ECT, Depression and Cognition

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RCPsych, London, November 28th 2014
Disclosures: none
Cognitive Effects of ECT

1. Immediate

2. Short-term / long-term

3. The retrograde amnesia “problem”

4. The EFFECT-Dep Trial
Results – summary illustration

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
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.
Boxplots of (A) MMSE and (B) FSRS versus re-orientation time.
Summary: Recovery of orientation following ECT

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

• Recovery hastened by:
  • anti-epileptic medication

• Reorientation speed correlates with later retrograde amnesia (Sobin, 1995)
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Objective Cognitive Performance Associated with Electroconvulsive Therapy for Depression: A Systematic Review and Meta-Analysis
Maria Semkovska and Declan M. McLoughlin

Unilateral brief-pulse electroconvulsive therapy and cognition: Effects of electrode placement, stimulus dosage and time
Maria Semkovska\textsuperscript{a,b}, Deborah Keane\textsuperscript{b}, Oyemi Babalola\textsuperscript{a}, Declan M. McLoughlin\textsuperscript{a,b,*}

Systematic review and meta-analysis of bifrontal electroconvulsive therapy versus bilateral and unilateral electroconvulsive therapy in depression
ROSS A. DUNNE\textsuperscript{1,2} & DECLAN M. MCLoughlin\textsuperscript{1,2}
Cognitive effects of ECT in depression: a meta-analysis

- Cognitive impairments caused by ECT, as measured by standardised tests, are **limited to the first 2 weeks** 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 (lack of standardised and validated measures; lack of within subject designs).

Semkovska & McLoughlin (2010), *Biol Psychiatry*
Unilateral ECT and Cognition: a Meta-analysis

• <3 days: unilateral ECT was associated with significantly smaller decreases in cognition

• >3 days: no significant differences between the electrode placements

• interval between final treatment and retesting is a more useful long-term predictor of cognitive function

• Significant publication bias for autobiographical memory

TMS vs ECT Trial (HDRS-17)

Change in HamD scores in ECT and TMS groups

- **ECT group (N=22)**
- **rTMS group (N=24)**

The graph shows predicted mean scores, adjusted to group average baseline values in accordance with the ANCOVA model used.

TMS vs ECT Trial remission rates

TMS: 17%
ECT: 60%

HamD scores less than or equal to 8 at the end of the treatment period

Chi-square test, p = 0.005

<table>
<thead>
<tr>
<th>Measure From CAMCOG Section of Cambridge Examination for Mental Disorders of the Elderly (24)</th>
<th>Score</th>
<th>Statistical Analysis (ANCOVA)</th>
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<tbody>
<tr>
<td></td>
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<td>Interaction of Group and Time</td>
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<td></td>
<td>ECT Group (N=16)</td>
<td>rTMS Group (N=22)</td>
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<td>Total (maximum=107)</td>
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<td>Mini-Mental State Examination (maximum=30)</td>
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<td>End of treatment</td>
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<td>CAMCOG subscales</td>
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<td>12.8</td>
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<td>6 months</td>
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<td>Verbal fluency (number of animals named in 1 minute)</td>
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<td>6 months</td>
<td>6.9</td>
<td>2.8</td>
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TMSplus Trial RESULTS

ANCOVA: group x time, $\chi^2=6.61$, df=3, $p=0.09$; group main effect, $z=-0.19$, $p=0.85$
Overall group mean difference = 0.3 (95% CI=-3.4 to 2.8)
End-of-tx mean difference = 2.9 (95% CI=-0.7 to 6.5)
Blinding: 67% (34/51) correctly guessed their treatment

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Retrospective memory and retrograde amnesia

- Public events (semantic) memory

- Autobiographical memory (AM)
  - Dynamic process that allows maintenance of one’s past, representing the basis of one’s identity and continuity

- Types of AM
  - semantic - general, decontextualised information about one’s past
  - episodic components - events situated in space and time
    - episodic-specific
    - episodic-extended

- Retrograde Amnesia: difficulty in retrieving memories of events or facts acquired before commencing ECT

Semkovska & McLoughlin (2013, 2014), *J ECT*
Autobiographical memory, depression and retrograde amnesia

• Normal AM function
  - “reminiscence bump”: late adolescence to early adulthood
  - progressive transition from episodic to semantic AM
  - AMs lose consistency over time (Bahrik, 1998; Anderson, 2000; Coluccia, 2006; Rubin, 2004)
    - measured as % consistency over ≥2 time points (test/re-test): **27-42%** over 6-20 weeks;
    - stable thereafter (e.g. Anderson, 2000; Coluccia 2006; Weaver, 1993; Talarico, 2003, etc.)

• AM in depression
  - overgeneralistion (*Autobiographical Memory Test* (Williams & Broadbent, 1996; a cue word test; does not control for retention time interval or encoding age; does not test consistency)
  - less specific than controls (Van Vreeswijk, 2004)
  - ? Persisting deficits in remission
Autobiographical memory and ECT – consistency loss

• Janis, 1950: *open-ended* questions about personal events before and after ECT
• Further developed by Squire et al (1981): amnesia score with a temporal gradient

• **Personal Memory Questionnaire**, Weiner et al (1986):
  - structured and *specific*,
  - only measured *consistency* with baseline – RUL > BL
  - no distinction between semantic and episodic components

• **Columbia Autobiographical Memory Interview (CAMI)** and the **CAMI-Short Form (CAMI-SF)** (McElhiney et al, 1995 & 2001)
  • No construct, discriminant, etc., validation studies
  • No normative data for healthy or depressed controls
  • Often confused with the validated *Kopelman AMI* (1989)
  • Cannot capture improvement
  • Can only score *inferior* to baseline, which is 100% for all irrespective of performance!!!
C-AMI-SF: Highest reported % consistency loss is **28-40%** 4-8 weeks after pre-ECT assessment (Sackeim et al, 1993 & 2000)
Figure 1: Schematic representation of the content, administration and scoring of the original Columbia Autobiographical Memory Interview – Short Form (McElhiney et al., 2001)

New components: **Semantic**, **Episodic-specific**, **Episodic-extended**

Measuring consistency of autobiographical memory recall in depression

Maria Semkovska *, Martha Noone, Mary Carton, Declan M. McLoughlin
ECT & Autobiographical Memory: Conclusions

1) Publication bias for retrograde amnesia/ECT studies

2) Standardised assessments are required for retrograde amnesia following ECT

3) Need to control for
   - normal loss in consistency over time
   - contribution of persisting depressive symptoms
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Goal: Decrease side-effects but maintain effectiveness

RCTs of bitemporal vs high-dose RUL ECT

1. Sackeim et al (2000) *Arch Gen Psychiatry* (n=20/group)
5. Sackeim et al (2009) *Arch Gen Psychiatry* (+pharmacotx; n~45-70/group)
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.
EFFECT-Dep Trial

Design: two-group parallel-design randomised non-inferiority trial; continued on usual care. Treated at St Patrick’s University Hospital, Dublin (ECTAS-accredited).

Randomisation: minimisation stratification with variable block sizes (stratified for: source of referral; previous ECT; age, ≥65); just before 1st ECT session; independent & computerised - Clinical Trials Unit, IOP, KCL

Blinding: patients, clinicians, raters, statistician

Inclusion: major depressive episode (DSM-IV; SCID) referred for ECT; HDRS-24 ≥21; ≥ 18 years

Exclusion: unfit for general anaesthesia; ECT in previous six months; dementia or other Axis 1 diagnosis; alcohol/other substance abuse in previous six months; inability/refusal to consent.

Ethical approval: St Patrick’s University Hospital Research Ethics Committee
ECT
• twice weekly

• Mecta 5000M device (Mecta Corporation, USA)

• methohexitone (0.75-1.0 mg/kg) and suxamethonium (0.5-1.0 mg/kg)

• EEG monitoring

• seizure threshold (ST) was established by a method of limits at the first session and subsequent treatments given at 1.5 x ST for BT ECT and 6.0 x ST for RUL ECT

• Stimulus charge is titrated upward as required during treatment courses following a standard stimulus dosing protocol.

• number of ECTs determined by referring physicians, up to 12 sessions (as per Mental Health Commission)
Clinical outcomes

Primary: 24-item Hamilton Rating Scale for Depression (HDRS)

- baseline; after every 2 ECTs; during 12 mth follow-up
- **Response**: ≥60% decrease in HDRS from baseline and score ≤16

- **Remission**: ≥60% decrease in HDRS from baseline and score ≤10 on two occasions separated by one week

- **Relapse**: ≥10 point increase in HDRS compared to end-of-treatment score plus HDRS ≥16; increase in the HDRS should be maintained two weeks later. Hospital admission, further ECT, and deliberate self-harm/suicide also constitute relapse.
Sample size estimation & clinical significance

In a large series ($n = 253$) of depressed patients, Petrides et al. (2001) found a mean (SD) reduction in 24-item HDRS of 25.6 (9.4) after treatment with BT ECT (1.5 x ST).

We estimated that:

- **69 patients** required per treatment group
- to have **80% power**
- to demonstrate, using a one-sided equivalence $t$-test at **5% level**
- that mean reduction in 24-item HDRS achieved using high-dose RUL ECT is **no more than 4 points** (i.e. equivalent to 3 points on 17-item HDRS) less than that achieved using standard BT ECT, assuming a common within-group SD of change scores of 9.4 and equal expected group mean change scores.
Statistical inferential analyses

• Intention to treat
• Single primary experimental hypothesis
• No planned subgroup analyses
• No planned interim analysis
• Statistician blinded
• Linear mixed models for HDRS
• Multiple imputation for missing data
35.3% of all ECT referrals in Ireland May 2008 to October 2012; age 62.0, [SD=5.1], female %= 67.7%

Comparing the 138 participants to the 113 potentially eligible non-participants:

- participants were younger (56·7 [SD 14·8] vs 63·4 [SD 14·3] years; p=0·0001 )
- but did not differ regarding gender (% female: 63% vs 67%) or
- baseline CGI-severity (5·3 [SD 0·7] vs 5·2 [SD 0·9] (n=101); p=0·35) and
- MMSE scores (27·7 [SD 2·1] (n=119 ) vs 27·8 [SD 2·5] (n=85); p=0·79 ).
Limitations

- depression only
- unable to include very severe cases (maybe bitemporal is better?)
- multiple imputation (but similar to complete case analyses)

Conclusions

- RUL ECT (6xST) is **not** inferior to standard BT ECT (1.5xST)
- RUL ECT has cognitive advantages
- real-world trial, reflecting Irish and UK practice
- good generalisability
- overall remission similar to community studies