ECT and cognition – what do my patients and I need to know?

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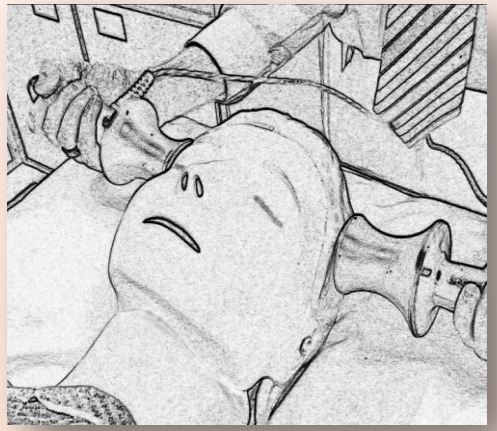
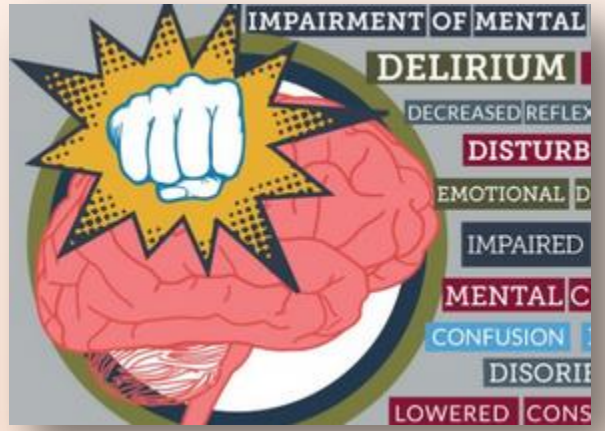




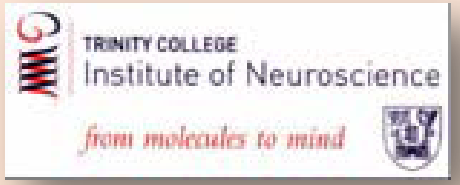
NACT NORDIC ASSOCIATION FOR CONVULSIVE THERAPY

St Patrick's Mental Health Services
Empowering recovery

TRINITY COLLEGE
Institute of Neuroscience
from molecules to mind

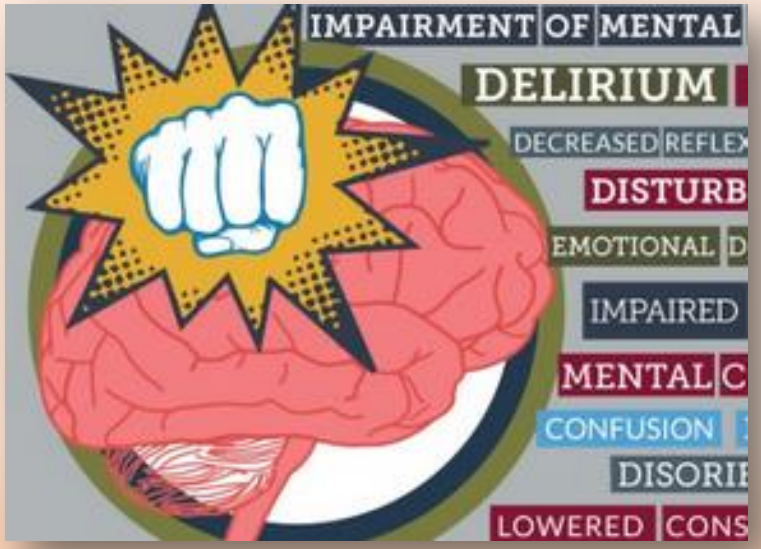
Disclosures

- Grant funds from Health Research Board (Ireland), NARSAD (USA)
- Speaker honorarium from Mecta



Cognitive Effects After ECT

- Immediate, after each ECT session
- Subacute and longer-term, during and after completing an ECT course
- Retrograde autobiographical amnesia

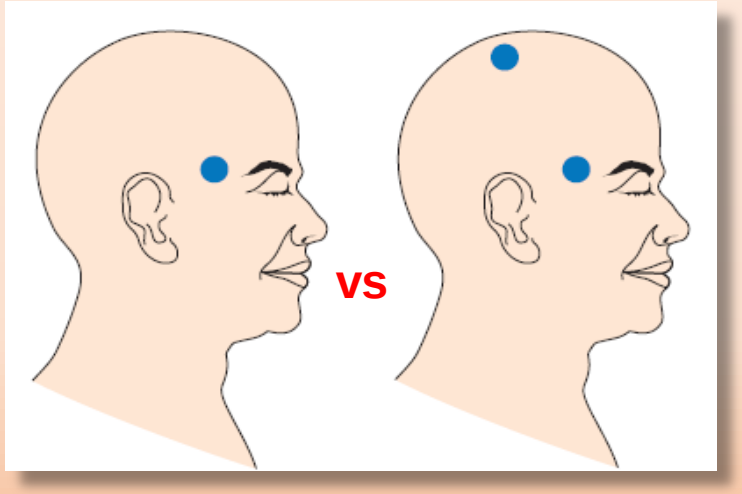


EFFECT-Dep Trial

Enhancing the Effectiveness of ECT in Severe Depression

ISRCTN23577151

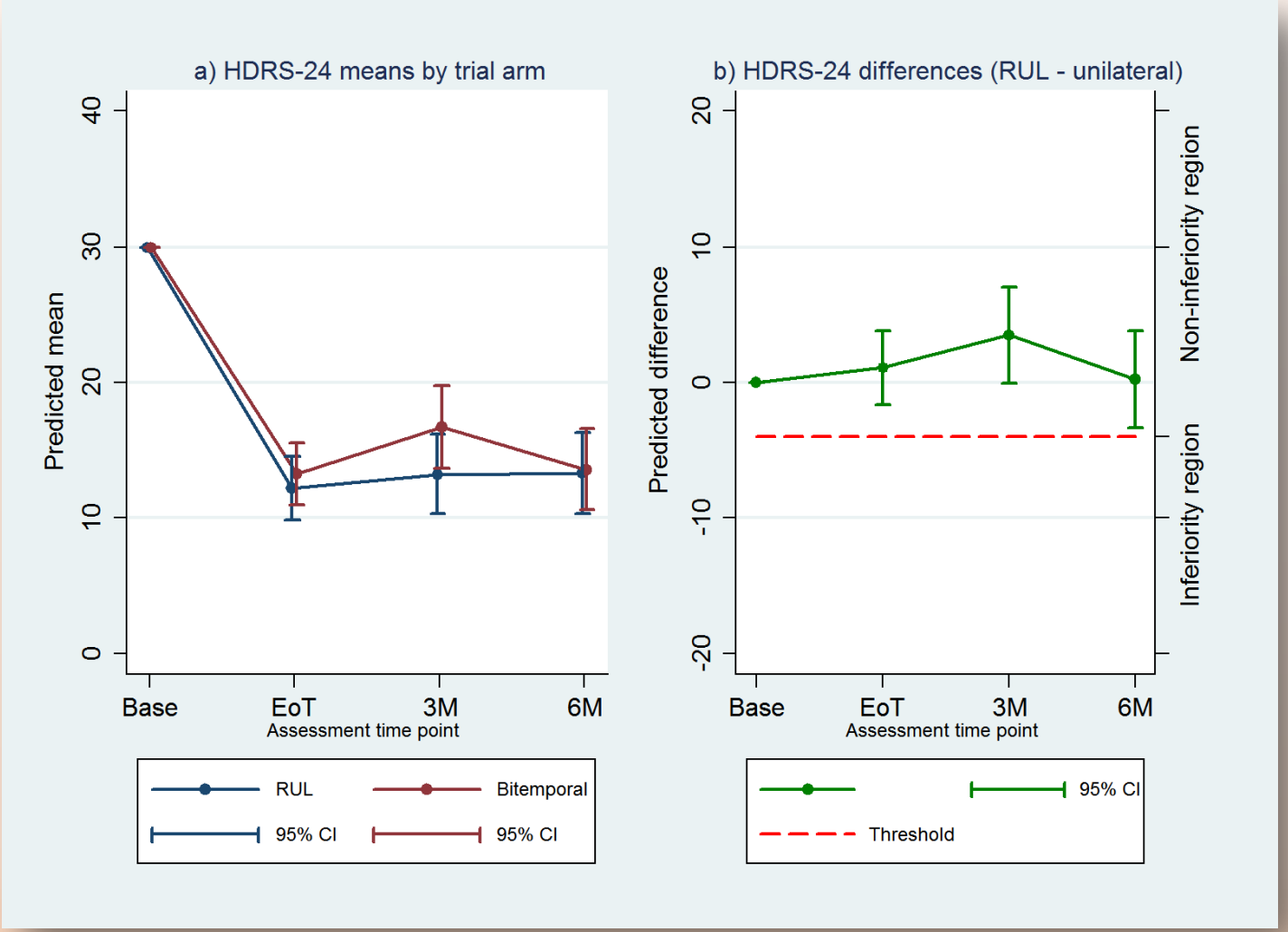
OBJECTIVE: to perform a pragmatic, randomised, non-inferiority trial comparing standard bitemporal ECT (1.5 x ST) and high-dose unilateral ECT (6 x ST) in severe depression in routine practice



Semkovska *et al.*, 2016 *Am J Psychiatry* 173:408-417

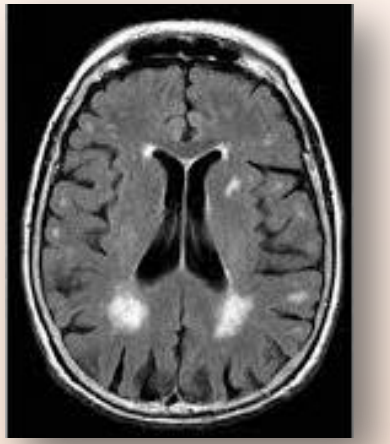
Primary outcome: HDRS-24

Mean HDRS estimated to be 1.2 points higher in the Bitemporal group; 95% CI, -1.510 to 3.995,
i.e. within the non-inferiority threshold.

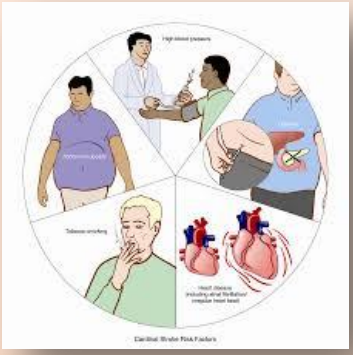


Immediate cognitive effects of ECT

Disorientation: transient, but sometimes → Delirium



- Reorientation speed correlated with later retrograde amnesia (as was impaired pre-treatment cognition) (Sobin et al., 1995; Martin et al., 2015)
- Delayed reorientation associated with:
  - deep white matter abnormalities on MRI (Coffey et al., 1987; Figiel et al., 1990)
  - older age, longer seizure duration, bilateral electrode placement and greater number of treatments (Daniel and Crovitz, 1982; Calev et al., 1991; Kellner et al., 2010)
- TRD associated with deep white matter changes on MRI (Coffey et al., 1990; Simpson et al., 1998)
- Framingham Stroke Risk Score (FSRS) correlates with deep white matter changes on MRI brain in middle-aged populations (Jeerakathil et al., 2004)
- Such risk factors are also predictors of cognitive decline (Swan et al., 1998; Novak and Hajjar, 2010) and therefore may be markers for decreased cognitive reserve in vulnerable populations.



Observational study: reorientation time

PATIENTS

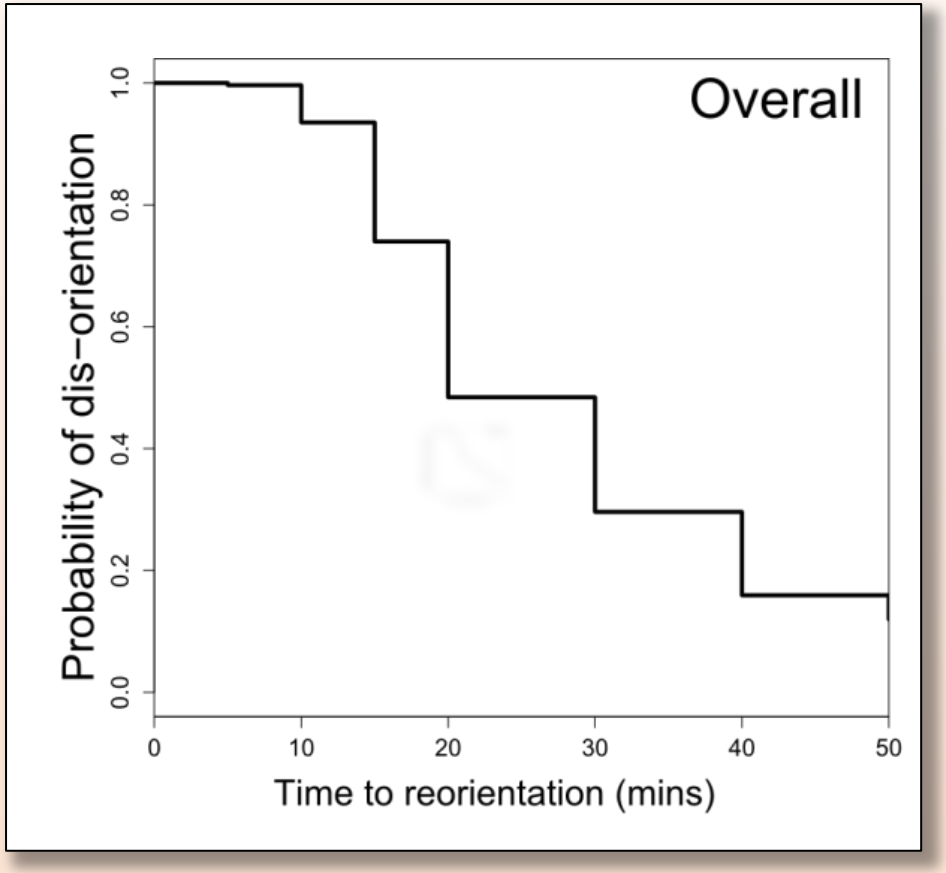
- 1,110 ECT treatments
- 149 courses of bitemporal ECT
- 129 patients
- reoriented if 4/5 items correct

RESULTS

Reorientation time >50 mins:

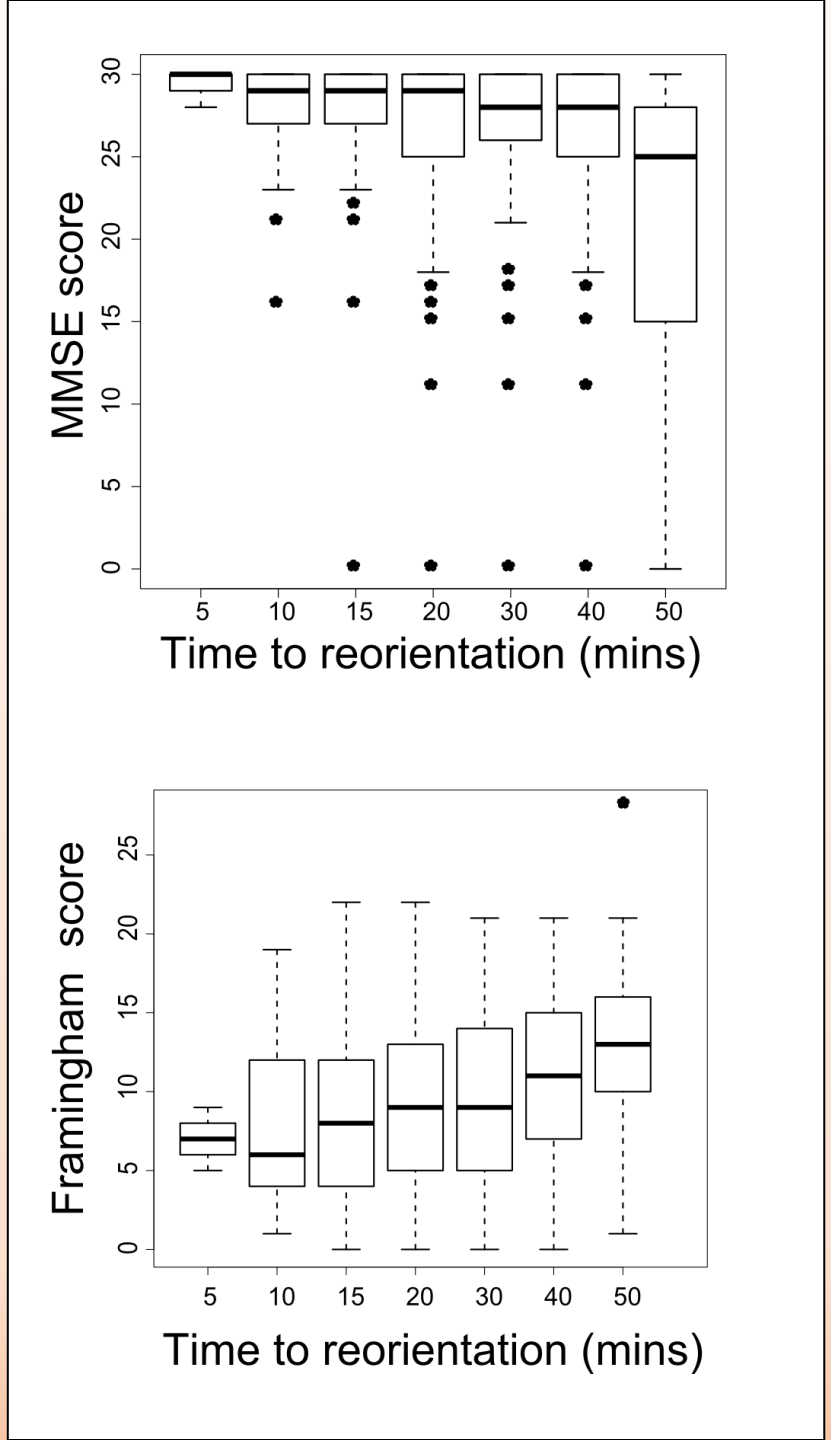
- 132(12%) of treatments
- 45(30%) of ECT courses
- 43(33%) of patients

74% ≤4 episodes
18% 5-6 episodes
7% 7-10 episodes



Kaplan-Meier survival curve for reorientation time

Boxplots of
(A) MMSE and
(B) FSRS versus re-orientation time.



Results – summary of analyses*

• **Higher FSRS scores** ↑ed reorientation time, each additional 5 points reducing instantaneous reorientation probability by 25% (95%CI, 5-40%; P<.001). [**Note**: Age and education less informative than FSRS; no r'ship with CGI change score]

• **Higher pre-ECT MMSE scores** predicted faster full reorientation, each additional point increasing probability 4% in the multivariate model (p<.001)

• **Lithium** ~60% less likely to answer each question at each time point (OR=.41; 95% CI, .2-.8; P=.007), the effect waning with time (OR=1.15; 95%CI,1.1-1.2; P<.001). [**Note**: no effect in univariate model]

****

• **Each additional 10s of EEG seizure** decreased instantaneous probability of full reorientation by 10% at each timepoint (95% CI, 9-11%; P<.001)

• Cumulative effect, **with each treatment** decreasing probability of reorientation at each timepoint by 10% (95%CI, 4-16; P<.01), despite shortening seizures.

*Ordinal logistic mixed-effects regression with random terms for individuals, treatments and courses (*ordinal* in R); coefficients are exponentiated to produce odds ratios (OR).

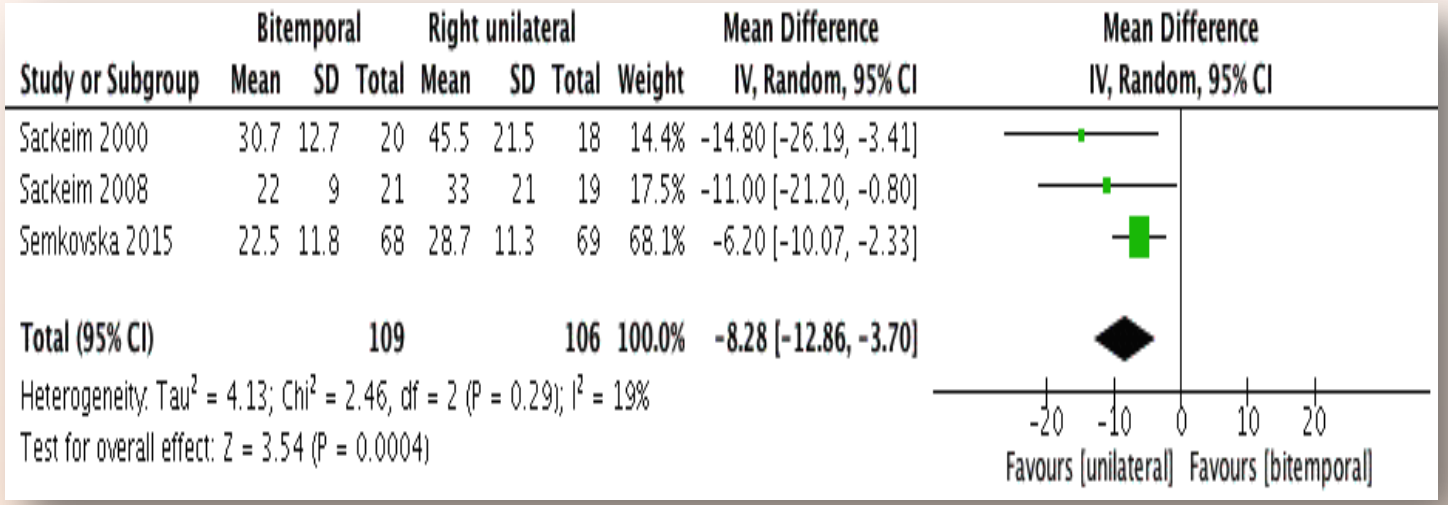
EFFECT-Dep Trial

	RUL ECT (*n*=69)	Bitemporal ECT (*n*=69)	Formal test*
ECT treatment characteristics			
Anaesthesia*			
Methohexitone (mg/kg)	1·08 (0·20), *n*=67	1·02 (0·21)	NA
Suxamethonium (mg/kg)	0·8 (0·19), *n*=68	0·75 (0·17)	NA
Initial seizure threshold (mC) [median and range]	75 (50-500), *n*=67	150 (50-500)	NA
Stimulus charge (mC), all sessions	620 (224), *n*=67	368 (192)	NA
Stimulus charge (mC), non-titration sessions**	742 (276), *n*=67	403 (208)	NA
Duration of seizures (s) [median and range]			
Motor	28 (12-55), *n*=67	28 (14-63)	NA
EEG	42 (17-87), *n*=67	40 (16-116)	NA
Total number of sessions	7·77 (2·48)	8·25 (2·39)	*t*(131)=1·13, *p*=0·26
Number of sessions to establish ST [1 session:2 sessions:3 sessions]	81%:18%:1%, *n*=68	56%:41%:3%	*z*=3·07, *p*=0·002
Recovery of orientation* [medians and ranges]**			
Time to recovery (mins), initial titration session	10 (5-60), *n*=68	20 (5-60)	*t*(130)=6·82, *p*<0·001**
Time to recovery (mins), non-titration sessions**	19·1 (10-55), *n*=68	26·4 (10-60)	*t*(130)= 3·88, *p*<0·001**

Data are expressed as means and standard deviation. *All models used to construct inferences conditioned on stratifiers. **Formal inferences carried out after log-transformation. NA=not attempted. mC=millicoulombs. EEG=electroencephalogram. ST=seizure threshold. *Six patients received propofol during their ECT course at standard doses due to temporary shortage of methohexital, four in the bitemporal group and two in the unilateral group. **Sessions following the definite establishment of ST. ***Recovery of orientation was defined as correctly answering 4/5 reorientation questions.

Table 2: ECT session measures

Meta-analysis of high-dose RUL vs BT ECT: Recovery of orientation



Forest plot of mean time (in minutes) to achieve reorientation after ECT treatments.

Kolshus, Jelovac, McLoughlin (2017) *Psychol Med*

Summary: Recovery of orientation following ECT

- **Recovery retarded by:**
  - ***cardiovascular risk factors (e.g. FSRS)**
  - **lower MMSE score**
  - **longer EEG seizure duration**
  - **more treatments**
  - **Lithium (early disorientation <u>but</u> no effect on likelihood of full re-orientation)**

- **Recovery hastened by:**
  - **anti-epileptic medication**
  - **unilateral electrode placement**

Cognitive Effects After ECT

- Immediate, after each ECT session
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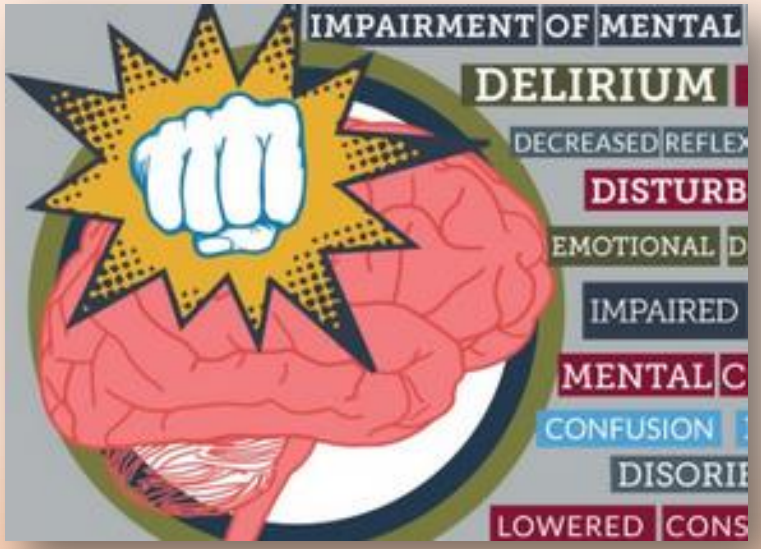
- Retrograde autobiographical amnesia



Cognitive effects of ECT: subacute and longer term

Cognitive effects of ECT in depression: a meta-analysis

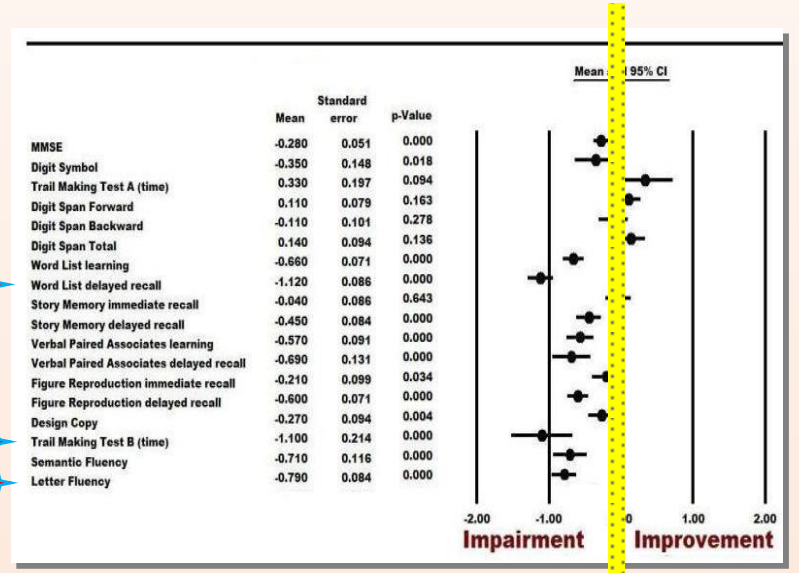
- A wide range of **memory and non-memory** cognitive impairments, as measured by *standardised tests*, are evident after end of treatment.

- Afterwards, most cognitive functions improve beyond baseline.

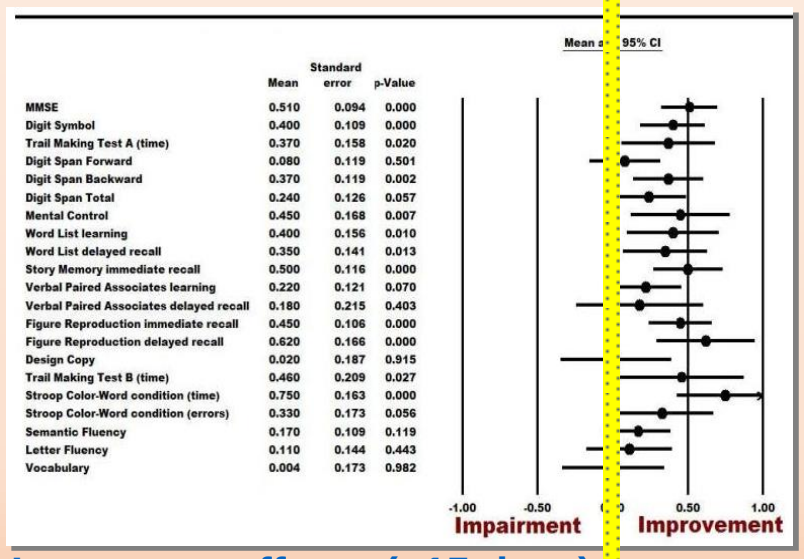
- Differences in ECT techniques, parameters or patient characteristics contributed mainly to short-term effects.

- Unable to include retrograde memory.

- Need to consider depression severity and residual symptoms; medications; type of ECT



Sub-acute effects (0-3 days)



Long-term effects (>15 days)

Semkovska & McLoughlin (2010), *Biological Psychiatry*

Subacute and longer-term cognitive outcomes

FCSRT: immediate verbal recall

- EOT: est difference=-3.1, p=0.043*
- 3 mths: no significant difference
- 6 mths: no significant difference

Digit span forward (attention)

- EOT: est difference=-0.69, p=0.11
- 3 mths: est difference=-1.17, p=0.015*
- 6 mths: est difference=-0.87, p=0.08

No difference between groups at any time point for:

- MMSE (global cognition)
- Digit span backwards (working memory)
- Trail making test A (processing speed)
- Trail making test B (executive function)
- Category fluency (executive function)
- Rey delayed recall (visual episodic memory)
- FCSRT delayed recall (verbal episodic memory)

EFFECT-Dep Trial

Enhancing the Effectiveness of ECT in Severe Depression

TABLE S4: Results of analyses of cognitive outcomes by post treatment time point						
Cognitive tasks			Comparison of randomisation groups[a]			
	Predicted mean[b] RUL (N=69)	Predicted mean[b] Bitemporal (N=69)	Estimated difference in means		Statistical significance test	
			BT-RUL	95% CI	z	p
Global cognitive status: MMSE						
Baseline (sample average)	27.7 (N=59)	27.7 (N=60)				
EOT	27.8 (N=62)	27.4 (N=63)	-0.4	-1.2 to 0.4	-0.93	0.35
3 months	27.9 (N=45)	28.1 (N=31)	0.2	-0.6 to 1.0	0.44	0.66
6 months	28.2 (N=38)	28.1 (N=32)	-0.1	-1.1 to 1.0	-0.12	0.90
Psychomotor speed: TMT-A[c]						
Baseline (sample average)	51.4 (N=49)	51.4 (N=54)				
EOT	53.1 (N=54)	47.9 (N=59)	0.9	0.8 to 1.0	-1.52	0.13
3 months	44.1 (N=40)	43.8 (N=28)	1.0	0.8 to 1.2	-0.07	0.94
6 months	41.0 (N=34)	43.1 (N=30)	1.1	0.9 to 1.3	0.52	0.61
Auditory attention: Digit span forward						
Baseline (sample average)	8.0 (N=53)	8.0 (N=52)				
EOT	8.8 (N=55)	8.1 (N=58)	-0.7	-1.5 to 0.2	-1.51	0.14
3 months	8.8 (N=41)	7.7 (N=30)	-1.2	-2.1 to -0.2	-2.36	0.02
6 months	9.3 (N=38)	8.4 (N=29)	-0.8	-1.8 to 0.1	-1.76	0.08
Verbal working memory: Digit span backward						
Baseline (sample average)	5.7 (N=53)	5.7 (N=52)				
EOT	5.9 (N=55)	5.8 (N=58)	-0.04	-0.9 to 0.8	0.08	0.93
3 months	6.4 (N=41)	5.6 (N=30)	-0.8	-1.6 to 0.0	2.01	0.05
6 months	7.0 (N=37)	6.3 (N=29)	-0.6	-1.7 to 0.5	-1.16	0.25
Verbal learning: FCSRT immediate recall						
Baseline (sample average)	24.9 (N=47)	24.9 (N=48)				
EOT	25.7 (N=49)	22.5 (N=50)	-3.2	-6.1 to -0.2	-2.15	0.03
3 months	27.3 (N=36)	26.7 (N=31)	-0.6	-3.5 to 2.4	-0.40	0.69
6 months	28.5 (N=33)	27.6 (N=28)	-0.9	-4.9 to 3.0	-0.46	0.65
Verbal delayed memory: FCSRT delayed recall						
Baseline (sample average)	9.6 (N=47)	9.6 (N=47)				
EOT	8.5 (N=49)	7.7 (N=49)	-0.8	-2.1 to 0.5	-1.24	0.22
3 months	9.3 (N=36)	9.2 (N=31)	-0.2	-1.5 to 1.2	-0.23	0.82
6 months	9.6 (N=32)	9.2 (N=28)	-0.4	-1.8 to 1.05	-0.53	0.60

Q: What is the nature and pattern of cognitive change post-ECT?

A: Some decline followed by recovery and maybe a "general" trend for improvement

EFFECT-Dep Trial

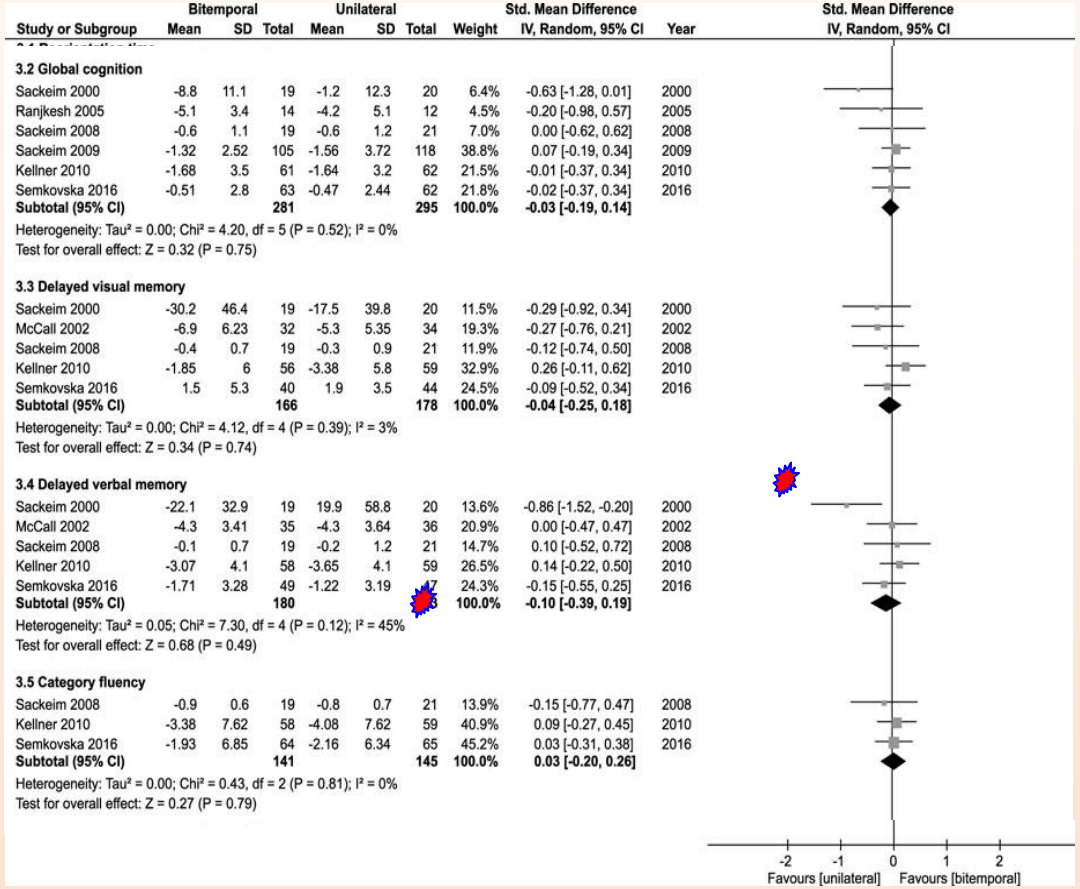
EFFECT-Dep Trial

	Predicted mean* RUL (*n*=69)	Predicted mean* Bitemporal (*n*=69)	Comparison of randomisation groups**	
			Estimated difference in means (95% CI) BT - RUL	Statistical significance test (p-value)
Total side effects: CSSES total score* **				
Baseline (sample average)	22.42 (*n*=50)	22.42 (*n*=48)		
EOT	14.15 (*n*=63)	17.25 (*n*=62)	1.22 (0.93 to 1.60)	*z*=1.44 (*p*=0.15)
3 Months	12.45 (*n*=47)	13.40 (*n*=32)	1.08 (0.73 to 1.58)	*z*=0.38 (*p*=0.71)
6 Months	8.72 (*n*=39)	12.09 (*n*=38)	1.39 (0.90 to 2.13)	*z*=1.49 (*p*=0.14)
Cognitive side effects: CSSES cognitive score* **				
Baseline (sample average)	5.0 (*n*=52)	5.0 (*n*=48)		
EOT	**3.80** (*n*=63)	**5.48** (*n*=62)	**1.44 (1.06 to 1.96)**	***z*=2.32 (*p*=0.02)**
3 Months	4.21 (*n*=47)	4.86 (*n*=32)	1.15 (0.82 to 1.61)	*z*=0.83 (*p*=0.41)
6 Months	**3.28** (*n*=39)	**4.91** (*n*=38)	**1.50 (1.05 to 2.13)**	***z*=2.24 (*p*=0.025)**

* Means are predicted for patients with average baseline outcome value, who are of younger age (≤65 years), referred from St. Patrick's and have no previous experience of ECT **All analyses were carried out using multiple imputation with 200 imputations (see Statistical Analysis). *** Analysis carried out on the log-scale, means backtransformed and effect estimates representing factor changes, MMSE: Mini-Mental State Examination TMT: Trail Making Test (versions A and B); FCSRT: Free and Cued Selective Reminding Test; CFT: Complex Figure Test.

Subjective cognitive complaints: less with RUL ECT

Meta-analysis: general cognitive measures



MMSE

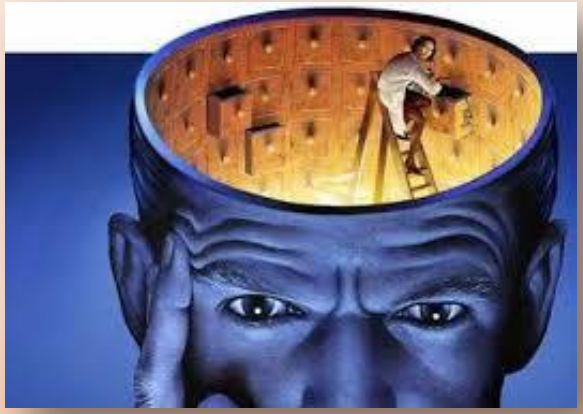
Delayed visual memory

Delayed verbal memory

Category (semantic) fluency

No differences between groups.

Forest plots of standardised mean change scores from baseline to end of treatment.



Kolshus, Jelovac, McLoughlin (2017) *Psychol Med*

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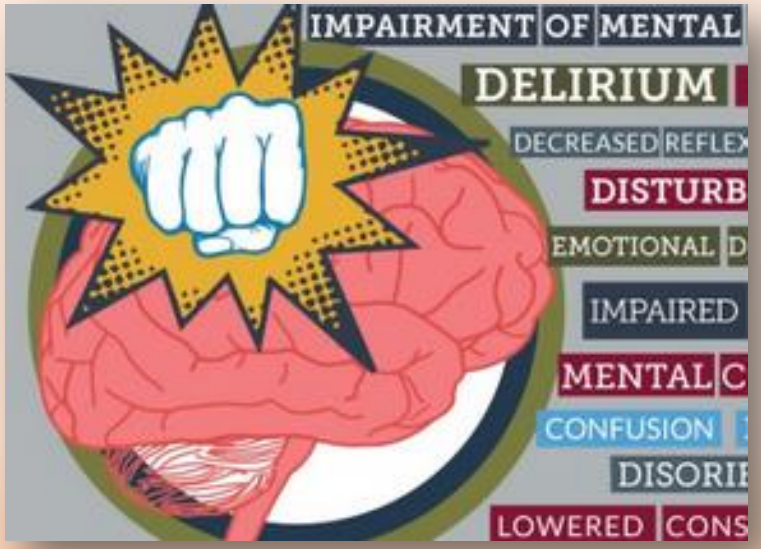
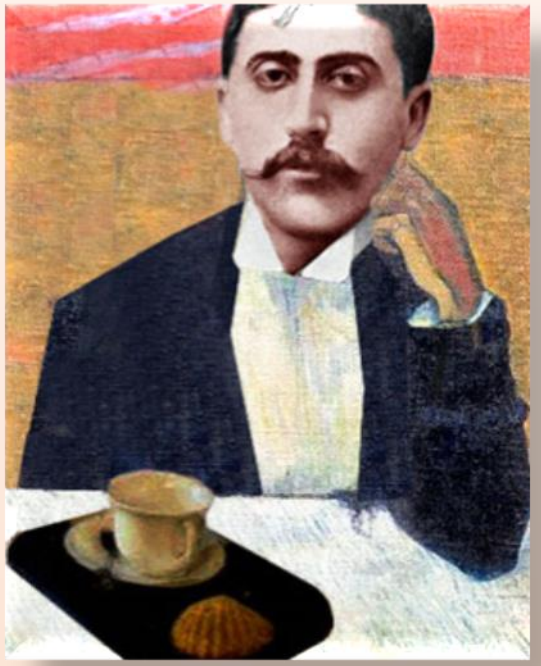
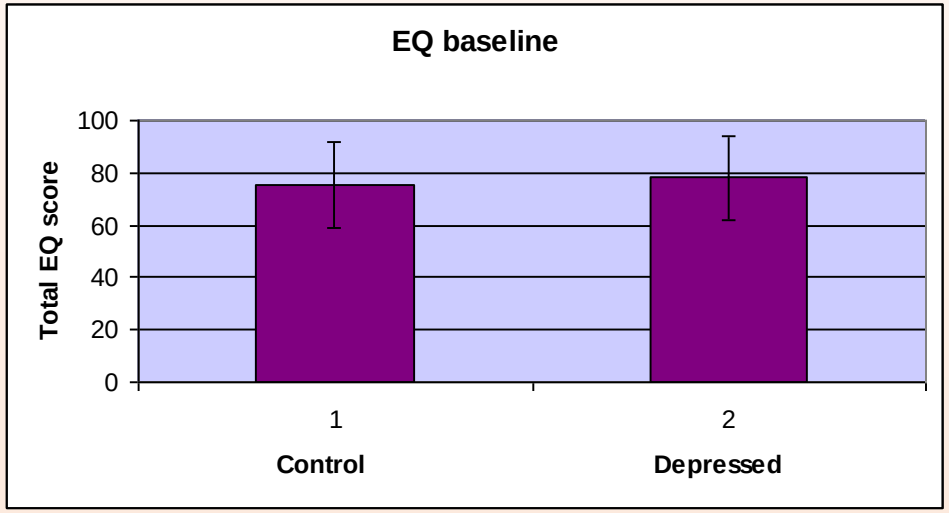
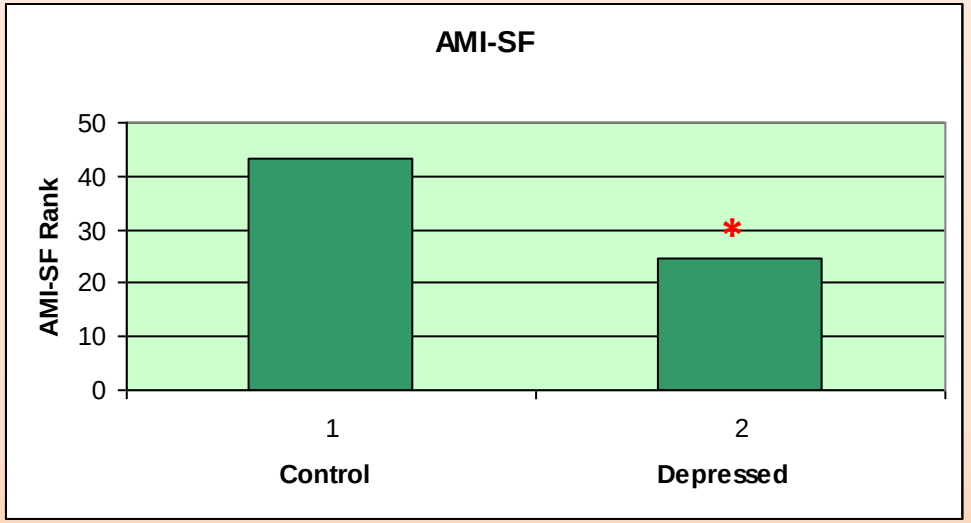


Retrospective Memory and Depression





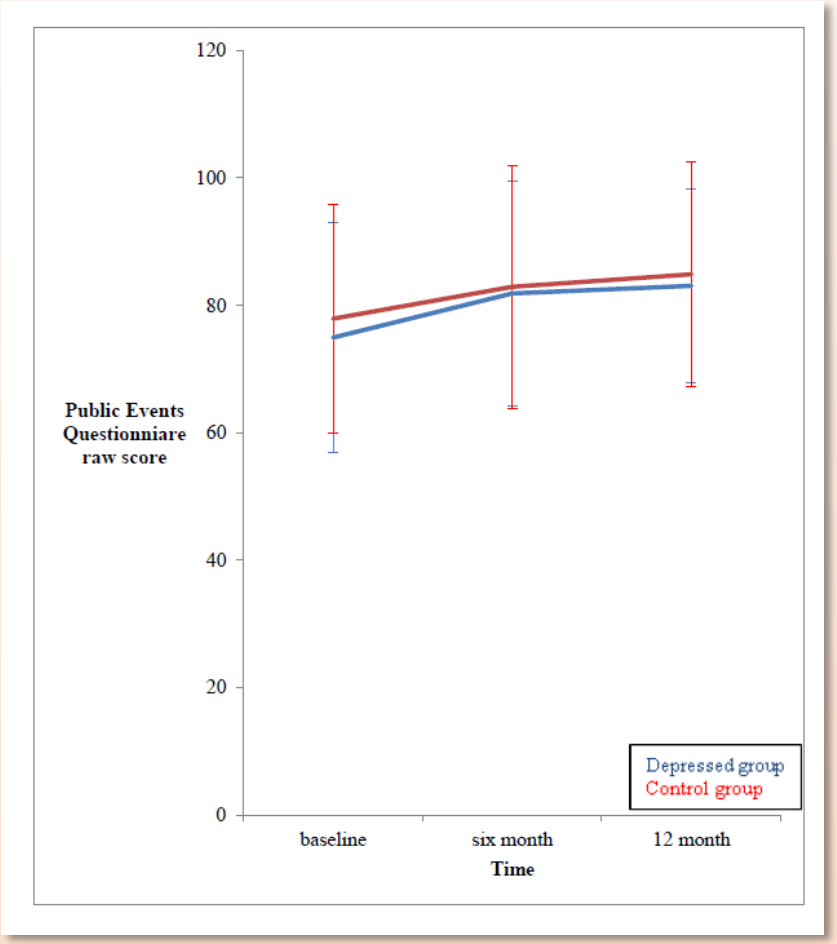
EVENTS QUESTIONNAIRE
(Max = 120 points)
Independent t-test
Control (n=30) 75.2 (16.38)
Depressed (n=30) 78.0 (17.71)
P=0.496



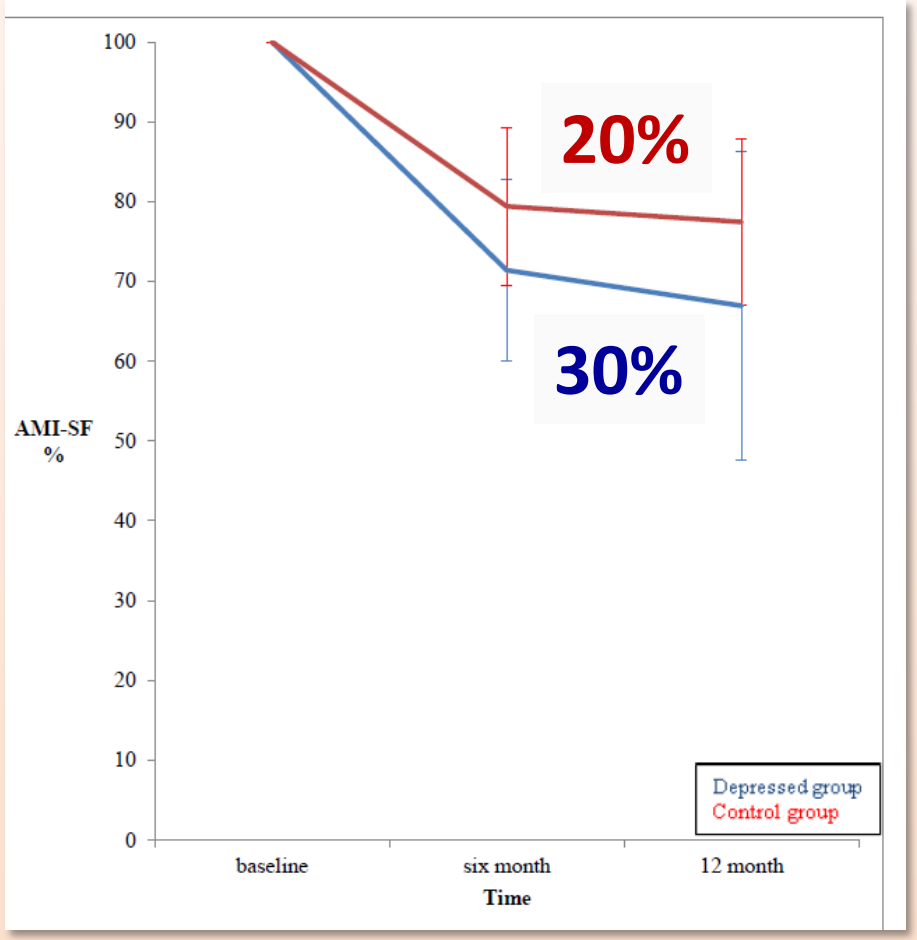
AUTOBIOGRAPHICAL MEMORY (CAMI-SF)
(max = 60 points)
Mann-Whitney Test
Mean rank
Control 43.3
Depressed 24.7
P<0.001

Noone et al (2014) *Front Psychology*
Noone et al (2018), *in preparation*

Retrograde amnesia, depression and time



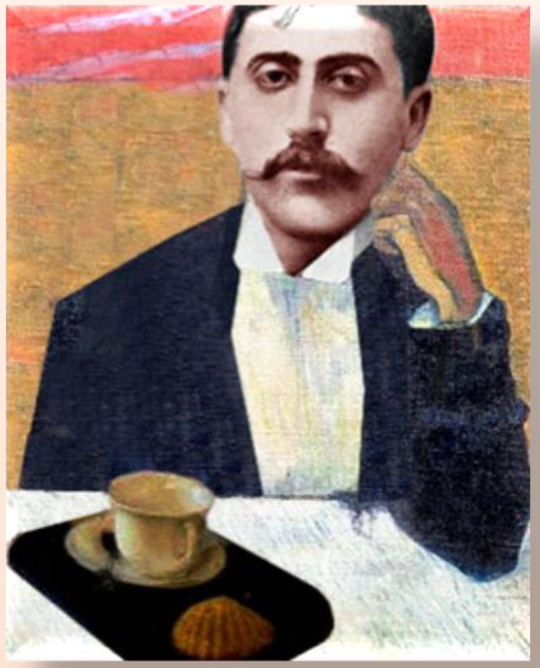
Public events memory

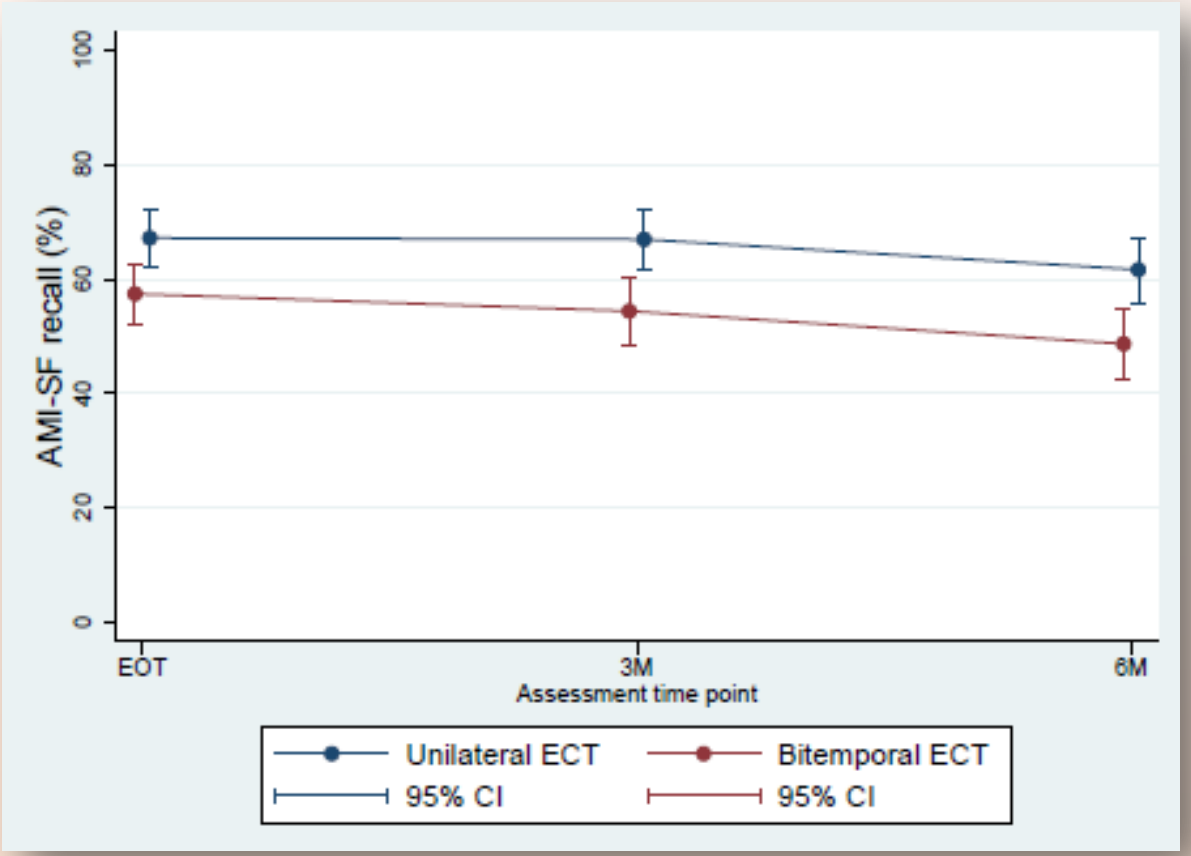


Autobiographical memory

EFFECT-Dep Trial

CAMI-SF: % recall of baseline performance

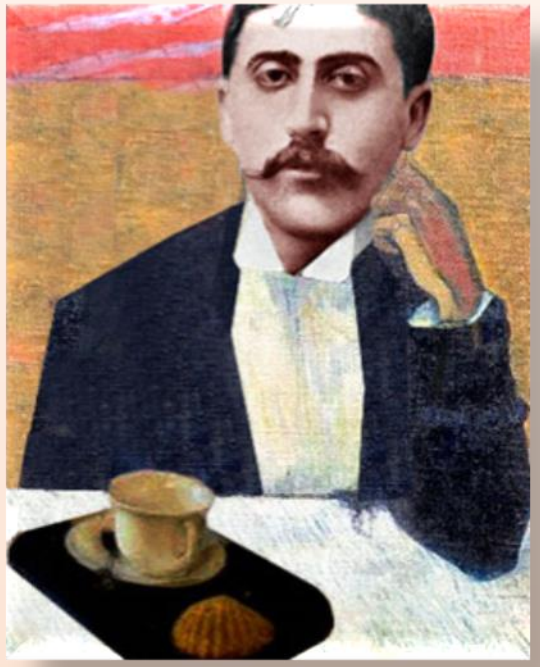


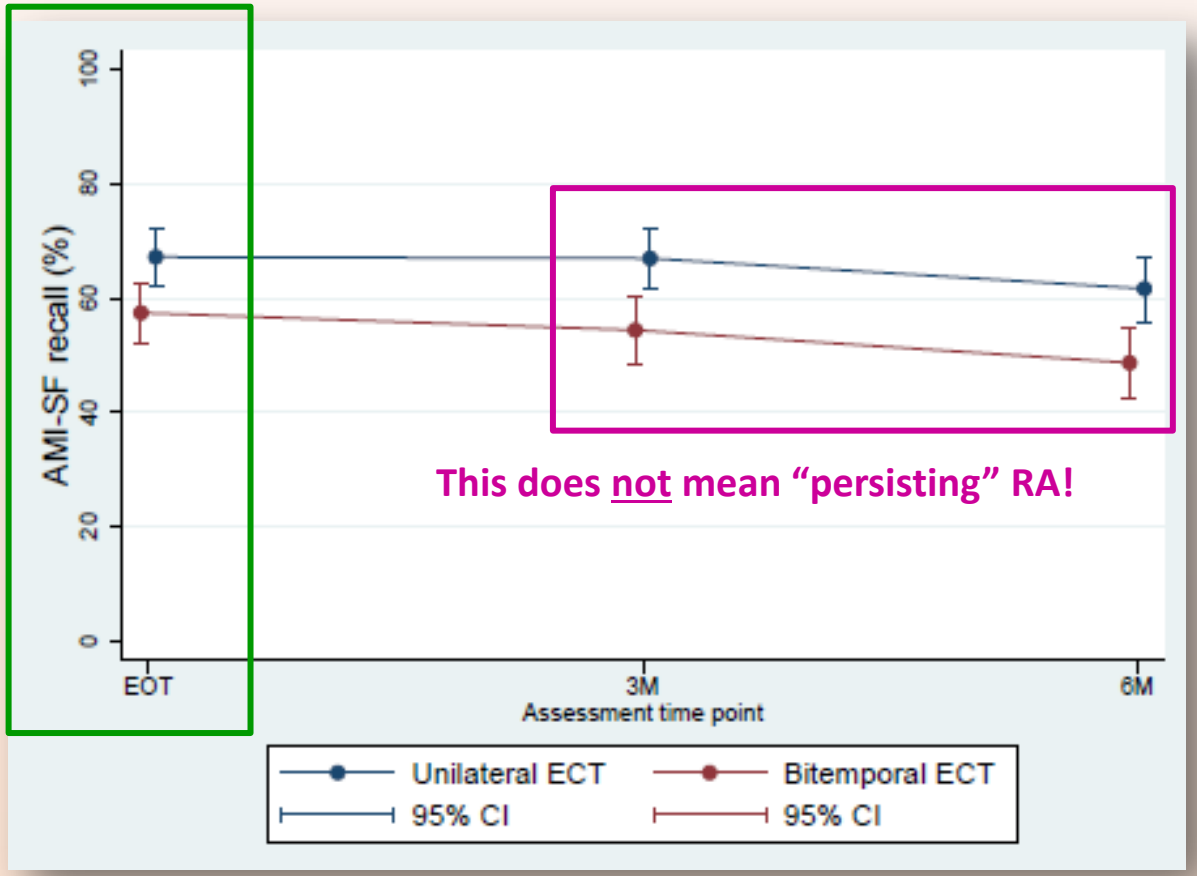


The % consistency of recall of these baseline memories was lower in the bilateral group at end-of-treatment (OR=0.658, 95% CI 0.513 to 0.846, p=0.001) and this was maintained at the 3-month (OR=0.59, p<0.001) and 6-month (OR=0.59, p<0.001) follow-ups.

EFFECT-Dep Trial

CAMI-SF: % recall of baseline performance





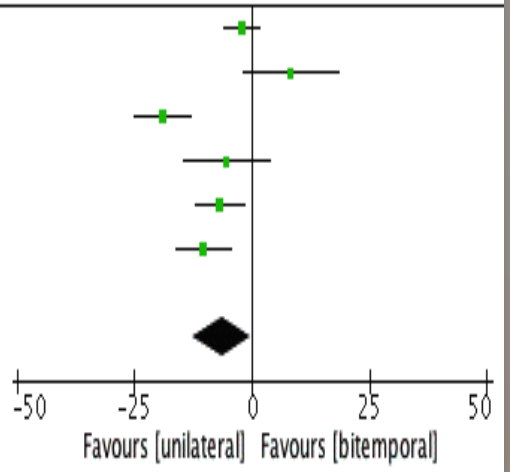
The % consistency of recall of these baseline memories was lower in the bilateral group at end-of-treatment (OR=0.658, 95% CI 0.513 to 0.846, p=0.001) and this was maintained at the 3-month (OR=0.59, p<0.001) and 6-month (OR=0.59, p<0.001) follow-ups.

Meta-analysis: retrograde autobiographical amnesia

Study or Subgroup	Bitemporal Mean	SD	Total	Unilateral Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kellner 2010	66.7	7.75	60	68.9	13.1	60	19.2%	-2.20 [-6.05, 1.65]
McCall 2002	64.2	17.4	36	56	26.6	39	13.5%	8.20 [-1.90, 18.30]
Sackeim 2000	42.2	10	19	61.3	8.8	20	17.4%	-19.10 [-25.02, -13.18]
Sackeim 2008	57.8	16.72	17	63.31	10.52	19	14.3%	-5.51 [-14.76, 3.74]
Sackeim 2009	54.54	20.02	108	61.36	19.11	111	18.1%	-6.82 [-12.01, -1.63]
Semkovska 2015	56.7	17.3	64	67.1	16.3	64	17.5%	-10.40 [-16.22, -4.58]
Total (95% CI)			**304**			**313**	**100.0%**	**-6.50 [-12.78, -0.21]**

Heterogeneity: $Tau^2 = 49.78$; $Chi^2 = 32.05$, df = 5 ($P < 0.00001$); $I^2 = 84\%$

Test for overall effect: Z = 2.03 (P = 0.04)



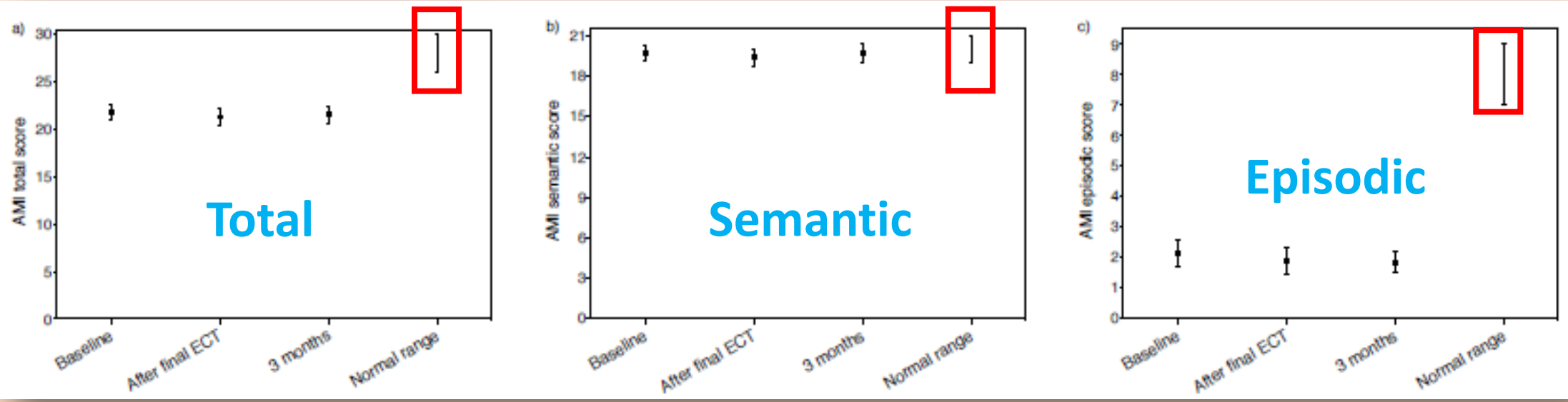
Forest plot of retrograde amnesia (as % of baseline) for autobiographical memory (CAMI-SF) at end of treatment.

Kolshus, Jelovac, McLoughlin (2017) *Psychol Med*

Cognitive effects of ECT: Kopelman AMI - recent

- N=48 depressed pts (mean age, 61.6; female, 62.5%) having bitemporal ECT
- "Recent Life" section of the Kopelman Autobiographical Memory Interview (AMI)
- 77% response rate
- no significant changes over time on either AMI total score or semantic and episodic subscales. However, patients were markedly impaired on episodic autobiographical memory compared with the normative sample at all 3 assessment points, whereas personal semantic memory recall was normal.

- **Does this mean that there is no retrograde amnesia?**



Jelovac et al (2016) *J ECT*

Kopelman AMI – Childhood, Early Adult Life, and Recent Life

KEEP WELL

Cases vs Controls

- Balanced for age and sex
- Controls had higher IQ
- Slightly better educated
- Similar socioeconomic status

Variable	Depressed Patient Group N =27	Healthy Control Group N =72	Statistical Analysis (p)
Age in years	54.8 (14.0)	49.3 (15.0)	0.071
Number of medical conditions	1.7 (1.7)	0.34 (0.34)	<0.001
Baseline HRSD-24	30.4 (7.3)	3.6 (3.0)	<0.001
Handedness Quotient[a]	81.7 (16.3)	70.7 (35.6)	0.136
Predicted full-scale IQ, median (range)[b]	111.0 (106.8, 118.0)	118.0 (110.0, 122.0)	0.012
Gender, n (%) female	14 (51.9%)	45 (62.5%)	0.365
Employment, n (%) working	11 (42.3%)	49 (68.1%)	0.064
Marital status, n (%) married	17 (63.0%)	39 (54.2%)	0.905
Level of education[c]			
Primary	1 (3.7%)	0 (0)	
Secondary	11 (40.7%)	11 (15.3%)	<0.001
Tertiary	13 (48.1%)	35 (48.6%)	
Quaternary	2 (7.4%)	26 (36.1%)	
Socioeconomic status, n (%)[d]			
Professional	2 (7.4%)	19 (26.4%)	0.096
Managerial/Technical	6 (22.2%)	21 (29.2%)	
Skilled Occupations	17 (63.0%)	29 (40.3%)	
Partly Skilled	2 (7.4%)	3 (4.2%)	

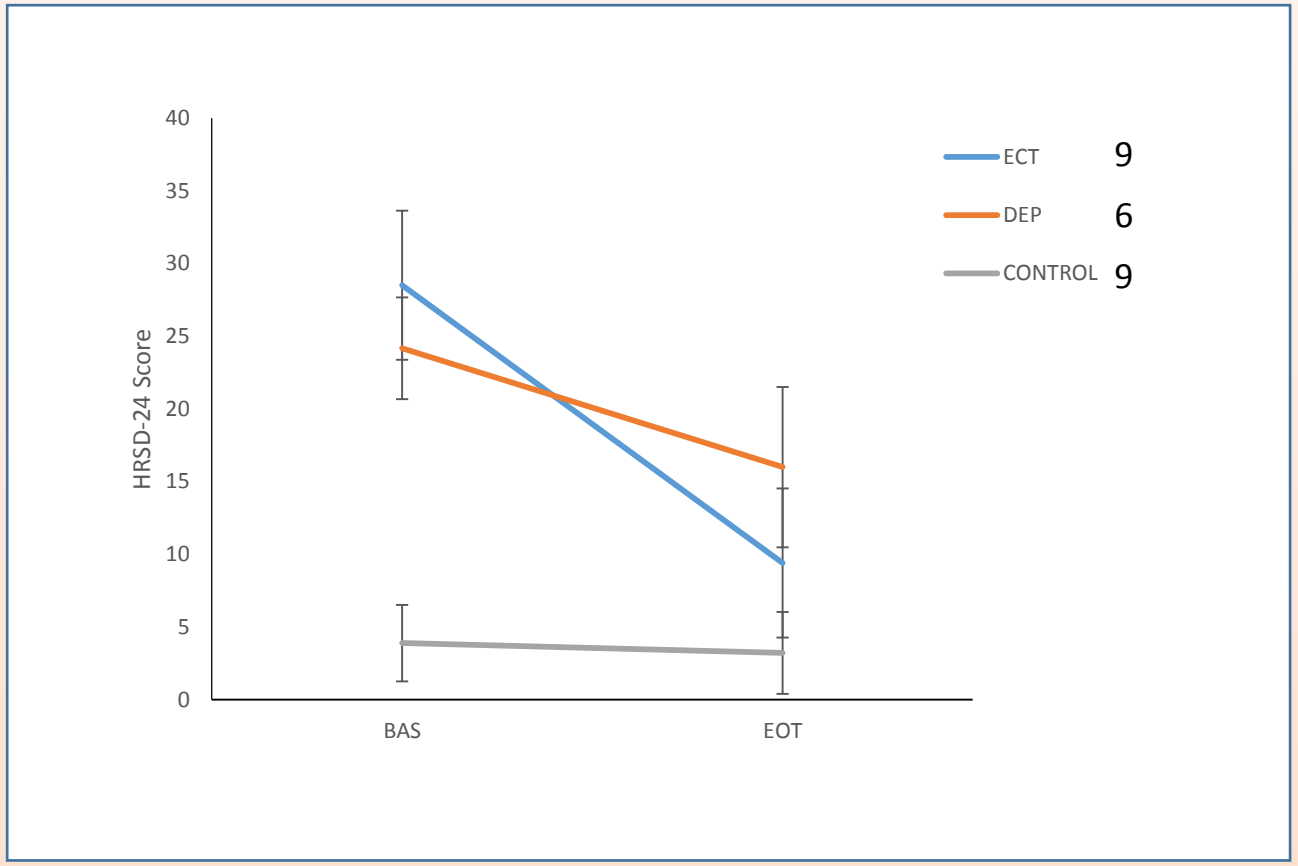
Finnegan et al (2016) *Pilot Feasibility Stud.*

Kopelman AMI - scores of depressed patients and healthy controls at two time points

	Pre-ECT/Baseline			Post-ECT/After 4 Weeks			Statistical analysis: change between assessments (p)	
	Depressed Patients (N=27)	Healthy Controls (N=72)	Statistical analysis (p)	Depressed patients (N=27)	Healthy Controls (N=72)	Statistical analysis (p)	Depressed patients (N=27)	Healthy controls (N=72)
Semantic Memory								
Recent Life	19 (6.5, 21)	21 (16.5, 21)	<0.001	18 (10, 21)	21 (17.5, 21)	0.001	0.104	0.166
Early Adult Life	19.5 (6, 21)	21 (14.5 , 21)	0.014	20 (0, 21)	21 (17.5, 21)	<0.001	0.958	0.726
Childhood	18.5 (0, 21)	19.5 (12.5, 21)	0.094	18.5 (0, 21)	19.75 (14, 21)	0.006	0.614	0.380
Total	57 (12.5, 63)	60.25 (49.5, 63)	0.001*	55.5 (13, 62)	60.75 (52.5, 63)	<0.001*	0.467*	0.312*
Episodic Memory								
Recent Life	4 (0, 9)	8 (5, 9)	<0.001	3 (0, 8)	8 (5, 9)	<0.001	0.486	0.205
Early Adult Life	4 (0, 9)	8 (4, 9)	<0.001	4 (0, 9)	8 (4, 9)	<0.001	0.903	0.464
Childhood	5 (0, 9)	7 (3, 9)	<0.001	3 (0, 9)	8 (2, 9)	<0.001	0.131	0.164
Total	13 (0, 25)	22 (15, 27)	<0.001*	13 (0, 24)	23 (11, 27)	<0.001*	0.415*	0.128*

Data are presented as median (range) due to non-parametric distribution. Mann-Whitney U test was performed for all comparisons.
*Bonferroni correction was applied to total scores to correct for multiple comparisons owing to the contribution of subscale scores, p was set at 0.01 for total scores.

Merge CUAMI and K-AMI?



Gusciete et al (2018) *MSc thesis*

Merge CUAMI and K-AMI?

Raw scores: the same questions asked as at BAS, but marked without reference to the original responses

	BAS			EOT		
	ECT	Depressed	Control	ECT	Depressed	Control
Total	44.7	48.92	61.56	40.3	46.33	58.22
Semantic	15.15	17.92	20.5	15.15	17.92	20.5
Episodic-extended	17.15	18.17	21	14.25	15.25	17.83
Episodic-specific	12.4	12.83	20.06	10.5	11.58	19.94

Gusciete et al (2018) *MSc thesis*

Merge CUAMI and K-AMI?

Consistency scores *Participants asked questions regarding the same events discussed at BAS.*

	ECT	Depressed	Control
Total	51.1 % (19.71)	66.33% (10.17)	73.56% (10.68)
Semantic	62.1 % (26.49)	87.83% (5.0)	90.22% (8.15)
Episodic – extended	54.2% (16.82)	52.17% (15.8)	62.22% (8.11)
Episodic – specific	36.1% (29.95)	58.33% (18.39)	69.67% (20.35)

Gusciete et al (2018) *MSc thesis*

Risk factors for cognitive deficits

Patient-related

- Old age
- Diminished cognitive reserve
- Existing brain disease

Treatment-related

- Concomitant psychotropic agents, e.g. lithium
- Higher anaesthetic dose, ?anticholinergics
- Bitemporal ECT
- High-dose ECT
- Sine wave ECT
- Greater pulse-width
- Greater frequency of ECT
- Greater number of treatments

Andrade et al (2016) *Psychiatr Clin N Am*

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Retrospective memory

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Ana Jelovac
Martha Noone
Maria Semkovska

HRB Health Research Board

TRINITY COLLEGE Institute of Neuroscience *from molecules to mind*

St Patrick's Mental Health Services *Empowering recovery*

BRAIN & BEHAVIOR RESEARCH FOUNDATION Awarding NARSAD Grants

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