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A systematic review of pretreatment predictors

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Review article

Psychotic depressive subtype and white mater hyperintensities do *not* predict cognitive side effects in ECT: A systematic review of pretreatment predictors

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ABSTRACT

Background: Most studies regarding cognitive side-effects following ECT for treating depression report transient forms of cognitive disturbances. However, a growing number of studies also report considerable differences among individual patients.
Objective: The aim of this systematic review was to identify pretreatment patient characteristics for predicting the risk of developing cognitive side-effects following ECT.
Methods: Online databases PubMed/Medline, Embase, and PsycINFO were searched for articles published from 2002 through May 2019, using the following relevant search terms: #cognitive deficits AND #Electro Convulsive Therapy. Inclusion and exclusion criteria were applied for full-text inclusion. PRISMA guidelines were used.
Results: Our initial search yielded 2155 publications; 16 studies were included. A total of 16 possible predictive factors were identified. Two factors, psychotic features and white matter hyperintensities, were conclusively found to not predict cognitive side-effects following ECT; the remaining 14 factors were inconclusive.
Conclusions: There is robust evidence that psychotic features and white matter hyperintensities are not predictive of cognitive side-effects following ECT. None of the other 14 factors examined were predictive, however these levels of evidence were weak and therefore inconclusive. Additional studies focusing primarily on pretreatment patient characteristics for predicting cognitive side-effects following ECT are needed, including demographic, clinical, physiological, neurobiological, and genetic factors. Finally, we provide suggestions for future research.

Introduction

Most studies regarding electroconvulsive therapy (ECT) for treating depression focus primarily on treatment efficacy, with the results strongly suggesting that ECT is the most effective treatment for drug-resistant depression (Lisanby, 2007). In recent decades, research has contributed to the continued improvement and advancement of treatment applications/techniques and treatment parameters (Sienaert et al., 2017). Although not fully understood, several neurobiological and neurophysiological mechanisms underlying the therapeutic effect of ECT have been suggested and include changes in gene expression, functional connectivity, neurochemicals, hormones, and neuroplasticity, as recently reviewed (Pirnia et al., 2016; Singh and Kar, 2017).

Despite its clinical advantages, there is ongoing concern regarding the cognitive side effects of ECT. These can include disorientation in the postictal stage, anterograde amnesia, and retrograde amnesia. Other side effects have been reported in neuropsychological domains, including attention and executive functioning (e.g., fluency and cognitive flexibility) (McClintock et al., 2011, Semkovska et al., 2011). Most studies report that ECT-related cognitive side effects are transient irrespective of the patient's age and the ECT protocol used, including electrode position and stimulus parameters (Verwijk et al., 2014).

Knowledge regarding post-ECT changes in cognitive performance is based primarily on the average outcome measured in group studies; however, a growing number of studies have reported considerable

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inter-individual differences with respect to cognitive side effects (Dybedal et al., 2014, Hausner et al., 2011). For example, Obbels & Verwijk et al. (Obbels et al., 2018) used the Reliable Change Index (Jacobson and Truax, 1991) and detected individual post-ECT differences in multiple cognitive domains in subgroups of elderly patients with depression. Importantly, these adverse cognitive outcomes were not revealed when analyzing overall group data, and these inter-individual differences occurred regardless of treatment outcome (i.e., successful treatment of depression) and regardless of differences in stimulus parameters, such as pulse width and bilateral versus unilateral ECT electrode placement. Moreover, Dybedal et al. (2014) reported that a subgroup within their cohort had a significant post-ECT decline in functioning measured using at least two neuropsychological tests, although cognitive performance either improved or was unchanged in the overall group analysis. These findings suggest that robust individual differences exist with respect to the brain's response to ECT, leading to either improved or impaired cognitive performance.

Although the mechanisms that underlie ECT-related cognitive side effects are largely unknown, researchers recently attempted to develop a model that combines several factors, including demographic and neuropsychological characteristics, neuropsychiatric symptoms, ECT parameters, and ECT-associated neurophysiological changes (McClintock et al., 2014). However, this model does not take into consideration inter-individual differences; in other words, although most patients tolerate ECT relatively well, a small subgroup of patients experience severe adverse cognitive effects. Therefore, the ability to identify patients who might be at risk for developing these adverse cognitive outcomes would be extremely valuable. Sobin et al. (1995) emphasized the importance of better understanding these individual differences and they suggest a possible relation between baseline cognitive functioning and post ictal reorientation time and vulnerability to persistent retrograde amnesia post ECT. In this respect, several factors for predicting ECT-related cognitive side effects have been suggested, including demographic, clinical, physiological, anatomical, and genetic factors (Sobin et al., 1995, Goder et al., 2016, Neylan et al., 2001). The aim of this systematic review was therefore to examine the published literature in order to identify individual patient characteristics that could be used to predict the risk of cognitive side effects in patients who undergo ECT for treating depression.

Material and Methods

In this systematic review, we used PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Liberati et al., 2009).

We performed an online search of the databases PubMed/Medline, Embase, and PsycINFO for papers published from 2002 through May 2019 using the search terms “cognitive deficits” and “electroconvulsive therapy”, including related MeSH terms (Figure 1). The search results were combined, and duplicates were removed. Two researchers (authors MvK and EV) independently screened the titles and abstracts of all 1838 unique records. Of the remaining records, the full-text articles were retrieved and were again screened for eligibility independently by authors MvK and EV. In case of disagreement, consensus was sought through discussion, if necessary, with a third researcher (author JvdV).

The following inclusion criteria were used: 1) a randomized control study or prospective (observational) design; 2) the study population consisted of patients 18 years of age or older who had unipolar, bipolar, or psychotic depression and were treated with index ECT; 3) the primary focus of the study was cognition or treatment outcome; 4) pre-treatment predictive factors and pre-ECT and post-ECT cognitive functioning were reported; and 5) the article was written in Dutch, English, German, or French. Cohen's kappa (κ) was used to determine the level of agreement between two raters with respect to article selection.

The patient and study characteristics, inclusion and exclusion criteria, and univariate or multivariate results were extracted from the included articles by author MvK and were checked independently by author EV. Only pretreatment patient characteristics and cognitive outcome were extracted; treatment outcome and treatment predictors were not extracted. If relevant multivariate results were reported in a study, the univariate results were not extracted; if relevant multivariate analyses were not available, the univariate results were extracted.

To evaluate the methodological quality of all included studies, authors MvK and EV used a list of criteria based on a framework for assessing the validity of prognostic/predictive studies (Altman, 2001). This list consisted of 15 items that were scored as either positive (1) or negative (0). A study was considered to be “high quality” if the total score was ≥ 8; a total score of ≤ 7 was considered to indicate a “low quality” study. In the case of disagreement, the ratings were discussed in a consensus meeting with author JvdV available as needed. Cohen's kappa (κ) was again used to determine the level of agreement between two raters with respect to the quality scores.

To establish the level of evidence for each putative factor for predicting cognitive outcome, a best-evidence synthesis was performed using the following criteria: a “strong level of evidence” refers to consistent findings ($\geq 75\%$) in ≥ 2 high-quality articles; a “moderate level of evidence” refers to one high-quality article and consistent findings ($\geq 75\%$) in ≥ 1 low-quality article; a “limited level of evidence” refers to consistent findings ($\geq 75\%$) in ≥ 2 low-quality articles; and an “inconclusive level of evidence” refers to inconsistent findings irrespective of article quality or a predictive factor mentioned in only one article.

Results

Selected articles

Our initial search yielded a total of 2155 records. After duplicate records were moved, a total of 1838 unique records remained, for which the titles and abstracts were screened. In total, 154 full-text articles were screened, of which 16 articles met the inclusion criteria (Dybedal et al., 2014, Hausner et al., 2011, Obbels et al., 2018, Boere et al., 2016, Bosboom and Deijen, 2006, Bousman et al., 2015, Haghighi et al., 2013, Lekwauwa et al., 2006, Martin et al., 2015, Nehra, 2007, Nuninga et al., 2018, Oudega et al., 2014, Piccinni et al., 2013, Sackeim et al., 2007, Schat et al., 2007, van Waarde et al., 2013). The search strategy is shown in Figure 1. The overall inter-observer agreement regarding the article selection process was extremely high ($\kappa = 0.90$).

Methodological quality

The overall inter-observer agreement regarding the methodological quality was also extremely high ($\kappa = 0.94$). For the most part, any disagreement was due to differences in interpretation and was easily resolved. Table 1 summarizes the outcome of our methodological quality assessment. Of the 16 studies included in our analysis, 15 were considered “high quality” and 1 study (Lekwauwa et al., 2006) was considered “low quality”. A meta-analysis was considered, but not deemed feasible due to the large diversity between the different studies.

The most common methodological shortcomings among the studies were exceeding a 20% dropout rate, an absence of—or incomplete—information regarding dropouts, and loss to follow-up.

Some of the studies reported primarily percentages or frequencies, whereas other studies reported associations between groups. In addition, the use of appropriate univariate and/or multivariate analyses differed significantly between studies. When relevant multivariate results were presented, the univariate results were usually not displayed. No multivariate analyses regarding predictive patient characteristics were presented in five studies (Bosboom and Deijen, 2006, Lekwauwa et al., 2006, Nehra, 2007, Oudega et al., 2014, Piccinni et al., 2013), and cognitive outcome was limited to the Mini-

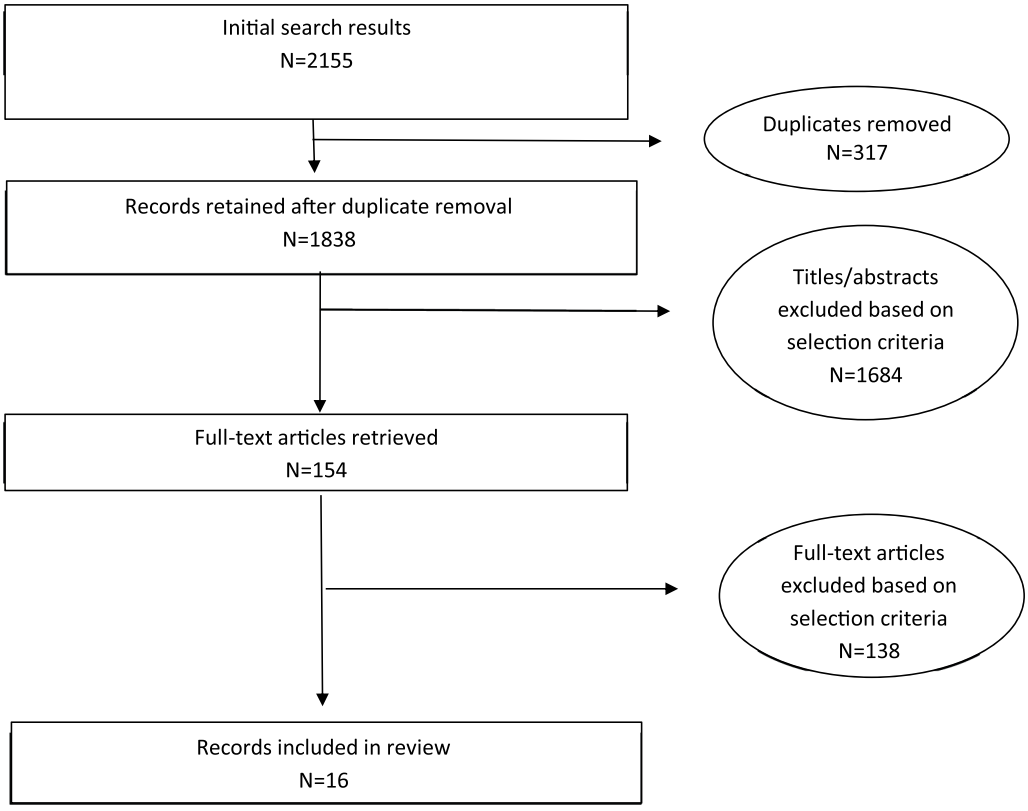

Figure 1. Flow chart depicting search strategy and selection criteria for the articles used in this review.

Mental State Examination (MMSE) in five studies (Hausner et al., 2011, Haghighi et al., 2013, Lekwauwa et al., 2006, Oudega et al., 2014, van Waarde et al., 2013).

Pretreatment predictors of cognitive side effects following ECT

The 16 studies that reported pretreatment factors for predicting cognitive outcome are summarized in Table 2. Among these 16 studies, sample size ranged from 11 to 347 patients (Boere et al., 2016, Sackeim et al., 2007), and the timing of the cognitive assessment ranged from immediately after the last ECT session to 12 months after the last ECT session (Bousman et al., 2015, Lekwauwa et al., 2006, Martin et al., 2015, Sackeim et al., 2007, Schat et al., 2007). Cognitive outcome was measured using a wide variety of methods, including different tests and different ways of analyzing and/or standardizing the results. Moreover, the cut-off points, nominal classifications, and analyses used to classify test scores varied widely among the studies. With respect to the statistical methods used to determine a possible "pretreatment predictive factor" for cognitive outcome, these included correlations, associations, and regression analyses. Some studies used a stepwise method for including covariates in their analysis, and some studies controlled for factors such as age and/or gender.

In total, we identified 16 pretreatment factors that might predict cognitive outcome following ECT (Table 3). Our analysis revealed that 14 of these 16 pretreatment factors were inconclusive with respect to serving as possible predictive factors. Moreover, we found strong evidence that the remaining two factors—namely, psychotic features and white matter hyperintensities—are conclusively not predictive of cognitive side effects following ECT in depressed patients.

Discussion

To the best of our knowledge, this is the first systematic review of published literature regarding pretreatment predictors of cognitive side effects in patients following ECT treatment for depression.

Among the 16 factors that were identified, 14 had an inconclusive level of evidence for their predictive value, and this was due largely to conflicting results among the studies that were included in this review. On the other hand, we found strong evidence that two factors—psychotic features and white matter hyperintensities—are conclusively not predictive of cognitive side effects following ECT.

With respect to the efficacy of ECT in treating depression, a recent meta-analysis by van Diermen et al. (2018) found that psychotic depression is a significant predictor of both response and remission in these patients. Taken together with our finding that psychotic features do not appear to increase the risk of cognitive side effects, these results suggest that ECT is both highly effective and well tolerated for treating psychotic depression.

Two of the studies in our analysis found that white matter hyperintensities do not predict cognitive side effects following ECT, providing a strong level of evidence (Oudega et al., 2014, van Waarde et al., 2013). We believe this is a clinically relevant finding, particularly given that the presence of white matter hyperintensities is often regarded as a sign of vulnerability with respect to developing cognitive deficits (Breteler et al., 1994).

One study reported that the presence of white matter lesions in combination with atrophy (Hausner et al., 2011) was not predictive factor of cognitive deficits. Another study examined other anatomical features on MRI, including cerebrospinal fluid, gray matter, white matter, and hippocampal volume (van Waarde et al., 2013). Based on the data given in these two studies, it is unclear how these features were specifically assessed, and therefore how comparable they are. However, all of these features—which are closely related to white matter hyperintensities—were also found to be not predictive of cognitive side effects. Given that they were mentioned in only one study, the level of evidence in our review is therefore considered inconclusive in accordance with PRISMA guidelines. As a whole, our results do not

Table 1
Methodological quality of the 16 studies included in this review.

	1. Patient samples			2. Follow-up			3. Treatment	4. Predictive factors			5. Cognitive outcome			6. Analysis		Quality
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	
Obbels et al. (2018)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	High (15)
Nuninga et al. (2018)	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	High (14)
Boere et al. (2016)	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	High (13)
Dybedal et al. (2014)	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	High (13)
Sackeim et al. (2007)	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	High (13)
Martin et al. (2015)	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	High (12)
Schat et al. (2007)	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	High (12)
Bosboom and Deijen, 2006)	1	1	1	1	0	1	1	1	1	0	1	1	0	1	0	High (11)
Bousman et al. (2015)	1	0	1	0	0	0	1	1	1	1	1	1	1	1	1	High (11)
Hausner et al. (2011)	1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	High (11)
van Waarde et al. (2013)	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	High (11)
Haghighi et al. (2012)	1	1	1	0	0	0	1	1	1	1	0	0	1	1	1	High (10)
Piccinni et al. (2013)	1	1	1	0	0	0	1	1	1	1	0	1	1	1	0	High (10)
Nehra, (2007)	1	1	1	0	0	0	1	1	1	0	1	1	0	0	0	High (8)
Oudega et al. (2014)	1	1	1	0	0	0	1	1	1	1	0	0	1	0	0	High (8)
Lekwauwa et al. (2006)	1	1	1	0	0	0	0	1	1	1	0	0	0	0	0	Low (6)
Total	16/16 (100%)	15/16 (94%)	16/16 (100%)	7/16 (44%)	2/16 (14%)	6/16 (38%)	14/16 (88%)	16/16 (100%)	1-6/16 (-1-0-0-		%)	13/16 (81%)	10/16 (63%)	11/16 (69-%)	13/16 (81-%)	12/16 (75%)
11/16 (69%)																

A = Prospective cohort; B = Description of source population; C = Description of relevant inclusion and exclusion criteria; D = Follow-up ≥3 months; E = Drop out and loss to follow-up <20%; F = Description of drop out and loss to follow-up; G = Treatment in cohort fully described/standardized; H = Clinically relevant potential predictive factor; I = Standardized or valid measurements; J = Presentation of most important predictive factors; K = Clinically relevant outcome measurements; L = Standardized or valid measurements; M = Presentation of most important outcome measurements; N = Appropriate univariate crude estimates; O = Appropriate multivariate analysis techniques used.

Table 2
Summary of pretreatment factors for predicting cognitive outcome.

Study	No. of patients	Age in years	ECT method No. of sessions	Cognitive assessment	Post-ECT assessment	Pretreatment predictors of cognitive outcome	Result (S or NS)
Boere et al. (2016)	11	M: 59.55 (SD: 15.3)	BL M: 12.6	Rey Auditory Verbal Learning Test, Visual Association Test	1 month	Age, Depression severity Change in depression severity Psychotic features	S NS NS NS
Bosboom and Deijen, 2006)	21	M: 56,76 (SD: 14.12)	RUL, BT M: 12.7	Stroop Color-Word Interference Test, Dutch 10-Word List Memory Test, The subtests Information, Orientation, Mental Control, Logical Memory, Digit Span Forward and Backward, Visual Reproduction, and Associative Learning from the Wechsler Memory Scale, GIT subtests Verbal Meaning, Word Fluency, Word Matrices, Visualization, and Closure Speed, Memory and Orientation Questionnaire, Benton Revised Visual Retention Test, The Subtest Digit Symbol of the Dutch Wechsler Adult Intelligence Scale	1-2 weeks, 6 & 12 months	Age	NS
Bousman et al. (2015)	117	M: 48 (SD: 14)	RUL, BF, BT M: 9	Medical College of Georgia Complex Figure Test, Hopkins Verbal Learning Test-Revised, Letter Fluency, Animal Fluency, Cross Out task, Symbol Digit Modalities Test, Autobiographical Memory Inventory Short Form	0-3 days	Interaction effect DRD2xBDNF polymorphisms (less decline) COMT APOE	S NS NS
Dybedal et al. (2014)	54	M: 74.2 (SD: 6.7)	RUL, BF M: not specified	Stroop Color-Word Interference Test, Hopkins Verbal Learning Test-Revised) Tower Test (D-Kefs), Letter fluency, Animal Naming Test, Media Questionnaire, AMISF	1 week & 3 months	Not cognitive impaired at baseline Cognitive impaired no dementia at baseline	NS NS
Haghighi et al. (2012)	40	M: 31.8 (SD: 8.06)	BF M: not specified	MMSE	Post-ECT (not specified)	Gender (female) Age Educational level	S NS NS
Hausner et al. (2011)	44	M: 73 (SD: 6)	BL M: 12	MMSE	6 weeks & 6 months	Preexisting cognitive deficits Preexisting MRI pathology and age	S NS
Lekwauwa et al. (2006)	15	M: 73.6 (SD: 7.96)	Not specified M: 11.4	MMSE	Post-ECT (not specified)	Hippocampal volume	NS
Martin et al. (2015)	74	M: 56.4 & 47.3 (SD: 9.9 & 12.9)	RUL, BT M: 8.8 & 8.9	AMI-SF	1-3 days	Age Gender Baseline MMSE Predicted premorbid IQ	NS NS NS NS
Nehra, 2007)	32	M: 37.65 (SD: 11.65)	BL M: 5.88	MMSE, PGIMS	1 week & 1 month	MMSE	S
Nuninga et al. (2018)	43	M: 51.1 SD: 14.48)	BT M: 20.64	Rey Complex Figure test, Rey Auditory Verbal Learning Test, Letter Fluency Test, Category Fluency Test, Stroop Color-Word Interference Test, Digit Span subtest of the Wechsler Adult Intelligence Scale IV, Trail Making Test A & B, National Adult Reading Test	After 10 sessions & 6 months after the 10th session	Premorbid IQ	NS
Obbels et al. (2018)	110	M: 73.0 (SD: 8.4)	RUL, BT M: 14.3	Trail Making Test A & B, Clock drawing, Meander Figure subtest of the Amsterdam Dementia Screening Test, Letter Fluency Test, Rey Auditory Verbal Learning Test, 8-Words subtest of the ADS-6, Visual Association Test, Category Fluency Test.	1 week, 4 weeks and 6 months	Age Psychosis	NS NS
Oudega et al. (2014)	81	M: 74.0 (SD: 7.8)	RUL, BL M: 12.8	MMSE	1 week	White matter hyperintensities	NS
Piccinni et al. (2013)	25	M: 44.1 (SD: 11.9)	BL M: 8.3	MMSE (total score and Percentage Cognitive Improvement)	1 week	Aβ40/Aβ42 ratio at T0 Plasma amyloid beta levels (Aβ40, Aβ42)	S NS

(*continued on next page*)

Table 2 (*continued*)

Study	No. of patients	Age in years	ECT method No. of sessions	Cognitive assessment	Post-ECT assessment	Pretreatment predictors of cognitive outcome	Result (S or NS)
Sackeim et al. (2007)	347	M: 56.7 (SD: 17.6)	RUL, BL, BF M: not specified	MMSE, psychomotor function, Stroop Color-Word Interference test, continuous performance test, Buschke Selective Reminding Test, Complex Figure Test, AMI-SF	Post-ECT & 6 months	Age, Gender Premorbid IQ	S S
Schat et al. (2007)	96	M: 55.7 (SD: 13.5)	RUL, BL M: not specified	Rivermead Behavioral Memory Test, categorical word fluency	3 & 12 months	Age	S
van Waarde et al. (2013)	83	M: 59.2 (SD: 15.3)	RUL, BL M: 17.4	MMSE	1 week	Age Gender Psychotic features Bipolar depression Anatomical MRI characteristics (CSF, gray matter, white matter, WMH)	NS NS NS S NS

ADS-6: Amsterdam Dementia Screening Test 6; AMI-SF: Autobiographical Memory Inventory – Short Form; BF: Bifrontal electrode placement; BL: Bilateral electrode placement; BT: Bitemporal electrode placement; CSF: Cerebrospinal fluid; GIT: Geriatric Intelligence Test; M: Mean; MMSE: Mini -Mental State Examination; NS: Not significant; PGIMS: Punit Govil Intelligence Memory Scale; RUL: right unilateral; S: Significant; SD: Standard deviation; WMH, white matter hyperintensities.

provide a compelling reason for not considering ECT in patients with white matter hyperintensities."

Age, gender, pre-ECT cognitive functioning, premorbid IQ, and educational level were included in nearly every study regarding post-ECT cognitive outcome. In some studies, these factors were used merely to match the study and control groups or were controlled for in the statistical analyses. However, we found that all of these factors were inconclusive as possible predictive factors. One possible explanation for inconclusive—or conflicting—study results may be that in some studies age was entered in the statistical analysis as a covariate (Hausner et al., 2011) in a stepwise manner, whereas in other studies age was adjusted for in the logistic regression analysis (Oudega et al., 2014) or was entered as an independent variable (Schat et al., 2007). Bosboom et al. (Bosboom and Deijen, 2006) concluded that although short-term cognitive outcome differs between different age groups, cognitive improvement increased similarly among all age groups over the long term. Finally, a possible interaction effect may exist between age and pre-ECT cognitive functioning, warranting further study. They hypothesize that although age and baseline cognitive functioning may not independently predict cognitive side effects, when combined they may serve to predict cognitive outcome. However, a recent study by Obbels et al. (2019) found that baseline cognitive impairment in elderly patients should not be used as a reason to avoid the use of ECT in these patients. Nevertheless, the underlying mechanisms are largely unknown and should be studied in more detail.

Similar hypotheses can be formulated with respect to other demographic factors such as gender. In some studies, female gender was associated with more severe cognitive side effects following ECT (Haghighi et al., 2013, Sackeim et al., 2007). One possible explanation for this apparent gender bias is that women tend to have a lower seizure threshold, possibly related to differences in cranial thickness (van Waarde et al., 2013). Thus, the use of a fixed and/or age-related ECT dosing strategy may result in women receiving a relatively higher electrical dosages, which may lead to an increased susceptibility to develop cognitive impairment (McCall et al., 2000). Another possible explanation is the potential influence of sex hormones; however, this effect may differ between older women and younger women, and the relatively higher levels of estrogen in younger women might even provide a protective effect (Fernandez et al., 2003, Zarate et al., 2017).

We also found inconclusive results with respect to several clinical factors, including bipolar depression, depression severity, and a change in depression severity. Interestingly, the way in which depression was classified and objectified often differs between studies. In many cases, depression severity is defined using the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and is used as a tool to measure the efficacy of ECT and the change in depression severity. On the other hand, the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) (Association, A.P. 2013) is often used to differentiate between subtypes of depression (e.g., unipolar vs. bipolar depression, depression with vs. depression without psychotic features, etc.). In our systematic review, we included subtypes of depression as a possible predictive factor only when they were mentioned explicitly in the article. However, in some studies the way in which (change in) depression severity or the subtypes of depression were entered into the statistical analysis was unclear (Nehra, 2007).

With respect to neurobiology, plasma amyloid beta (Aβ40 and Aβ42) levels, the ratio between Aβ40 and Aβ42, and polymorphisms in the *BDNF, COMT, APOE*, and *DRD2* genes have been suggested as possible predictors of cognitive side effects (Bousman et al., 2015, Piccinni et al., 2013). Because these factors were limited to only one study in our review, their predictive value is inconclusive in accordance with PRISMA guidelines, regardless of the study's quality or sample size.

Studies have shown that ECT parameters such as electrode positioning, pulse width, and the number of ECT sessions may have an

Table 3
Pretreatment predictive factors of cognitive outcome and their corresponding level of evidence.

Pretreatment predictive factor	No. of studies	Significant predictor	Not significant predictor	Level of evidence
Psychotic features	3	0	3	STRONG
White matter hyperintensities	2	0	2	STRONG
Age	9	3	6	Inconclusive
Gender	4	2	2	Inconclusive
Baseline cognitive functioning				Inconclusive
- Not cognitive impaired vs. cognitive impaired no dementia	1	0	1	
- Baseline MMSE	3	2	1	
Predicted premorbid IQ	3	1	2	Inconclusive
Educational level	1	0	1	Inconclusive
Bipolar depression	1	1	0	Inconclusive
Depression severity	1	0	1	Inconclusive
Change in depression severity	1	0	1	Inconclusive
Preexisting MRI pathology (white matter lesions or atrophy)	1	0	1	Inconclusive
Anatomical MRI characteristics (CSF, gray matter, white matter, WMH)	1	0	1	Inconclusive
Hippocampal volume	1	0	1	Inconclusive
Plasma amyloid beta levels (Aβ40 and Aβ42)	1	0	1	Inconclusive
Plasma amyloid beta ratio (Aβ40/Aβ42)	1	1	0	Inconclusive
Polymorphisms (*BDNF, COMT, APOE*, and/or *DRD2*)	1	1	0	Inconclusive

CSF: cerebrospinal fluid; MMSE: Mini -Mental State Examination; WMH, white matter hyperintensities.

impact on post-ECT cognitive impairment (Semkovska et al., 2011, Andrade et al., 2016, Verwijk et al., 2012). Therefore, we extracted data regarding electrode placement and the number of sessions for use in our review. However, Verwijk (Verwijk, 2015) recently noted inter-individual variability in post-ECT cognitive outcome regardless of treatment outcome and differences in ECT application/parameters. Thus, although these parameters differed between studies, they are not expected to account for the relatively large number of inconclusive predictors identified in our review.

A major complication associated with comparing cognitive outcome between studies is the different ways in which the concept of "cognitive outcome" is operationalized and analyzed between different studies. For example, several studies (Hausner et al., 2011, Haghighi et al., 2013, Lekwauwa et al., 2006, Martin et al., 2015) used the MMSE (Folstein et al., 1975) as a global cognitive screening instrument for assessing baseline cognitive functioning as well as cognitive outcome, whereas other studies defined cognitive performance using several domain-specific cognitive tests (Dybedal et al., 2014, Obbels et al., 2018, Bosboom and Deijen, 2006, Bousman et al., 2015). In addition, Nehra et al. (Nehra, 2007) used the Punit Govil Intelligence Memory Scale (PGIMS) (Pershad, 1979), an adapted version of the Wechsler Memory Scale (Wechsler, 1987); although this test has local population norms, to the best of our knowledge no study has been conducted in order to determine whether the data are comparable to the original normative data, which significantly limits our ability to compare and make generalizations between studies.

Until recently, ECT research has focused primarily on treatment efficacy. Far less research has been done focusing primarily on cognitive side effect. Therefore, cognitive side effects are typically mentioned as a secondary outcome measure, and statistical methods are limited largely to analyses of correlation and univariate regression.

Because PRISMA guidelines were followed for this systematic review only multivariate data was extracted, even when both univariate and multivariate data were available. Most studies reporting both types of results, use univariate methods as preliminary analyses. Subsequently, only those variables reaching statistical significance, are entered into the multivariate analyses. Examining these studies for preliminary univariate analysis on (possible) relevant demographic predictors, such as age and gender, leads to similar inconclusive results regarding possible relevant demographic predictors. For instance, two studies report non-significant bivariate associations between cognitive outcome on the one hand and age and gender on the other (Bousman et al., 2015, Martin et al., 2015), whereas in one study (Haghighi et al., 2013) this association does reach significance.

Interestingly, in two studies (Bousman et al., 2015, Martin et al., 2015), premorbid IQ was not significantly associated with cognitive functioning after ECT treatment. These results seem to add to the evidence for the absence of predictive value of premorbid IQ for cognitive functioning after ECT and would strengthen the level of evidence found in this review. However, the resulting lack of uniform multiple regression analyses and the appropriate use of covariates limits the way in which conclusions can be drawn with respect to causality.

Limitations of this review

This review has several possible limitations that warrant discussion. First, the studies included in this review were not matched with respect to age, and the study populations differed widely with respect to mean age and age ranges. While some studies explicitly focused on elderly patients (Obbels et al., 2018), other studies included a broader age range (Sackeim et al., 2007). Thus, when comparing studies regarding predictive factors, large differences in age between study populations may limit the certainty of any conclusions that can be drawn.

Second, the lack of studies that focused primarily on post-ECT cognitive side effects required us to include articles in which cognitive side effects were used as a secondary outcome measure. This may have led to an increase in the heterogeneity of the statistical methods used, possibly contributing to an increased risk of type I and/or type II errors in hypothesis testing.

Other limitations include the fact that sample size (which ranged from 11 to 347) and the time to follow-up (which ranged from 1 day to 12 months after ECT) were not defined as inclusion or exclusion criteria due to the relatively small number of eligible studies. A small sample size can limit the study's generalizability to the general population, thereby limiting comparisons with studies that used a large sample size. Similarly, the time to follow-up varied widely among the studies included in this review, and studies have shown that cognitive performance can improve even 6 months after ECT (Mohn and Rund, 2016). In our study, however, separating the different endpoints would not have led to different levels of evidence for any of the possible prognostic factors.

Given that 14 of the 16 factors were inconclusive, this review should be considered a first step towards additional research. Future studies regarding pretreatment predictors should focus on demographic, clinical, physiological, neurobiological, and genetic aspects in addition to the putative predictors that were included in our review. We also recommend the use of an extended cognitive assessment battery that is both sensitive to ECT-related cognitive change and focuses on memory

and executive functioning both before and immediately after ECT. Finally, we recommend that future studies include a follow-up period of 3-6 months.

In summary, our analysis supports the development of a model incorporating pretreatment patient characteristics for predicting the risk of cognitive side effects following ECT, taking into account inter-individual variability. Using such a model, patients who have a higher risk of developing cognitive deficits could be identified prior to the start of ECT and monitored more closely. This approach could also significantly improve joint decision-making with respect to treatment policy, as well as the way in which patients are informed regarding the potential cognitive side effects through psycho-education, as noted nearly two decades ago by Sackeim (Sackeim, 2000) and more recently by Verwijk et al. (2017).

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Disclosures

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Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.03.181.

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