Cognitive Side Effects in ECT Studies: Meta-analyses

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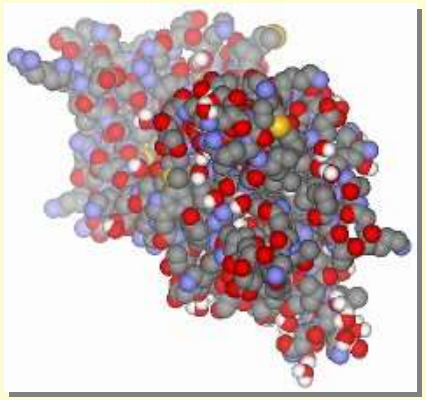


1. ECT in Ireland

2. EFFECT-Dep Trial

3. Meta-analysis #1 – Bitemporal vs Bifrontal ECT

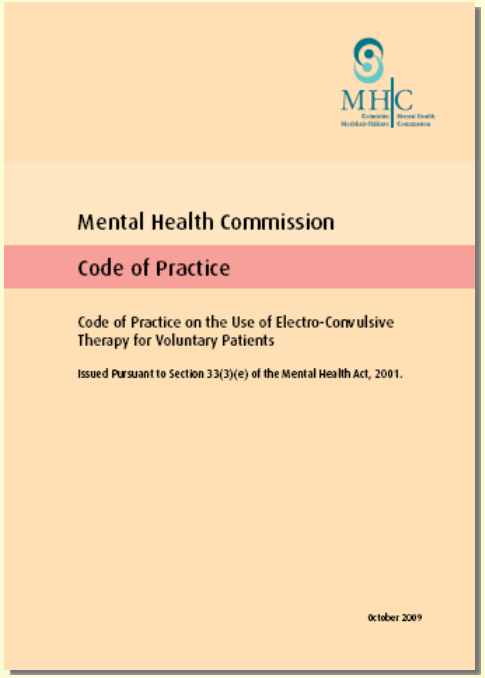
4. Meta-analysis #2 – Cognition following ECT

5. Meta-analysis #3 – Unilateral ECT and cognition

6. Future directions (Modest proposals)

1. Depression & ECT in Ireland

- 6,500 hospital admissions (2008)
- Costs the Irish economy €1bn with €283m direct costs (2004)
- Burden of morbidity ~959 DALYS lost per 100,000 population per year
- 450 persons had ECT in 2008
    - 403 voluntary
    - 47 involuntary (~90% improved)



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'He gave what little wealth he had
To build a house for fools and mad;
And show'd by one satiric touch,
No nation wanted it so much.

Dean Jonathan Swift (1667-1745)

A Tale of a Tub

A Modest Proposal

Gulliver's Travels

2. The EFFECT-Dep Study

OBJECTIVES OF THE 5-YEAR PROGRAMME

(1) to perform a pragmatic randomised controlled non-inferiority trial comparing standard bilateral ECT (1.5 x ST) and high-dose unilateral ECT (6 x ST) in severe depression

Primary outcome measures:

- **Hamilton Depression Rating Scale**
- **Autobiographical Memory Interview**
- **Events Questionnaire**

Recruitment began May 2008

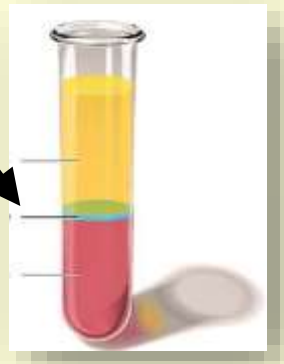
EFFECT-Dep Trial

Assessment	Baseline	Wk 1	Wk 2	Wk 3	End of course	F/U: 2 wk	F/U: 4 wk	F/U: 6 wk	F/U: 8 wk	F/U: 3 mth	F/U: 4 mth	F/U: 6 mth	F/U: 9 mth	F/U: 12 mth
DIAGNOSIS & TREATMENT														
Background	✓													
Treatment rev	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CLINICAL OUTCOMES														
HDRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BDI-2	✓				✓					✓		✓		✓
BPRS	✓				✓					✓		✓		✓
COGNITIVE OUTCOMES														
ACE-R	✓				✓					✓		✓		✓
AMI-SF	✓				✓					✓		✓		✓
Events quest	✓				✓					✓		✓		✓
Other tests	✓				✓					✓		✓		✓
SUBJECTIVE SIDE-EFFECTS														
CSSES	✓				✓					✓		✓		✓
FUNCTIONAL OUTCOMES														
PSMS	✓				✓					✓		✓		✓
IADL	✓				✓					✓		✓		✓
COSTS AND QUALITY OF LIFE														
CSRI	✓				✓							✓		✓
SF-36	✓				✓							✓		✓
ATTITUDES														
Attitudes	✓				✓					✓				✓
BLOOD SAMPLES														
Phlebotomy	✓				✓					✓		✓		✓

Translational work

EFFECT-Dep Trial

+ longitudinal clinical outcomes

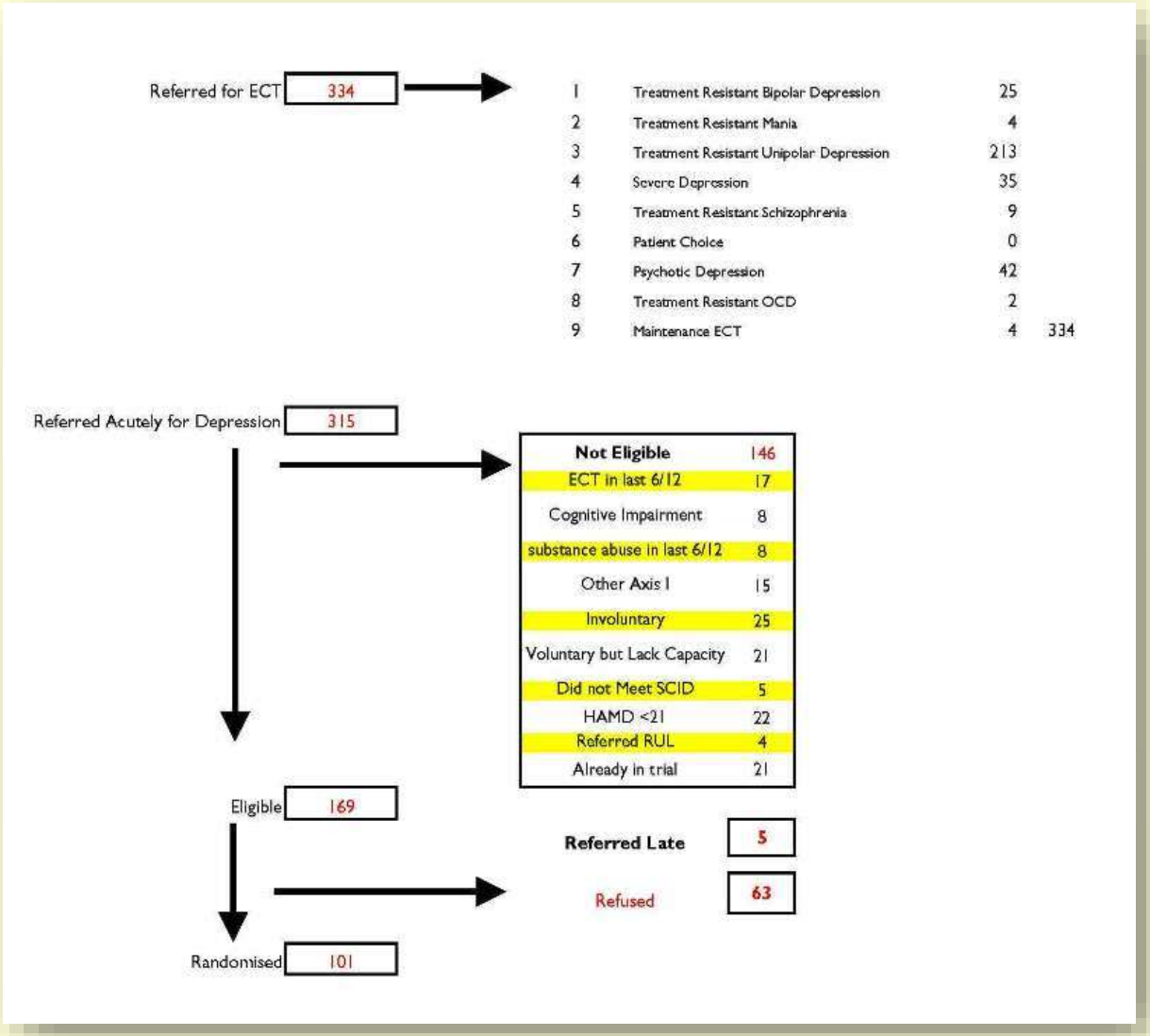


Rat plasma

Molecular biomarkers

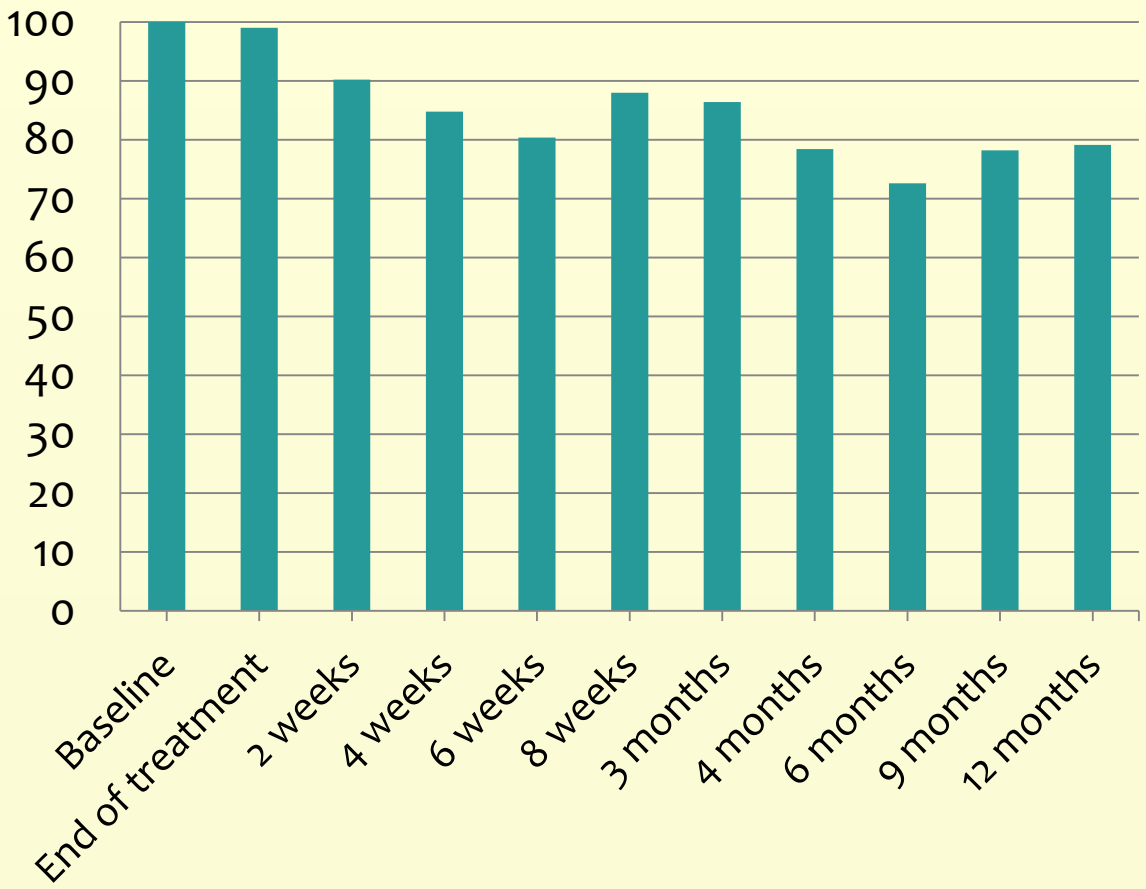
- Response
- Side-effects
- Relapse
- Diagnosis
- Neurobiology

EFFECT-Dep Trial: recruitment



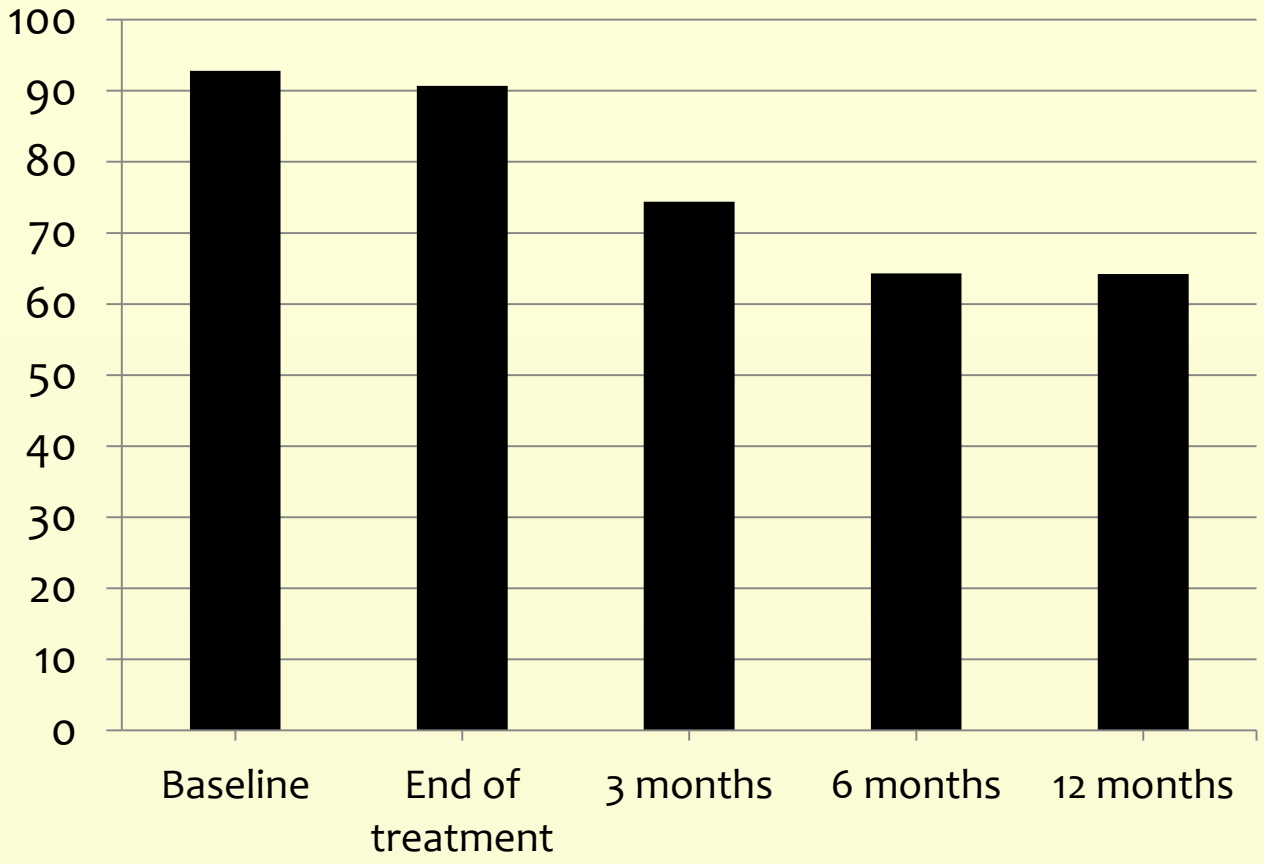
Primary outcome measure
Hamilton Depression Rating Scale
% completion rates

Baseline	End of treatment	2 weeks	4 weeks	6 weeks	8 weeks	3 months	4 months	6 months	9 months	12 months
100%	**99.0%**	**90.2%**	**84.8%**	**80.4%**	**88.0%**	**86.4%**	**78.4%**	**72.6%**	**78.2%**	**79.1%**
97/97	96/97	83/92	78/92	74/92	81/92	76/88	69/88	61/84	61/78	53/67



Columbia AMI - Short Form
% completion rates

Baseline	End of treatment	3 months	6 months	12 months
92.8%	**90.7%**	**74.4%**	**64.3%**	**64.2%**
90/97	88/97	67/90	54/84	43/67



Evidence-based Medicine

"The conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."

Grading of evidence:

- **Ia:** systematic review and meta-analysis of randomised controlled trials
- **Ib:** at least one randomised controlled trial
- **IIa:** at least one well-designed controlled study without randomisation
- **IIb:** at least one well-designed quasi-experimental study, such as a cohort study
- **III:** well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case–control studies and case series
- **IV:** expert committee reports, opinions and/or clinical experience of respected authorities

Some more definitions...

SYSTEMATIC REVIEW: A process by which a body of literature is reviewed and assessed using systematic methods which are intended to reduce bias in the review process and improve understandability.

META-ANALYSIS: a quantitative summary analysis that combines the results of several studies and assesses variability between studies. Usually by identification of a common measure of effect size.

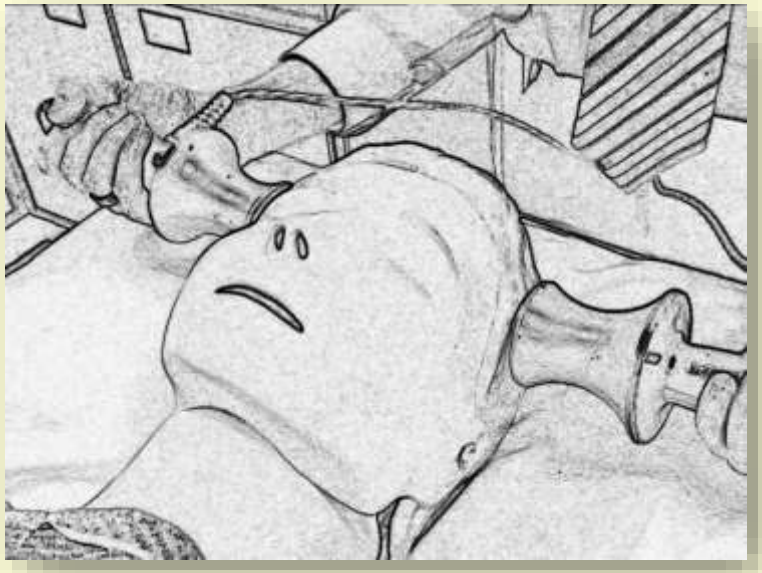
- randomised controlled trials
- observational data
- gene association studies, etc

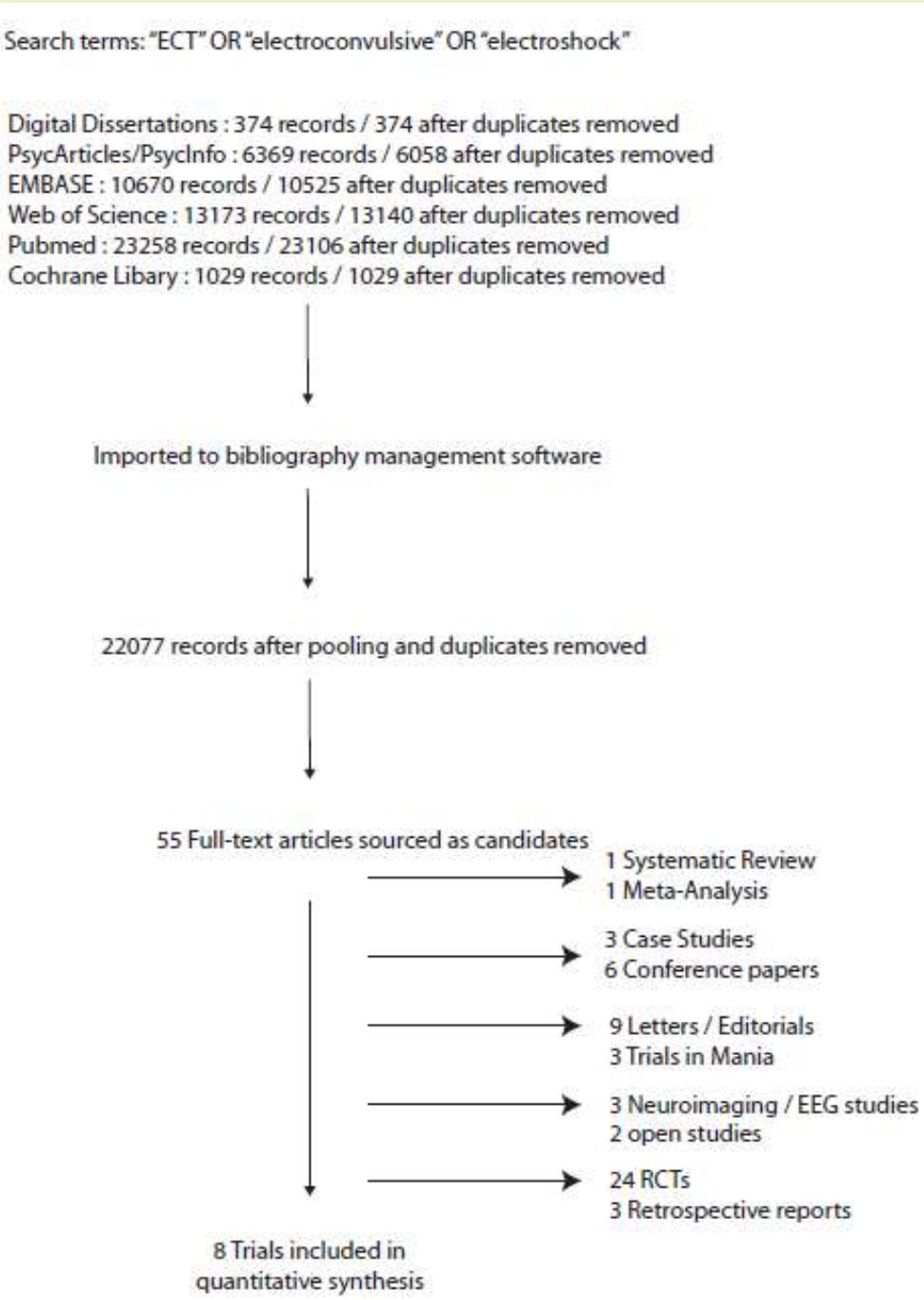
EFFECT SIZE: a measure of the strength of the relationship between two variables

3. Systematic review and meta-analysis of bifrontal ECT versus bitemporal and unilateral ECT for depression

Ross Dunne & Declan McLoughlin

vs




Search terms: "ECT" OR "electroconvulsive" OR "electroshock"
Digital Dissertations : 374 records / 374 after duplicates removed
PsycArticles/PsycInfo : 6369 records / 6058 after duplicates removed
EMBASE : 10670 records / 10525 after duplicates removed
Web of Science : 13173 records / 13140 after duplicates removed
Pubmed : 23258 records / 23106 after duplicates removed
Cochrane Libary : 1029 records / 1029 after duplicates removed
Imported to bibliography management software
22077 records after pooling and duplicates removed
55 Full-text articles sourced as candidates
1 Systematic Review
1 Meta-Analysis
3 Case Studies
6 Conference papers
9 Letters / Editorials
3 Trials in Mania
3 Neuroimaging / EEG studies
2 open studies
24 RCTs
3 Retrospective reports
8 Trials included in
quantitative synthesis

		Letemendia et al 1993 [1]	Bailine et al 2000	Heikman et al 2002	Ranjkesh et al 2005	Eschweiler et al 2007	Amiri et al 2009	Sienaert et al 2009	Kellner et al 2010
n		59	48	22	39	92	68	59	230
No. of females (%)		36 (61%)	26 (54%)	13 (59%)	24 (62%)	53 (58%)	36(53%)	42 (66%)	146 (63%)
Previous ECT		NS	NS	41%	NS	~10%[2]	NS	19%	9%
% Bipolar[3]		NS	23.0%	23.0%	25.6%	13.0%	0%	20.0%	23.0%
Duration[4]		NS	NS	0.5	NS	2.5	NS	NS	2.4
Pulse width (milliseconds)[5]		1.5	NS	1	1	0.5-1	NS	0.3-0.5	1.5
Frequency/week		3	3	3	3	2	NS	2	3
Mean no. of ECTs		6	5.7	8.9	8	6	8	6	NS
Multiple of seizure threshold	BF	1	1.5	1	1.5	1.5	1.5	1.5	1.5
	RUL	1	-	2.5,5	5	2.5	-	6	6
	BT	1	1.5	-	1	-	1	-	1.5
Drug washout		Yes	Yes	Yes	Yes	No	No	Yes	Yes
Randomisation method stated		No	No	No	No	Yes	No	No	Yes
Masking method stated		Yes	No	No	No	Yes	No	No	Yes
Days to assessment after last ECT		7	7	1-7	1	1-7	1	7	1-7
Mean age		55.9	52.8	57.2	34.2	54.6	35.8	55.4	53.1
Remission HDRS		<10	<10	10	NS	<9	NS	10	NS
HDRS Version (Items)		17	17	17	24	21	24	17	24
Anesthesia		M	M	M	NS	E	T	M	M,T,E,P[6]

Table 1 Characteristics of included studies

Statistical methods

Hedges's "g": effect size (unbiased estimator in small samples sizes)

• weighted-mean-square linear regression (Gleser and Olkin, 2009): treatment-wise ES for RULECT at various doses versus BF ECT (Heikman *et al, 2002)* as well as a pooled estimate

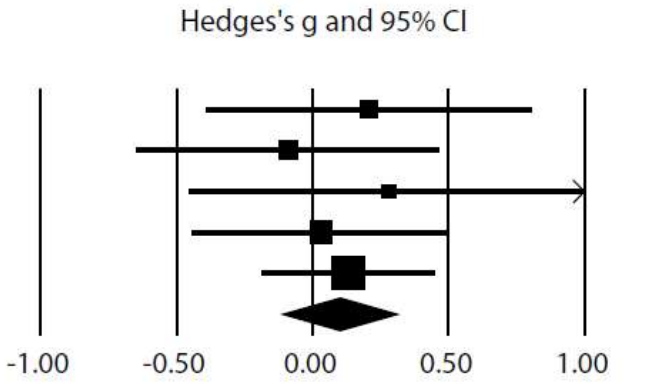
Higgins I^2: heterogeneity (the ratio of total dispersion to within study dispersion; the degree of overlap of confidence intervals, relative to dispersion of points)

Random effects model: to allow for systematic differences between studies in electrical stimulus dose-above-threshold, treatment frequency and number of treatments

Statistics for each study

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Letemendia et al 1993	0.206	0.304	0.092	-0.389	0.802	0.679	0.497
Bailine et al 2000	-0.090	0.284	0.081	-0.647	0.466	-0.318	0.751
Ranjkesh et al 2005	0.283	0.375	0.141	-0.453	1.019	0.753	0.451
Amiri et al 2009	0.031	0.241	0.058	-0.441	0.503	0.128	0.898
Kellner et al 2010	0.133	0.161	0.026	-0.184	0.449	0.822	0.411
	0.102	0.108	0.012	-0.110	0.313	0.943	0.345

Heterogeneity: Q=0.931, df(Q)=4, p=0.92, I^2<0.01



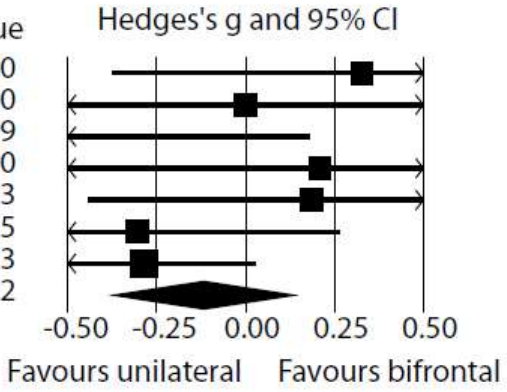
HDRS: Bitemporal vs Bifrontal

A

Statistics for each study

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	z-value	p-value
Letemendia et al (1993)	0.327	0.358	0.128	-0.374	1.029	0.914	0.360
Heikman et al (2002) (5 x ST)	0.000	0.557	0.311	-1.093	1.093	0.000	1.000
Heikman et al (2002) (2.5 x ST)	-1.159	0.682	0.465	-2.495	0.177	-1.700	0.089
Ranjkesh et al (2005)	0.209	0.388	0.151	-0.552	0.970	0.539	0.590
Eschweiler et al (2007)	0.185	0.320	0.103	-0.442	0.813	0.579	0.563
Sienaert et al (2009)	-0.304	0.290	0.084	-0.873	0.265	-1.048	0.295
Kellner et al (2010)	-0.286	0.159	0.025	-0.598	0.026	-1.795	0.073
	-0.118	0.130	0.017	-0.373	0.136	-0.912	0.362

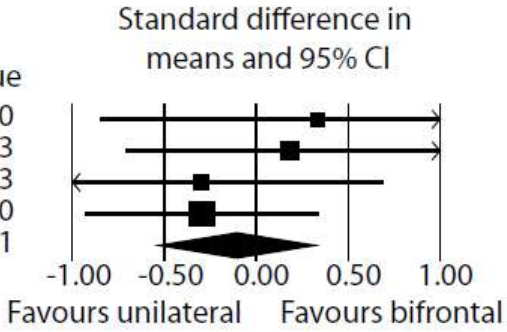
Heterogeneity: Q=7, df(Q)=6, p=0.32, I^2=14.20



B

Right unilateral ECT % of seizure threshold	Std diff in means	Standard error	Variance	Lower limit	Upper limit	z-value	p-value
100	0.334	0.605	0.366	-0.851	1.519	0.553	0.580
250	0.186	0.455	0.207	-0.706	1.078	0.408	0.683
500	-0.300	0.505	0.255	-1.290	0.691	-0.593	0.553
600	-0.295	0.322	0.104	-0.925	0.336	-0.915	0.360
	-0.104	0.218	0.047	-0.531	0.322	-0.480	0.631

Heterogeneity: Q=1.431, df(Q)=3, p=0.698, I^2< 0.01



HDRS: Unilateral vs Bifrontal

	Bailine et al	2000 Heikman et al	2002 Ranjkesh et al	2005 Eschweiler et al	2007 Amiri et al	2009 Sienaert et al	2009 Kellner et al	2010
MMSE	✓	✓	✓	✓	✓	✓	✓	
3MS				✓				
RAVLT Immediate						✓	✓	
RAVLT Delayed						✓	✓	
Continuous Performance Test						✓		
LNS						✓		
TMT-A						✓	✓	
TMT-B						✓	✓	
WCST Categories						✓		
AMI						Kopelman	Columbia	
SSMI						✓		
Stroop							✓	
Complex figure				MCG1/2			Rey/Taylor	
Phonemic fluency				NAI			COWAT	
Category fluency							✓	
Labyrinth subtest of NAI				NAI				

Table 2: Cognitive outcomes performed in each included study. NAI, Nuremberg age inventory; COWAT, Controlled Oral Word Association Test

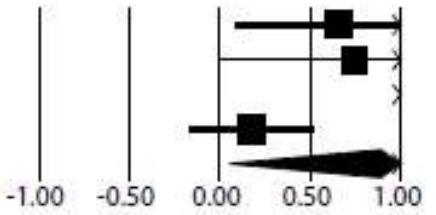
Cognitive measures

A

Statistics for each study

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	z-value	p-value
Bailine et al (2000)	0.661	0.292	0.085	0.089	1.233	2.265	0.023
Ranjkesh et al (2005)	0.747	0.387	0.150	-0.012	1.506	1.930	0.054
*Amiri et al (2009)	2.023	0.297	0.088	1.441	2.605	6.818	0.000
Kellner et al (2010)	0.175	0.174	0.030	-0.166	0.516	1.008	0.313
	0.889	0.426	0.182	0.054	1.724	2.086	0.037

Hedges's g and 95% CI



= 1 SD (1.4 pts)

*Heterogeneity: Q=28.93, df(Q)=3, p=<0.001, I²=89.63

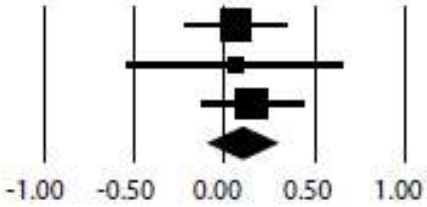
Favours bitemporal Favours bifrontal

B

Statistics for each study

Right unilateral ECT % of seizure threshold	Std diff in means	Standard error	Variance	Lower limit	Upper limit	z-value	p-value
250	0.062	0.142	0.020	-0.216	0.339	0.434	0.664
500	0.055	0.306	0.094	-0.545	0.655	0.180	0.857
600	0.151	0.143	0.021	-0.130	0.431	1.051	0.293
	0.101	0.096	0.009	-0.087	0.288	1.052	0.293

Std diff in meansand 95% CI



Heterogeneity: Q=0.22, df(Q)=2, p=0.89, I²<0.001

Favours unilateral Favours bifrontal

MMSE: Bitemporal/RUL vs Bifrontal

***Heterogeneity -** "one study removed analysis", removing the Amiri et al (2010) study did not change the direction or statistical significance of the advantage for bifrontal ECT

	Study	Hedges' 'g'	SE	p-value	I^2 (p-value)
RAVLT 1-5	Kellner et al (2010)	-0.94	0.19	<0.01	
	Sienaert et al (2010)	0.16	0.25	0.52	
	Pooled	-0.405	0.553	0.464	92 (p<0.001)
RAVLT 7 (delayed)	Kellner et al (2010)	-0.807	0.189	<0.01	
	Sienaert et al (2010)	-2.14	0.31	<0.01	
	Pooled	-1.45	0.665	0.029 *	93.1 (p<0.001)
TMT-A	Kellner et al (2010)	1.77	0.21	<0.01	
	Sienaert et al (2010)	-12.28	1.11	<0.01	
	Pooled	-5.5	6.74	0.46	99.35 (p<0.001)
TMT-B	Kellner et al (2010)	-0.477	0.184	0.01	
	Sienaert et al (2010)	123.7	10.94	<0.01	
	Pooled	61.13	62.1	0.325	99.2 (p<0.001)
Complex figure (delayed)	Echweiler et al (2007)	0.82	0.22	<0.01	
	Kellner et al (2010)	0.72	0.18	<0.01	
	Pooled	0.76	0.177	0.01 *	<0.01 (p=0.124)
Verbal Fluency (Letters)	Echweiler et al (2007)	0.246	0.208	0.235	
	Kellner et al (2010)	-0.007	0.176	0.966	
	Pooled	0.099	0.135	0.462	<0.01 (p=0.35)

Cognitive Performance: RUL vs Bifrontal ECT

Summary:
Efficacy and Cognitive Effects of Bifrontal ECT

• no difference in efficacy between bitemporal and bifrontal ECT or between unilateral and bifrontal ECT (65% received RUL at 5-6 x ST)

• bitemporal ECT caused greater decline than bifrontal ECT in global cognition as measured by the MMSE (but small difference)

• RUL ECT smaller decline in delayed verbal memory than bifrontal ECT but a greater decline in visual delayed memory than bifrontal ECT

• unable to study publication bias, anesthetics, drugs, other dx, other cognitive domains, longer term follow-up, pulse width (better to test in isolation)

• bifrontal electrode placement remains an experimental treatment in need of better characterization of its cognitive effects especially in the frontal-executive domain

Objective Cognitive Performance Associated with Electroconvulsive Therapy for Depression: A Systematic Review and Meta-Analysis

Maria Semkovska and Declan M. McLoughlin

BIOL PSYCHIATRY 2010;68:568–577

Unilateral brief-pulse electroconvulsive therapy and cognition: Effects of electrode placement, stimulus dosage and time

Maria Semkovska[a,b], Deborah Keane[b], Oyemi Babalola[a], Declan M. McLoughlin[a,b,*]

Journal of Psychiatric Research (2011)

4. Objective cognitive performance associated with ECT for depression

- **Cognitive side-effects** have been identified as the major complications limiting ECT use (APA, 2001)
- Nonetheless, while widely investigated, **extent** and precise pattern of **short-term** and **long-term** cognitive deficits following ECT, are **controversial**
- Issues with descriptive reviews of cognition and ECT
  - Discrepancies in reviewing methodology
  - Memory definition
  - Results derived from objective and subjective assessments jointly reviewed

- *UK ECT Review Group* (2003) suggests that differences in ECT modalities can possibly explain variations in cognitive impairment
- 7-8 days after a course of **brief-pulse bitemporal** ECT, verbal memory function relative to pretreatment levels has been described as:
  - impaired (Perera et al., 2004; Schat et al., 2007)
  - recovered (Mervaala et al., 2001; Sackeim et al., 1993)
  - improved (Bosboom and Deijen, 2006; Fujita et al., 2006)

Aims

- To **systematically review** research on cognitive function following ECT
- To provide a **quantitative estimate** of cognitive impairment following ECT
- To determine the **configuration** of ECT-induced cognitive dysfunctions and their resolution during the post-treatment period
  - Type
  - Severity
- To examine the contribution of potential **moderator** variables to heterogeneity of outcomes

Methods

Search strategy

- MEDLINE, EMBASE, PsycARTICLES, PsychINFO, and PsychLIT from their commencements to December 2008, using the terms
    - “ECT" or "electroconvulsive therapy" and

      ["cognitive", "neuropsychology", "neuropsychological", "memory", "attention", "executive", "spatial", or "intellectual"].

- Reference lists of available reviews and relevant articles were manually searched for additional studies. Only published reports were searched.

Study selection criteria

- Independent sample(s) of subjects older than 18 years and diagnosed with **Major Depressive Episode** occurring without comorbidities
- At least one **standardised** and **validated** cognitive test was administered with results reported as means and standard-deviations (SD)
- **Within-subjects** research design
- Quantitative information regarding the **time delay** between the end of ECT course and the post-ECT cognitive assessment
- **Electrode placement** details must be provided
  - B - bitemporal position
  - U - right unilateral d'Elia or Lancaster electrode placement
- Case reports and self-reported measures were excluded.

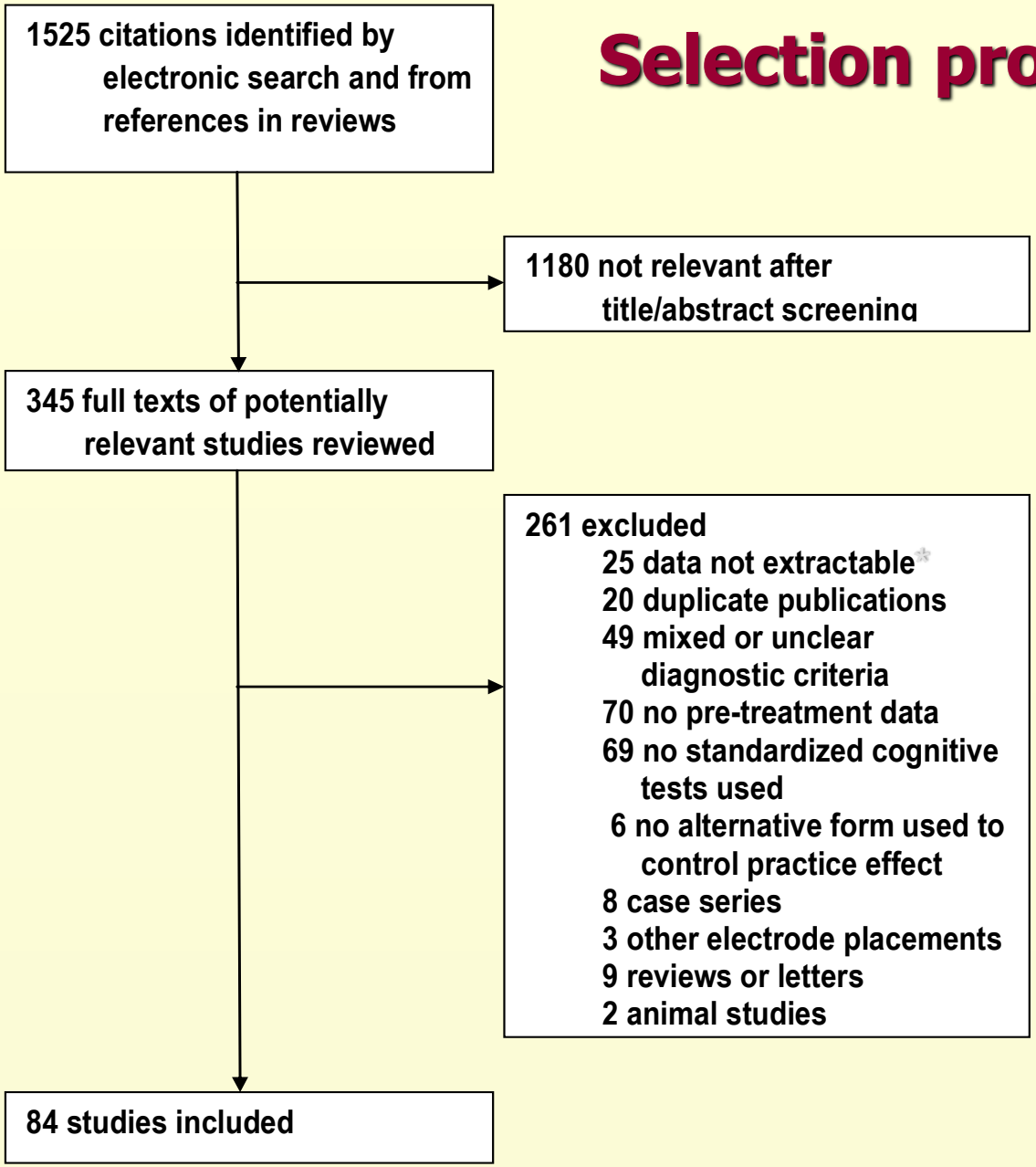
Statistical analyses

- Effect sizes (ES) were computed for each cognitive variable using Cohen's d index of individual effect: $d_i = (M_{post}-M_{pre})/SD_{pi}$
    - Positive ES indicates that post-treatment performance was superior to pre-treatment.
- Samples derived from all studies were subdivided into 3 groups with respect to **interval between end of ECT course and post-ECT cognitive testing**
    - sub-acute : delay 0 - 3 days
    - short-term : 4-15 days
    - long-term : <15 days
- ES were weighted and pooled by use of Cooper and Hedges (1994) **fixed-effects model** a priori
- Homogeneity of each weighted average ES was tested with the Q statistic.

Results

- Flow chart of selection of studies
- Identified cognitive variables
- Pooled effect sizes per time period
    - sub-acute : delay between 0 and 3 days
    - short-term : 4-15 days
    - long-term : more than 15 days
- Contribution of moderators

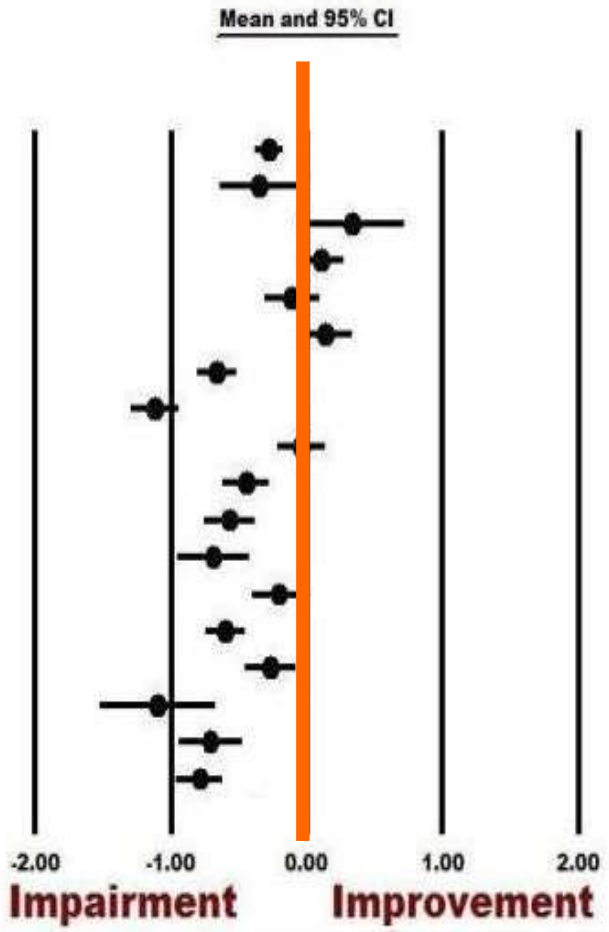
Selection process



Cognitive Domain	Cognitive variables	Number of studies	Number of participants
Cognitive status screening	MMSE	30	1199
Processing speed	Digit Symbol	11	269
	Trail Making Test A (time)	8	172
Attention/Working memory	Digit Span forward	13	435
	Digit Span backward	12	302
	Digit Span total	16	387
	Mental Control	4	78
	Spatial Span	3	53
Verbal episodic memory	Word List learning (pooled results from BSRT, RAVLT, CVLT, and HVLT)	17	518
	Word List delayed recall (pooled results from BSRT, RAVLT, CVLT, and HVLT)	13	500
	Story Memory immediate recall (pooled results from Logical Memory and Randt Short Story)	17	457
	Story Memory delayed recall (pooled results from Logical Memory and Randt Short Story)	11	374
	Verbal Paired Associates learning (pooled results from Verbal Paired Associates and Randt Paired words)	17	465
	Verbal Paired Associates delayed recall (pooled results from Verbal Paired Associates and Randt Paired words)	9	255
Visual episodic memory	Figure Reproduction immediate recall (pooled results from ROCF, Visual Reproduction, and Benton Visual Retention Test)	13	415
	Figure Reproduction delayed recall (pooled results from ROCF, and Visual Reproduction)	14	599
Spatial problem solving	Design Copy (pooled results from Block Design and ROCF copy)	7	276
Executive functioning	Trail Making Test B (time)	6	134
	Stroop Color-Word condition (time)	8	135
	Stroop Color-Word condition (errors)	4	71
	Semantic Fluency	11	322
	Letter Fluency	14	446
Intellectual ability	Vocabulary	3	49
	IQ Index	3	59

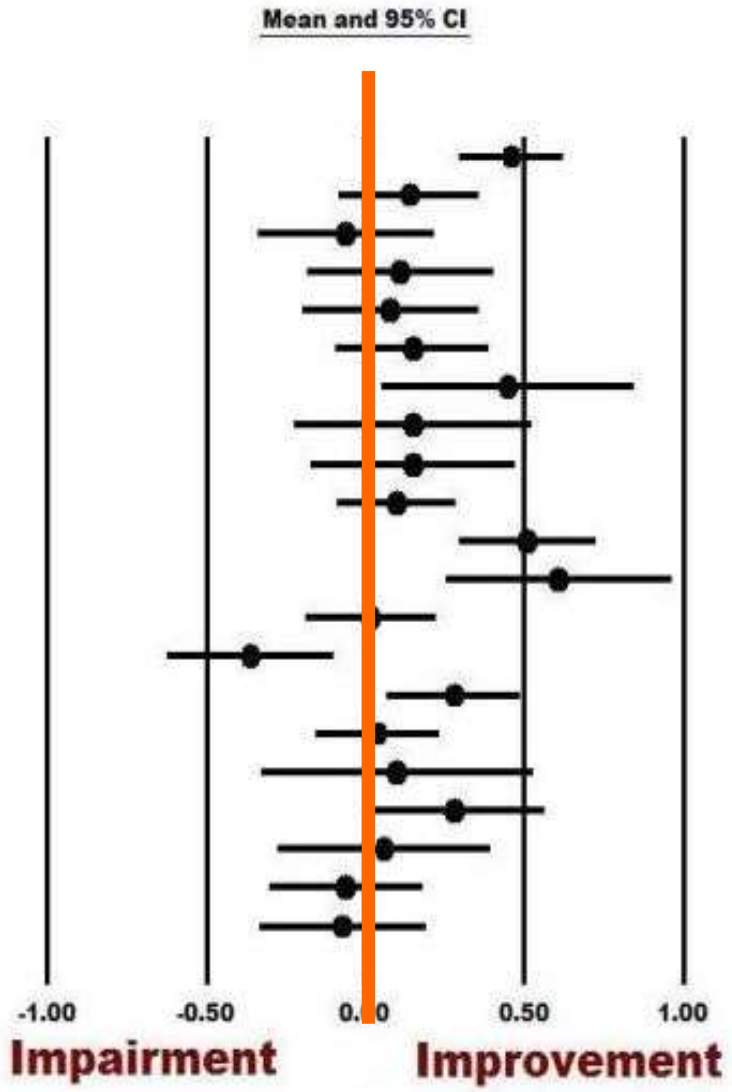
Sub-acute effects (0 - 3 days following ECT)

	Mean	Standard error	p-Value
MMSE	-0.280	0.051	0.000
Digit Symbol	-0.350	0.148	0.018
Trail Making Test A (time)	0.330	0.197	0.094
Digit Span Forward	0.110	0.079	0.163
Digit Span Backward	-0.110	0.101	0.278
Digit Span Total	0.140	0.094	0.136
Word List learning	-0.660	0.071	0.000
Word List delayed recall	-1.120	0.086	0.000
Story Memory immediate recall	-0.040	0.086	0.643
Story Memory delayed recall	-0.450	0.084	0.000
Verbal Paired Associates learning	-0.570	0.091	0.000
Verbal Paired Associates delayed recall	-0.690	0.131	0.000
Figure Reproduction immediate recall	-0.210	0.099	0.034
Figure Reproduction delayed recall	-0.600	0.071	0.000
Design Copy	-0.270	0.094	0.004
Trail Making Test B (time)	-1.100	0.214	0.000
Semantic Fluency	-0.710	0.116	0.000
Letter Fluency	-0.790	0.084	0.000



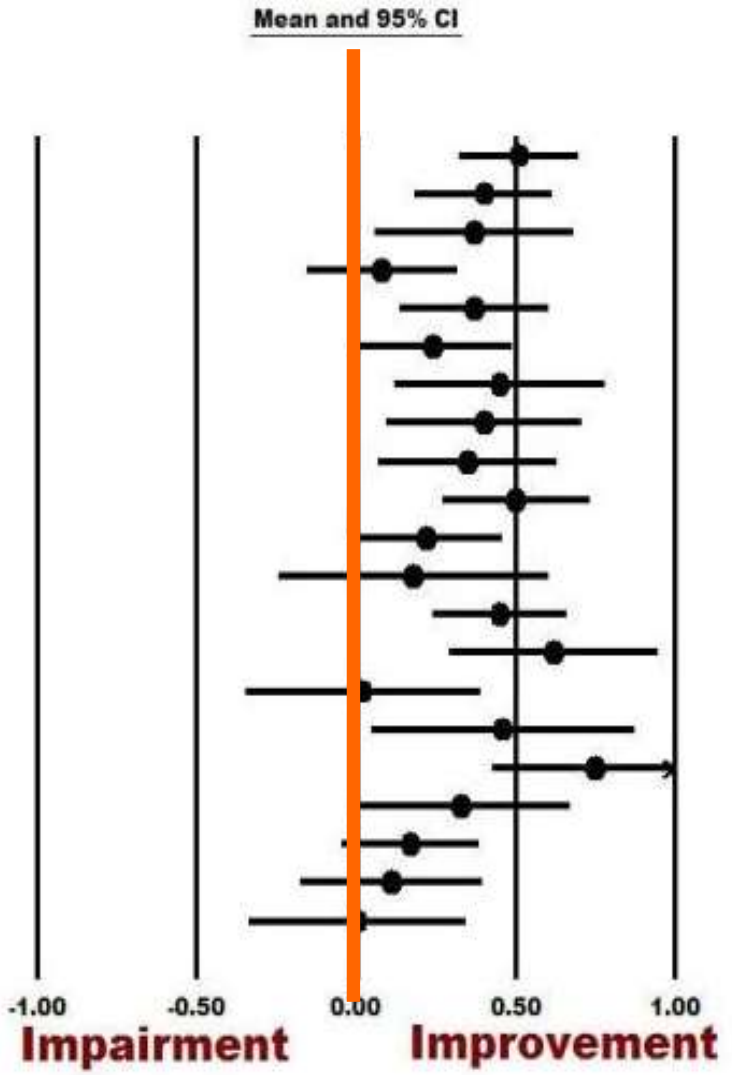
Short-term effects (4 -15 days following ECT)

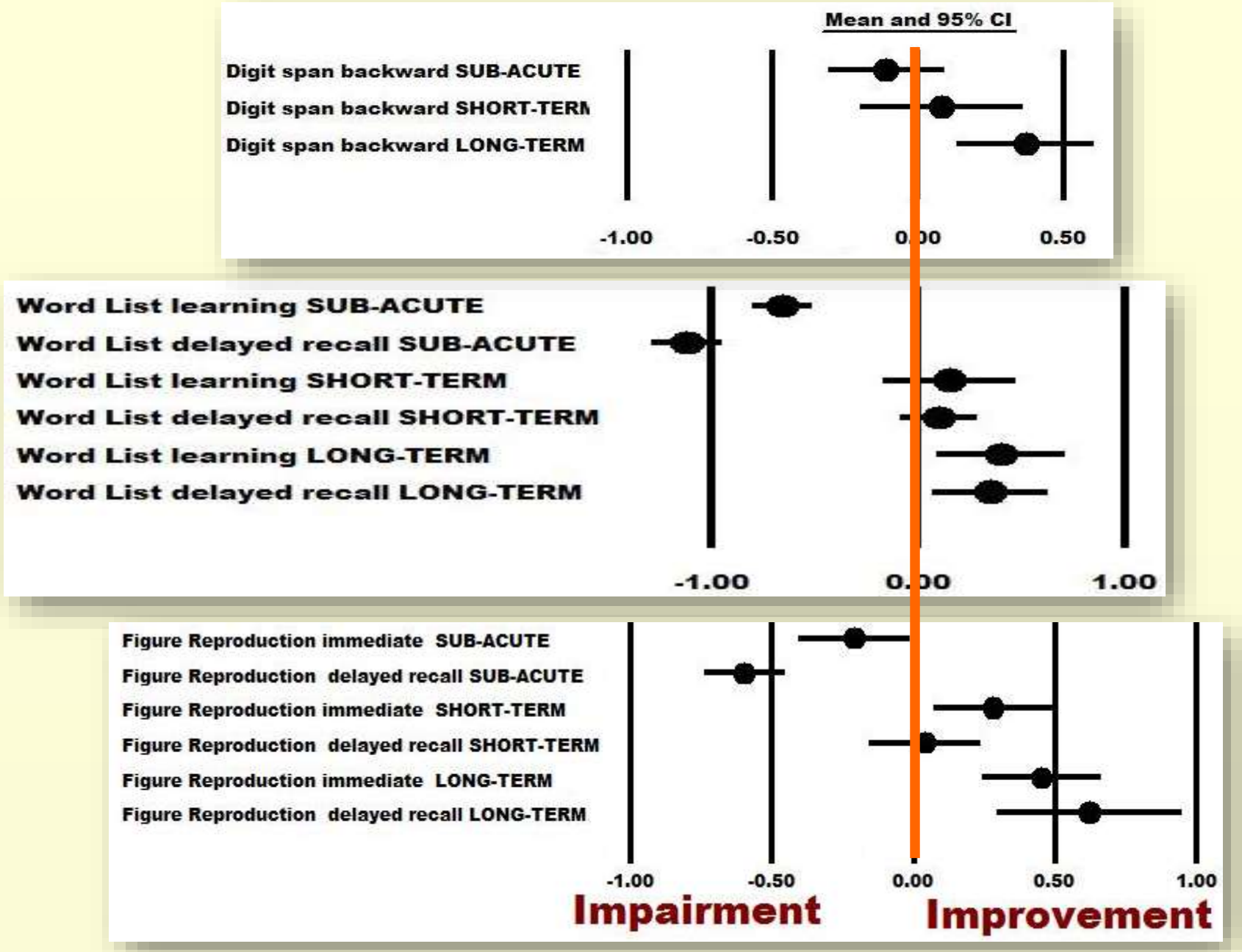
	Mean	Standard error	p-Value
MMSE	0.460	0.081	0.000
Digit Symbol	0.140	0.111	0.209
Trail Making Test A (time)	-0.060	0.141	0.671
Digit Span Forward	0.110	0.148	0.459
Digit Span Backward	0.080	0.141	0.571
Digit Span Total	0.150	0.121	0.216
Mental Control	0.450	0.201	0.025
Spatial Span	0.150	0.189	0.428
Word List learning	0.150	0.163	0.358
Word List delayed recall	0.100	0.094	0.287
Story Memory immediate recall	0.510	0.109	0.000
Story Memory delayed recall	0.610	0.181	0.001
Verbal Paired Associates learning	0.020	0.104	0.847
Verbal Paired Associates delayed recall	-0.360	0.131	0.006
Figure Reproduction immediate recall	0.280	0.106	0.009
Figure Reproduction delayed recall	0.040	0.099	0.686
Trail Making Test B (time)	0.100	0.218	0.646
Stroop Color-Word condition (time)	0.280	0.144	0.051
Stroop Color-Word condition (errors)	0.060	0.170	0.725
Semantic Fluency	-0.060	0.121	0.621
Letter Fluency	-0.070	0.134	0.601



Long-term effects (more than 15 days following ECT)

	Mean	Standard error	p-Value
MMSE	0.510	0.094	0.000
Digit Symbol	0.400	0.109	0.000
Trail Making Test A (time)	0.370	0.158	0.020
Digit Span Forward	0.080	0.119	0.501
Digit Span Backward	0.370	0.119	0.002
Digit Span Total	0.240	0.126	0.057
Mental Control	0.450	0.168	0.007
Word List learning	0.400	0.156	0.010
Word List delayed recall	0.350	0.141	0.013
Story Memory immediate recall	0.500	0.116	0.000
Verbal Paired Associates learning	0.220	0.121	0.070
Verbal Paired Associates delayed recall	0.180	0.215	0.403
Figure Reproduction immediate recall	0.450	0.106	0.000
Figure Reproduction delayed recall	0.620	0.166	0.000
Design Copy	0.020	0.187	0.915
Trail Making Test B (time)	0.460	0.209	0.027
Stroop Color-Word condition (time)	0.750	0.163	0.000
Stroop Color-Word condition (errors)	0.330	0.173	0.056
Semantic Fluency	0.170	0.109	0.119
Letter Fluency	0.110	0.144	0.443
Vocabulary	0.004	0.173	0.982




Mean and 95% CI
Digit span backward SUB-ACUTE
Digit span backward SHORT-TERM
Digit span backward LONG-TERM
-1.00
-0.50
0.00
0.50
Word List learning SUB-ACUTE
Word List delayed recall SUB-ACUTE
Word List learning SHORT-TERM
Word List delayed recall SHORT-TERM
Word List learning LONG-TERM
Word List delayed recall LONG-TERM
-1.00
0.00
1.00
Figure Reproduction immediate SUB-ACUTE
Figure Reproduction delayed recall SUB-ACUTE
Figure Reproduction immediate SHORT-TERM
Figure Reproduction delayed recall SHORT-TERM
Figure Reproduction immediate LONG-TERM
Figure Reproduction delayed recall LONG-TERM
-1.00
-0.50
0.00
0.50
1.00
Impairment
Improvement

Moderators

- **Cognitive change** data were
  - heterogeneous for a third of the studied variables during the **sub-acute** period,
  - mostly homogeneous for **short-** and **long-term** cognitive effects of ECT.

- Moderators examined:
  - age
  - electrode placement
  - stimulus waveform
  - mean number of ECT sessions
  - weekly ECT frequency
  - mean electrical charge dose

Contribution of electrode placement

- Sub-acute impairment

Cognitive variable	Bitemporal	Unilateral
Associate verbal learning	↓↓↓ (ES = -0.91)	↓ (ES = -0.33)
Delayed Word List Recall	↓↓↓↓ (ES = -1.51)	↓↓↓ (ES = -1.10)
Delayed Visual memory	↓↓↓↓ (ES = -1.46)	↓ (ES = -0.33)

- Short-term effects

Cognitive variable	**Bitemporal**	**Unilateral**
MMSE	Large Improvement (ES = 0.73)	Pretreatment level (ns ES)

Contribution of stimulus wave form

- Sub-acute impairment

Cognitive variable	**Brief-pulse**	**Sinewave**
Delayed Visual memory	↓↓ (ES = -0.51)	↓↓↓ (ES = -1.06)

No moderator effect of:

- Age
- Dose electrical stimulus
- Mean number of ECT treatments received

Summary: Sub-acute effects

- Episodic memory and executive functioning – moderate to large impairment
  - Delayed recall ↓↓↓ Immediate recall ↓
  - Verbal episodic memory ↓↓ visual episodic memory ↓
- Processing speed, spatial problem solving and global cognition – small impairment
- Attention/working memory – comparable to baseline level

Summary: Short-term effects

- **Processing speed, episodic memory and executive functioning –** cognitive variables that have demonstrated sub-acute deficits showed **recovery of baseline functioning**
- Global cognition and working memory – small improvement
- Story episodic memory – moderate improvement

Summary: Long-term effects

- Our meta-analysis did not demonstrate persisting cognitive deficits in any studied variable beyond 15 days after finishing ECT
- For the majority of variables, there was a **small to moderate improvement** beyond baseline

Limitations

- No estimate of autobiographical memory dysfunction
  - Lack of standardised and validated measures
  - Lack of within-subject research designs

- Little evidence available on effect of ECT on
  - Visual attention
  - Visuo-spatial abilities
  - Planning
  - Problem solving

5. Unilateral brief-pulse ECT and cognition

Effects of electrode placement, stimulus dosage and time

- Several modifications of ECT technique have been introduced to minimise side-effects
- Right Unilateral ECT
  - less cognitive deficits
  - efficacy contingent to stimulus dose
  - cognitive deficits increase with stimulus dose?

INCONSISTENT results

- Aims of the meta-analysis

Semkovska, Keane, Babalola & McLoughlin, *Journal of Psychiatric Research* 2011

Methods

Search strategy → May 2009

Study selection criteria

- Only brief-pulse ECT
- Only purely unilateral or purely bitemporal samples
- Mean charge of electrical dosage per session in mC should be provided for the unilateral samples
- At least one cognitive task (validated or not) administered by an external observer

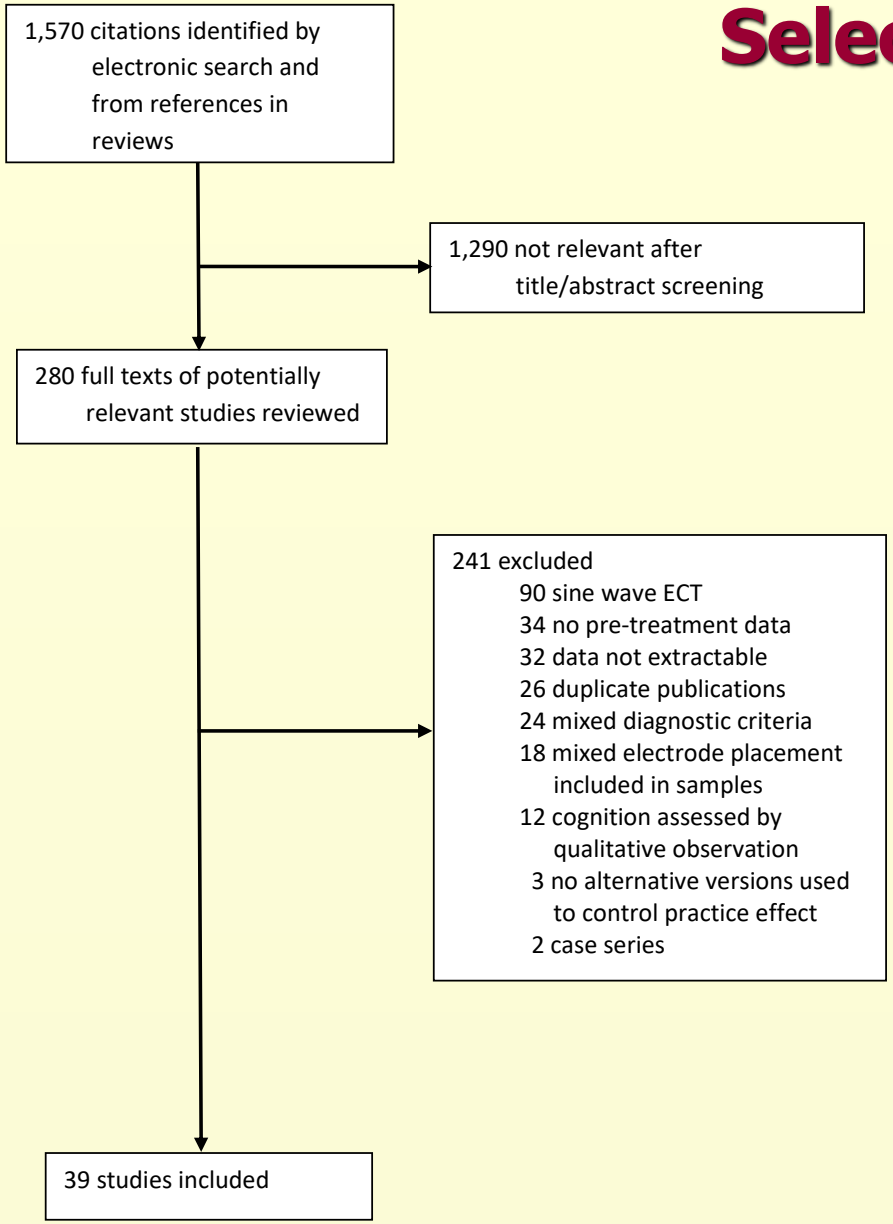
Cognitive domain	Type of cognitive tasks
Global cognitive status	Mental state and dementia brief rating tasks
Processing speed	Digit Symbol Substitution, Trail Making Test part A and timed cancellation tasks
Working memory	Digit span, Mental Control, Letter Number Sequencing tasks or any other standardized task requiring short-term mental manipulation of information
Verbal learning	Learning or immediate recall scores of verbal information
Delayed retrieval from verbal memory	Delayed spontaneous recall of previously learned and immediately recalled verbal information
Verbal recognition	Delayed recognition of previously learned and immediately recalled verbal information
Visual learning	Learning or immediate recall scores of visual information
Delayed retrieval from visual memory	Delayed spontaneous recall of previously learned and immediately recalled visual information
Visual recognition	Delayed recognition of previously learned and immediately recalled visual information
Visuo-spatial abilities	Reproduction of visually presented material requiring ability to comprehend visual representations and their spatial relationships
Executive functioning	Set-shifting (Trail Making Test Part B, Card sorting) and mental flexibility (Stroop Interference condition) tasks
Semantic memory retrieval	Verbal and semantic fluency tasks
Intellectual abilities	Tasks providing intellectual quotient estimates
Retrograde amnesia for information learned shortly before ECT	Post ECT tasks assessing information specifically learned the day before an ECT treatment with the aim of assessing retrograde amnesia
Retrograde autobiographical memory	Tasks specifically assessing the ability to recall personal events that occurred before ECT
Retrograde memory for public events	Tasks specifically assessing knowledge for past public events that occurred before ECT

Specific meta-analyses

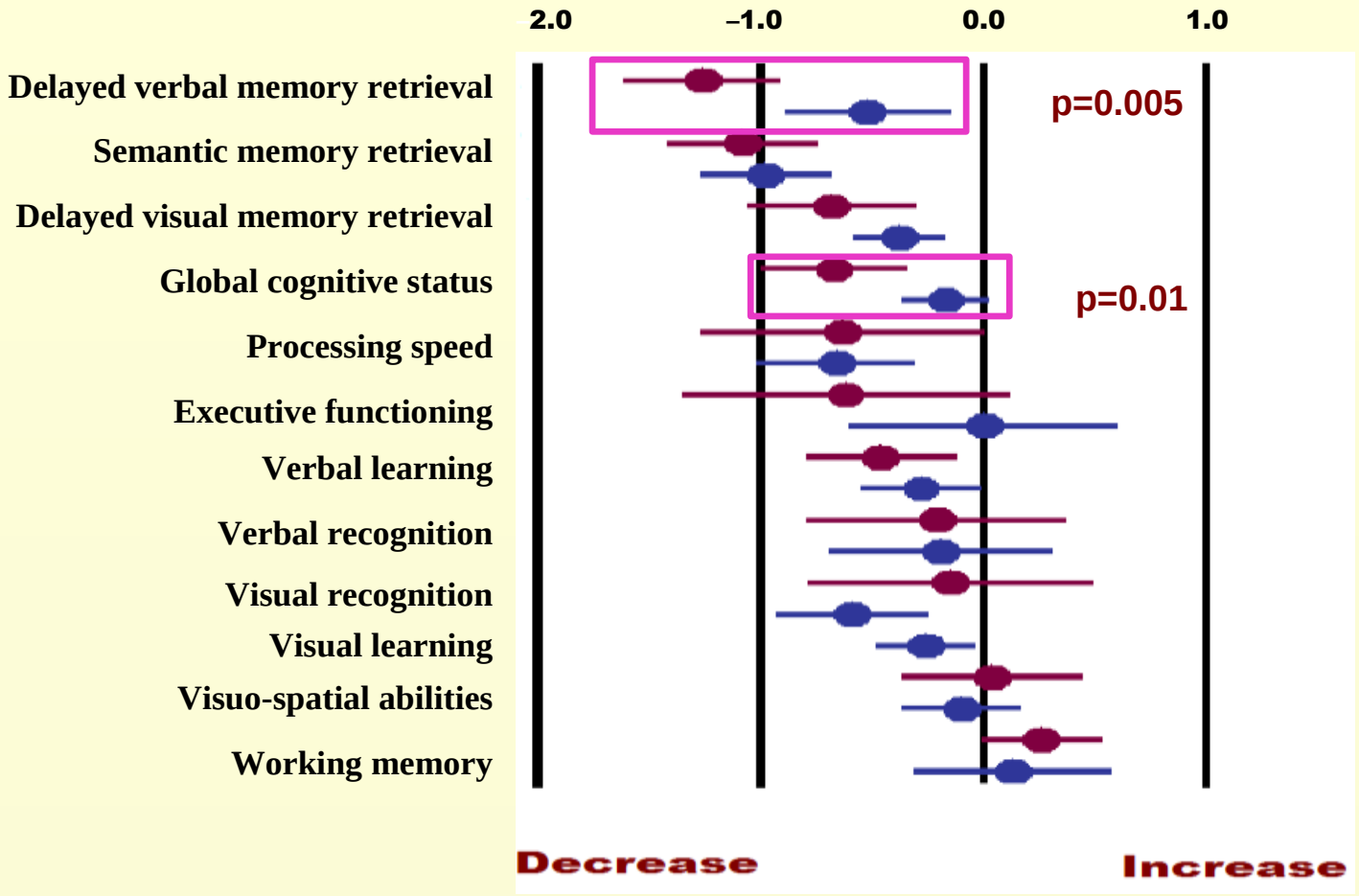
- Effect of **electrode placement** (unilateral versus bitemporal) by use of sub-group **mixed effect** analyses

- For unilateral samples, mixed effect meta-regression analyses were used to identify
  - (1) Effect of **electrical dosage** on cognitive outcome during both the subacute (0-3 days) and delayed (>3 days) periods
  - (2) Effect of **time** interval between end of treatment and cognitive testing only during the delayed period.

Selection process

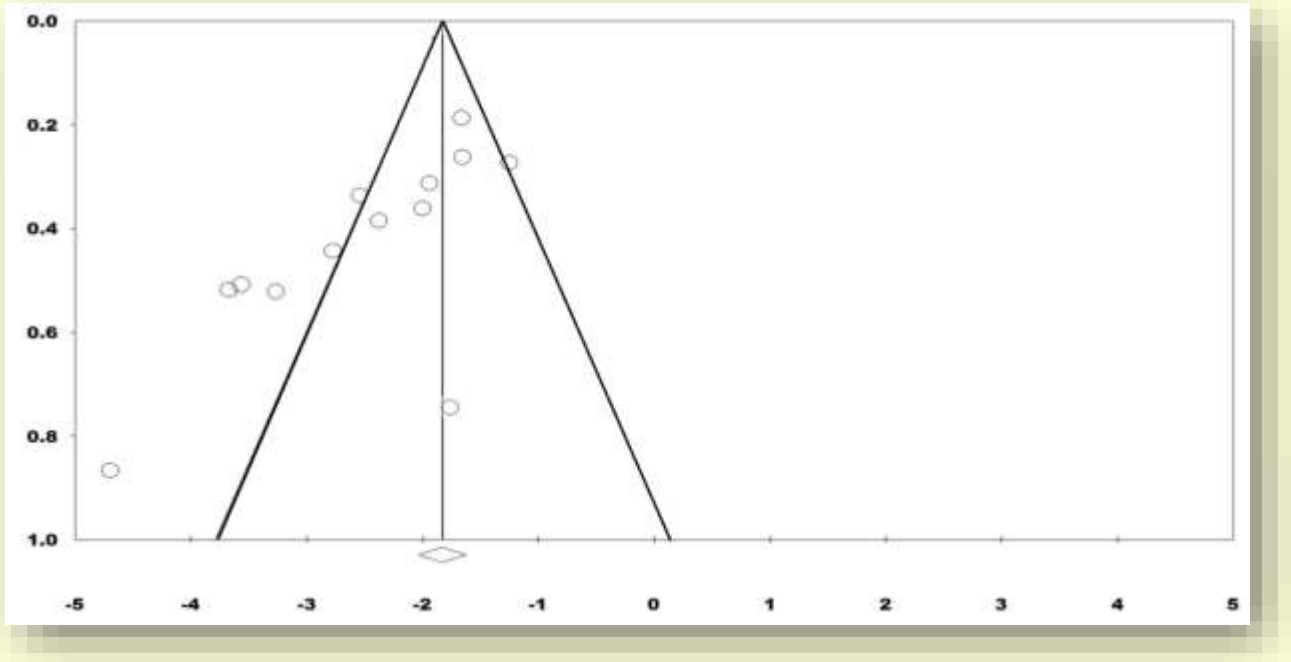


Effect of electrode placement on sub-acute cognitive outcomes (0-3 days post-treatment)



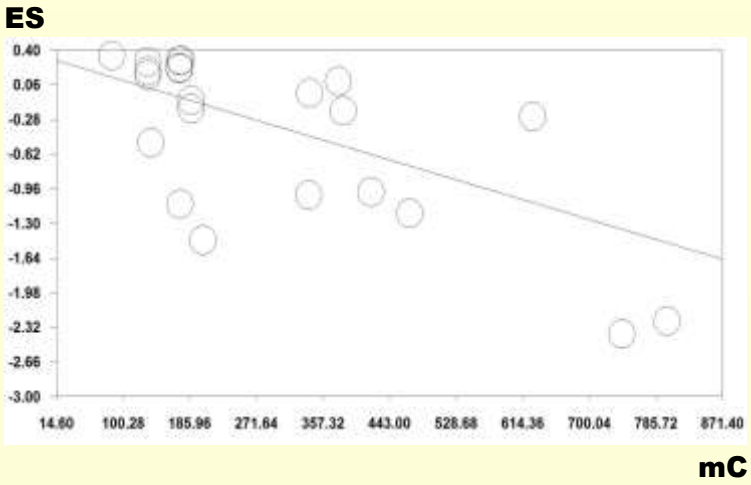
The issue of estimating the extent of retrograde amnesia remains

	n	k	N	Estimated percent decrease (95% CI)		Qb	P value for Qb
Retrograde autobiographical memory (0 to 3 days)							
Bitemporal	5	6	126	-3.93 (-5.26 to -2.59)			
Unilateral	8	13	285	-2.13 (-2.71 to -1.55)		5.83	0.016

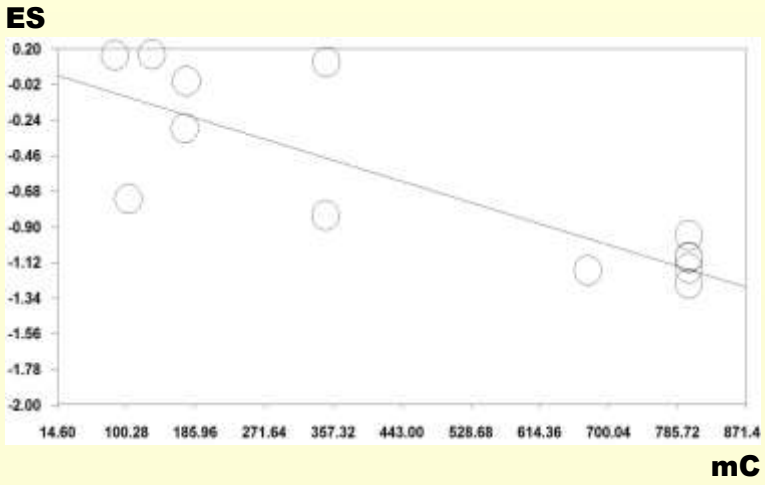


Effect of stimulus dose on cognitive effect sizes (ES) in unilateral samples (0-3 days)

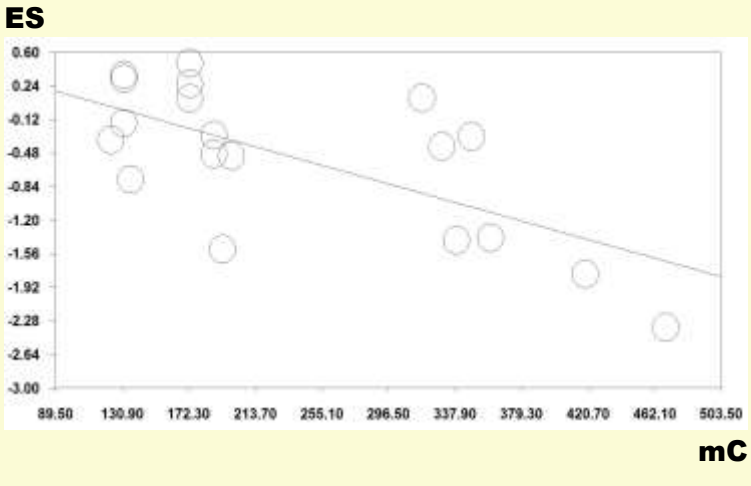
Verbal learning



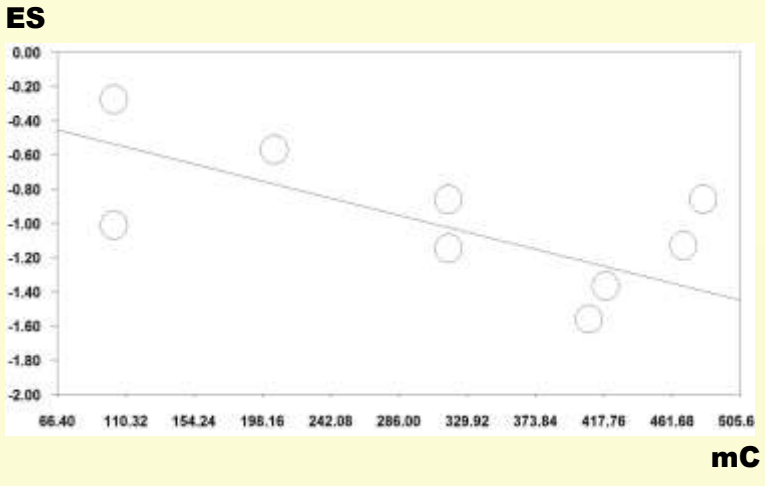
Visual recognition



Delayed verbal memory retrieval



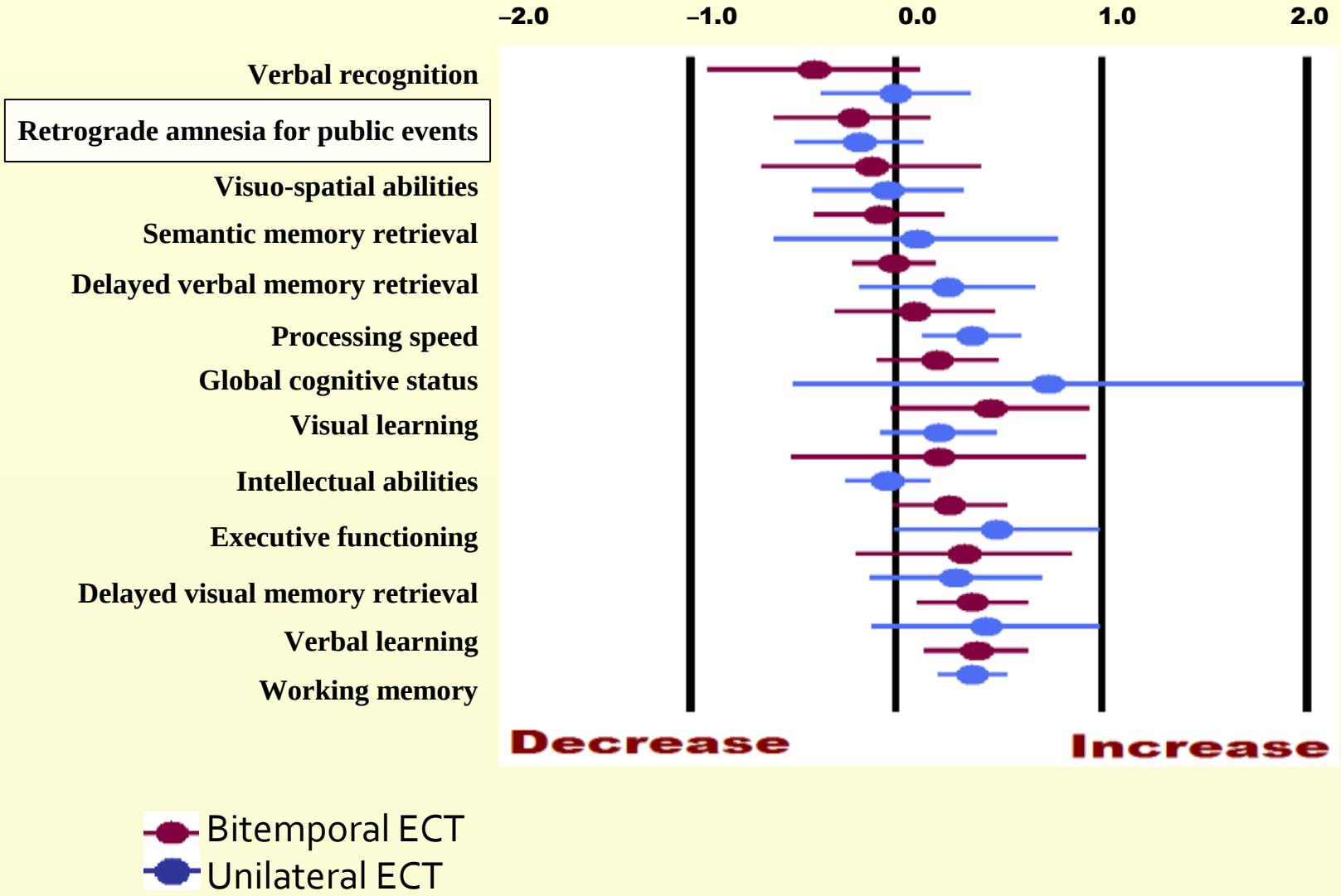
Semantic memory retrieval



Summary: Sub-acute effects

- Compared to bitemporal ECT, up to three days after final treatment, unilateral ECT was associated with significantly lower decreases in
  - global cognition
  - delayed verbal memory retrieval
  - autobiographical memory
- Higher electrical dosage in unilateral samples predicted larger decreases in
  - verbal learning,
  - delayed verbal memory retrieval,
  - visual recognition,
  - semantic memory retrieval.
- Moderator effect of age

Effect of electrode placement on delayed cognitive outcome (>3 days post-treatment)



Summary: Delayed effects

- When retested >3 days after completing ECT, **no significant differences** were observed between the two electrode placements, and electrical dosage was no longer a significant predictor of cognitive performance.

- **Increasing time interval** between final treatment and retesting predicted growing cognitive improvement in verbal, visual and autobiographical memory and in executive functioning.

6. MODEST PROPOSALS

I. RCTs – keep simple but large, using an established comparison

II. Incorporate long term outcomes into RCT design

III. Please include raw data (e.g. means (SD)) in reports to facilitate future meta-analyses

IV. Cognition: general deficits in depression, e.g. visual attention, spatial working memory
   - bifrontal studies: need to include frontal-executive tasks

V. Retrospective memory in depression vs retrograde amnesia in ECT?

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