versus the MA and OA group most likely failed to reach significance due to the small number of patients in the YA group. Furthermore, the high rate (70%) of patients that met the criteria for remission in the total study group made it difficult to detect potential differences in efficacy (i.e. ceiling effect).

4.2. Effect of symptomatology on the efficacy of ECT

As measured by mean reduction in HAM-D score, the ECT efficacy was significantly superior in patients with psychotic features and a large difference in effect was found. The fact that no difference was found between patients with versus without psychotic features when comparing rates of patients attaining remission, is probably due to the fact that the mean HAM-D baseline score of patients with psychotic features was 6 points higher compared to the non-psychotic patients. Also, the previous mentioned high remission rate of the total group made it difficult to detect potential differences.

Patients with psychomotor retardation had higher ECT efficacy with a significant difference when measured by mean reduction in HAM-D

Table 2
The impact of age and symptomatology on ECT treatment effect (N = 96).

	N	Mean reduction HAM-D (SD)	Test/Effect size	Remission, N (%)	Test/Effect size	Mean time to remission in weeks (SE)	K-M Test
Age			F(2) = 1.03; p = 0.36		$X^2(2) = .56$; p = 0.76		$X^2(1) = .91$; p = 0.34
< 50 yrs (YA)	13	18.3 (9.5)	YA vs MA: *d* = 0.44	8 (62)	YA vs MA: RR = 0.92	9.1 (0.8)	YA vs MA: $X^2(1) = 2.29$; p = 0.13
50–69 yrs (MA)	50	22.3 (8.8)	YA vs OA: *d* = 0.30	35 (70)	YA vs OA: RR = 0.86	7.4 (0.5)	YA vs OA: $X^2(1) = 1.87$; p = 0.17
> 69 yrs (OA)	33	21.1 (9.2)	MA vs OA: *d* = 0.13	24 (73)	MA vs OA:RR = 0.92	7.8 (0.5)	MA vs OA: $X^2(1) = 0.13$; p = 0.72
Psychotic features			T(95) = 4.05; p < 0.001		$X^2(1) = 0.30$; p = 0.58		$X^2(1) = 2.97$; p = 0.09
Present	57	24.2 (8.7)	*d* = 0.88	41 (72)	RR = 1.16	7.3 (0.4)	
Absent	39	16.9 (7.8)		26 (67)	reference	8.5 (0.5)	
Psychomotor retardation[a]			T(79) = 2.88; p = 0.005		$X^2(1) = 2.51$; p = 0.11		$X^2(1) = 2.91$; p = 0.09
Present	44	24.6 (9.2)	*d* = 0.66	33 (75)	RR = 1.48	7.5 (0.4)	
Absent	36	18.9 (8.1)		21 (58)	reference	8.5 (0.6)	
Psychomotor agitation[a]			T(79) = 1.35; p = 0.18		$X^2(1) = 0.61$; p = 0.43		$X^2(1) = 0.38$; p = 0.54
Present	29	23.8 (8.3)	*d* = 0.31	18 (62)	RR = 0.87	8.3 (0.7)	
Absent	51	21.0 (9.5)		36 (71)	reference	7.8 (0.4)	

Notes: [a] Missing N = 16.

Table 3
Path model: Standardized direct and indirect effects of age and clinical features on depressive symptoms in patients treated with ECT resulting from SEM-analysis (N = 96). Significant effects are in bold script.

	Reduction of Depressive Symptoms		
	Estimated	SE	p-value
Age (ordinal)			
Direct effect	-.19	.13	.143
Indirect effects	.25	.13	.058
Age-Agitation-Depressive symptoms	-.03	.04	.346
Age-Retardation-Depressive symptoms	**.16**	.08	.049
Age-Psychotic symptoms-Depressive symptoms	.13	.07	.071
Total effect	.06	.10	.580
Psychomotor agitation			
Direct effect	-.19	.14	.156
Psychomotor retardation			
Direct effect	**.45**	.12	< .001
Psychotic symptoms			
Direct effect	**.52**	.19	< .001

scores and trend towards significance when measured by remission rates.

4.3. Comparison with other studies: influence of age on the efficacy of ECT

Two recent meta-analyses (Haq et al., 2015; van Diermen et al., 2018) found a positive association between older age and higher ECT efficacy, but this association was weak. Also, the results of the present study with a homogeneous patient population found a larger symptom reduction in older age, but this was non-significant. The present study found that the association between age and ECT efficacy is mediated by psychomotor retardation (p = 0.049) and in lesser extent by psychotic features (p = 0.071). Thus heterogeneous results in previous studies (Birkenhager et al., 2010; Bloch et al., 2001; Damm et al., 2010; Nordenskjold et al., 2012; O'Connor et al., 2001; Spashett et al., 2014; Tew et al., 1999) may be explained by differences in mediatory factors between the studies.

4.4. Comparison with other studies: influence of symptomatology on the efficacy of ECT and mediating effects of symptomatology

The higher efficacy to ECT we found in patients with psychotic features is in agreement with others (Birkenhager et al., 2003; Loo et al., 2011; Petrides et al., 2001). Moreover, our finding of a higher efficacy of ECT in patients with psychomotor retardation is in accordance with Hickie et al. (1996) who found that marked psychomotor disturbance and psychotic features were independently associated with a superior response to ECT. In that study, the combination of psychotic features and marked psychomotor disturbance was associated with the best response to ECT. In depression with psychotic features, biological mechanisms such as shortened REM latency and dexamethasone non suppression are very often observed (Staner and Mendlewicz, 1991). Psychomotor disturbance is one of the strongest indicators of melancholic depression (Parker and McCraw, 2017) and melancholic features are also associated with biological mechanisms like shorter REM latency and dexamethasone non suppression (Rush and Weissenburger, 1994).

In the present study, the positive indirect pathway age-psychomotor retardation, meaning that older age was associated with more psychomotor retardation is in agreement with Brodaty et al. (1997) who found

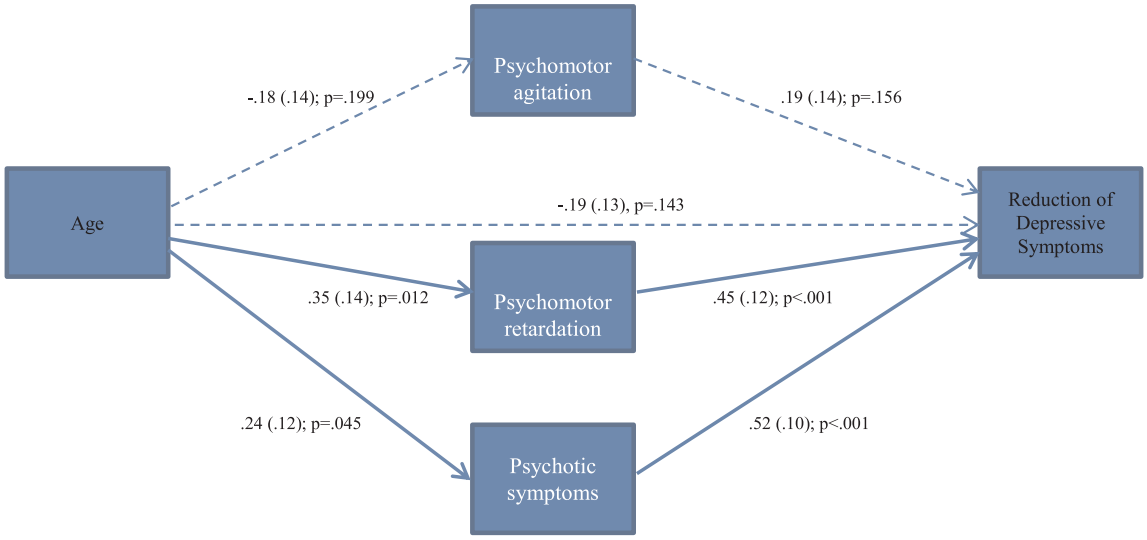

Fig. 2. Path model of the relationship between age, clinical features and ECT efficacy on depressive symptoms. . Age is modelled as ordinal variable (three age groups YA < 50 yrs; MA ≥ 50 and < 70 yrs; OA ≥70 yrs) (N = 96). Standardized coefficients, standard error and p-value are reported. Significant paths (p < 0.05) are depicted as bold lines; non-significant paths are depicted as dashed lines.

that psychomotor disturbance is more common in elderly patients.

Only a few studies investigated possible explanations for the finding that older age predicts a higher efficacy of ECT. O'Connor et al. (2001) suggested that the superior response to ECT they found in older age may be a function of a higher percentage of psychotic features in older age. In our study, we also investigated psychomotor disturbance and psychotic features as a possible explanation for the association between age and ECT efficacy. The path analysis showed that psychomotor retardation and psychotic features mediate the association between age and ECT efficacy. Therefore, the association between age and ECT efficacy may not always emerge since the presence of psychomotor retardation and psychotic features may vary between studies.

4.5. Strengths and limitations

The present study investigated a sample of severely depressed patients with a mean baseline HAM-D score of 29, of which 59% had psychotic features. The homogeneity of the diagnosis, the severity of the depressive symptoms and the wide age range of the population are considered major strengths. **Further, the fact that the use of benzodiazepines during ECT was not allowed is considered a strength since benzodiazepines have a negative effect at least on the efficacy of right unilateral (RUL) ECT** (Jha and Stein, 1996). **This may also apply to bilateral (BT) ECT.** Also, diagnosing major depression during a drug-free observation period and the prospective design are strengths of this study.

The most important limitations are the relatively small sample size and the fact that patients are not equally distributed between the three age groups, with only 14% of the patients in the young-age group and over 50% of the patients in the middle-age group. The exclusion of patients that refused further ECT treatment might have overestimated the efficacy of ECT. Our findings pertain to patients treated with BT ECT at 1 ms pulse width given twice weekly. The findings may not be generalizable to RUL, BF (bifrontal) or BT ECT at different frequency.

Psychomotor retardation and agitation were defined according to item 8 and 9 of the HAM-D17, respectively, which is another limitation. In analyzing reduction in total HAM-D scores it is possible that these specific HAM-D items were partly accountable for higher baseline scores since a higher score on item 8 and/or 9 leads to a higher total baseline HAM-D score.

Future studies could investigate mediating factors with more precise evaluation tools, like the CORE for psychomotor disturbance, and the Psychotic Depression Assessment Scale (PDAS) (Ostergaard et al., 2014) for psychotic features, since these tools might provide more convincing evidence.

5. Conclusion

ECT is most effective in patients with psychotic features and patients with psychomotor retardation showed. Furthermore, our results show that these symptoms also mediate the association between older age and ECT efficacy, thereby providing a rationale for the heterogeneous results found in scientific studies for the impact of age on ECT efficacy. The observation of obvious psychomotor retardation may be an argument for treatment with ECT earlier in the treatment algorithm in severely depressed patients.

Declaration of conflicting interests

All authors declare that there are no conflicts of interest.

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