Future directions and development in ECT technique May 2014

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Research trends

- Side effects
- Augmentation
- Maintenance
- Other Brain Stimulation approaches

Side Effects

- Dosing strategies
- Adjunctive pharmacological interventions
- Anesthesiological strategies.

Dosing strategies

- Electrode placement
- Stimulus architecture (pulse width)
- Interval between treatments

Elektrodeplacement

- Bitemporal
- Right Unilateral
- Bifrontal
- LART
- Alternating

Electrodeplacement and pulsewidth

- To reduce side effects
- It is possible to generate a nice looking seizure that do not work!

Response rates %

	unilateral	bilateral
Just above seizure threshold	28	70
2,5 x	50	70
1,5 x	35	
2,5 x	30	65
6 x	65	

From Sackeim

Sine wawe and brief pulse square wawe

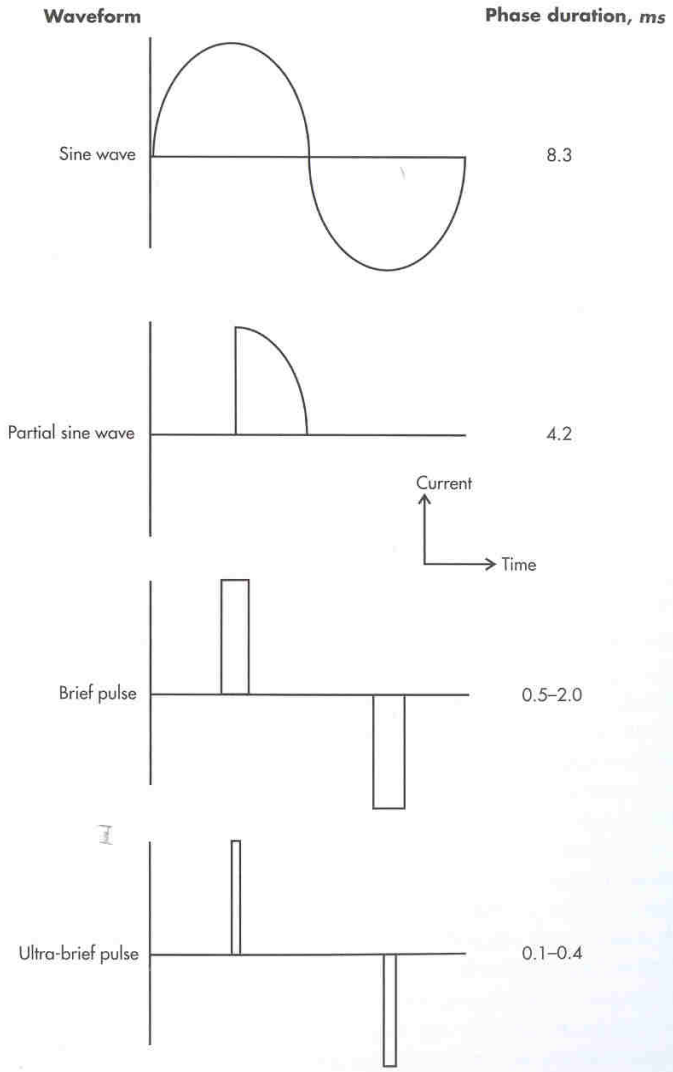


Figure 11–1. *Examples of representative waveforms.*
A single cycle of each waveform is shown, with current on the vertical axis and time on the horizontal axis.

Low energy brief-pulse induces ar nice – but less effekctive seizure

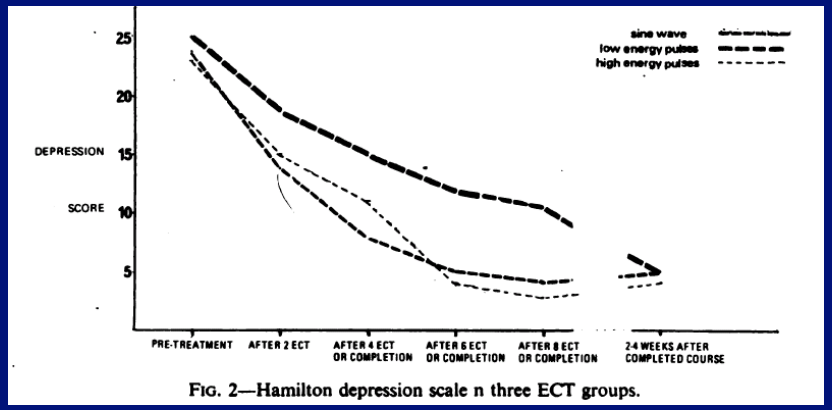


FIG. 2—Hamilton depression scale n three ECT groups.

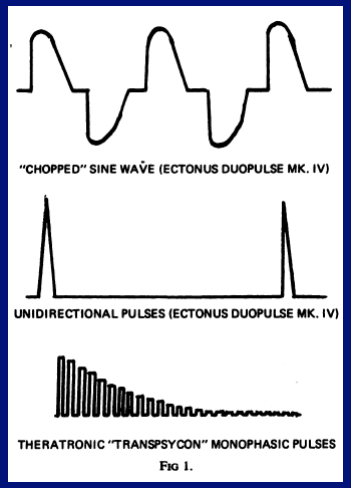


FIG 1.

- Cronholm og Ottoson 1963
- Robin og De Tissera 1982

TABLE II

Within treatment measures in three ECT groups

	Sine wave	Low energy pulses	High energy pulses
Prolactin—mu/l			
Before ECT			
Mean and standard deviation	213 ± 194	243 ± 118	230 ± 215
Anaesthetic agents			
Thiopentone, dose in mgms			
Mean and standard deviation	124 ± 20	108 ± 15	113 ± 16
Succinyl choline, dose in mgms			
Mean and standard deviation	25 ± 5	22 ± 3	23 ± 3
Anaesthetic—treatment time in seconds			
Mean and standard deviation	65 ± 14	69 ± 12	66 ± 14
Energy per treatment			
Joules, range	70–100	5.5–13	40–55
Millicoulombs, range	450–900	27–52.5	185–275
Convulsion time in seconds			
Mean and standard deviation	43 ± 16	44 ± 12	43 ± 15
Prolactin—mu/l			
After ECT			
Mean and standard deviation	1664 ± 618	1821 ± 1306	1514 ± 1079
Concurrent night sedation			
Nitrazepam 5 mgms nocte	1	3	5
10 mgms nocte	20	13	12
Concurrent day sedation			
Diazepam 2 mgms t.i.d.	1	0	0
5 mgms t.i.d.	3	0	3

TABLE III

Number of treatments to completion of course or change of treatment

	Sine wave	Low energy pulses	High energy pulses
Number of ECT's administered			
2–3	2	0	3 (+2††‡)
4	5	0	2 (+1†)
5	9	2	1
6	4	5	6
7–8	3	5	2
9+	1	5*	1
Total patients	24	17	15 (+3)

† Treatment changed in error to alternative ECT at this point.
‡ Treatment refused at this point.
* Treatment changed in all cases because of failure to respond.

Number of treatments in course to completion and change because of 'failure' only. Changes by error and refusal excluded§ Mean and standard deviation	5 ± 2	8 ± 3	5 ± 2

§ Kruskal-Wallis One Way Analysis of Variance (Seigel, 1956). H = 13.592, df = 2, P = < .01.

Hyrman 1985: Conclusion

- PW effectivity increases from 1 ms til 0,06 ms
- Ideal frequensy 100 - 200 Hz (200-400 pps)

Sackeim 2008

n

22 23 22 23

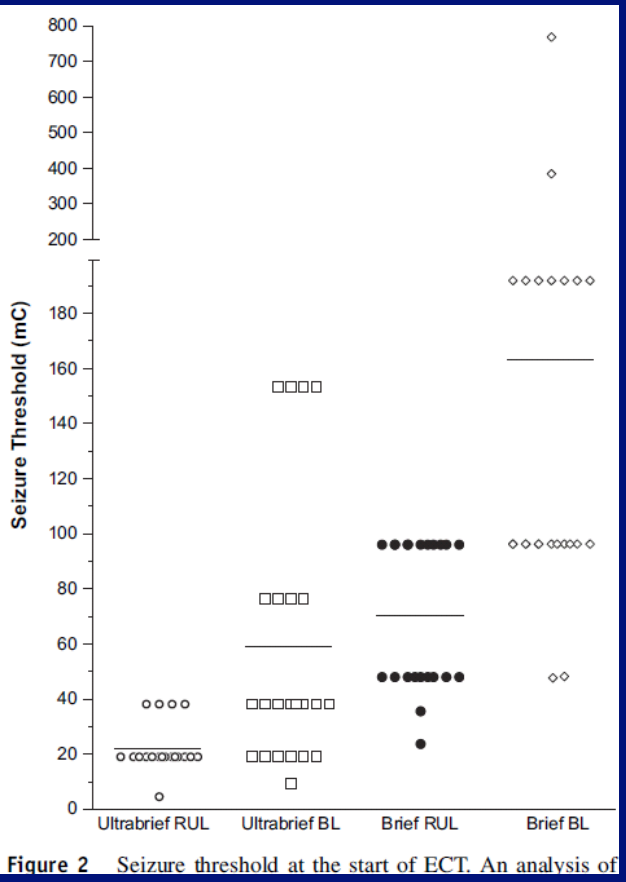


Figure 2 Seizure threshold at the start of ECT. An analysis of

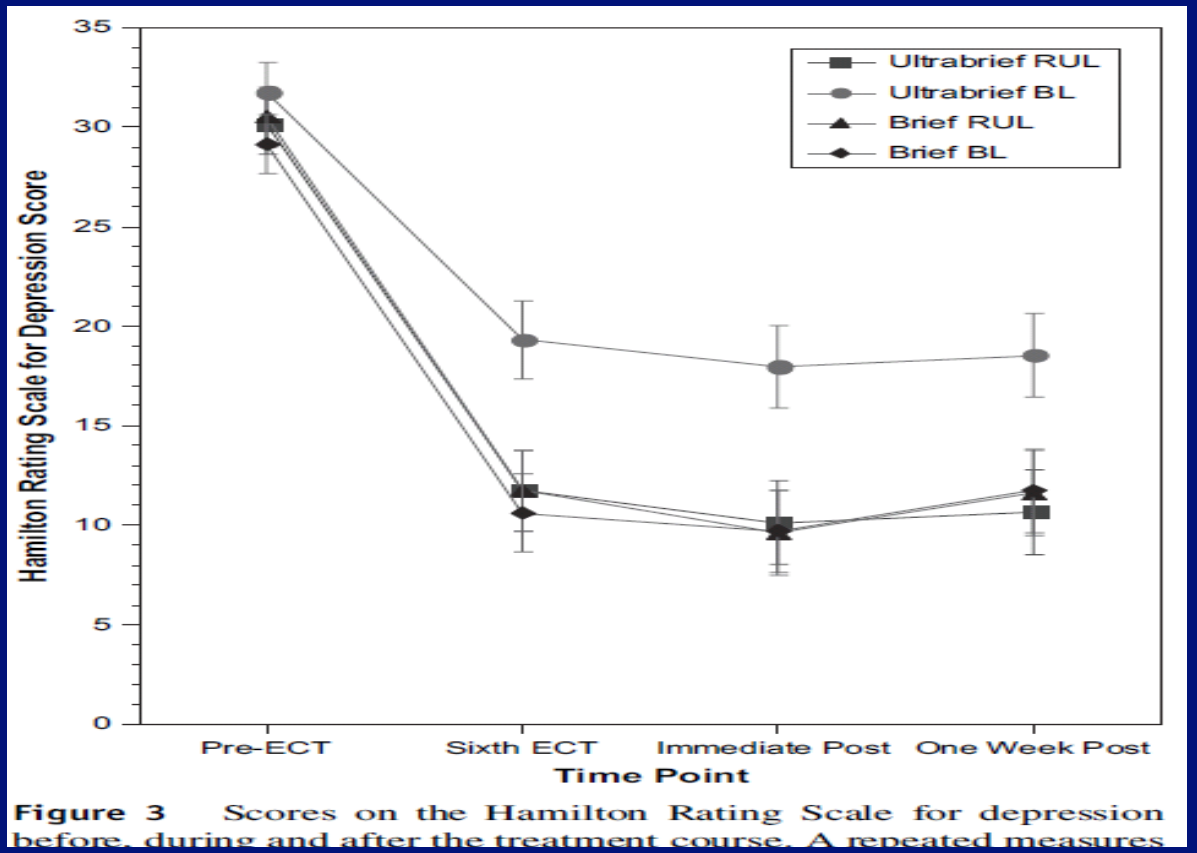


Figure 3 Scores on the Hamilton Rating Scale for depression before, during and after the treatment course. A repeated measures

- **Ultrabrief RUL: 0,3 ms, 6 x ST**
- **Ultrabrief BL: 0.3 ms, 2,5 x ST RH-DK: 0,5 ms 1,5 x ST**
- **Brief RUL: 1,5 ms, 6 x ST**
- **Brief BL: 1.5 ms, 2,5 x ST**

Sackeim 2008

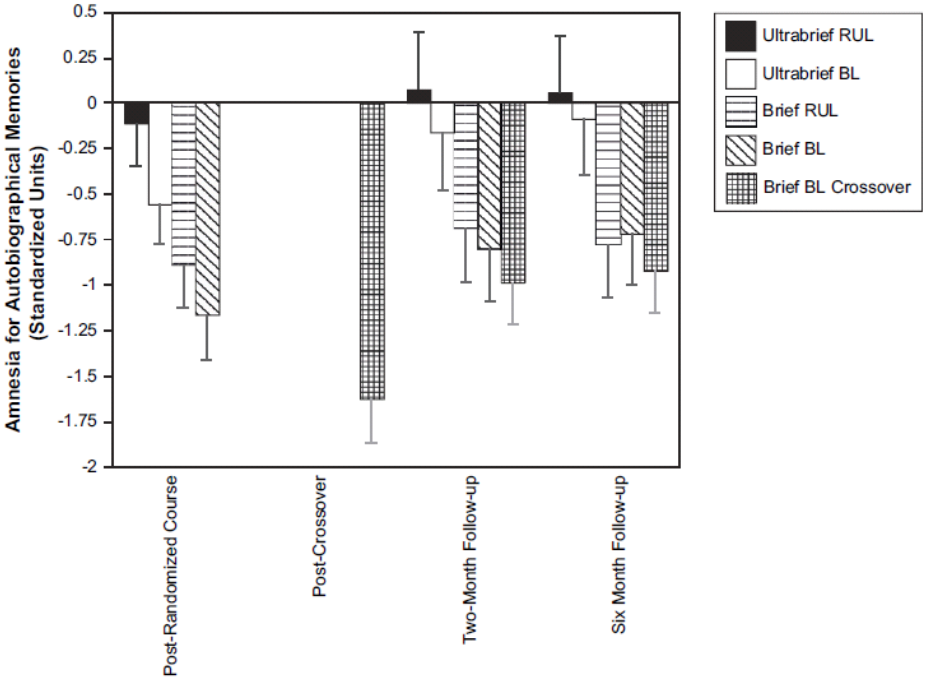
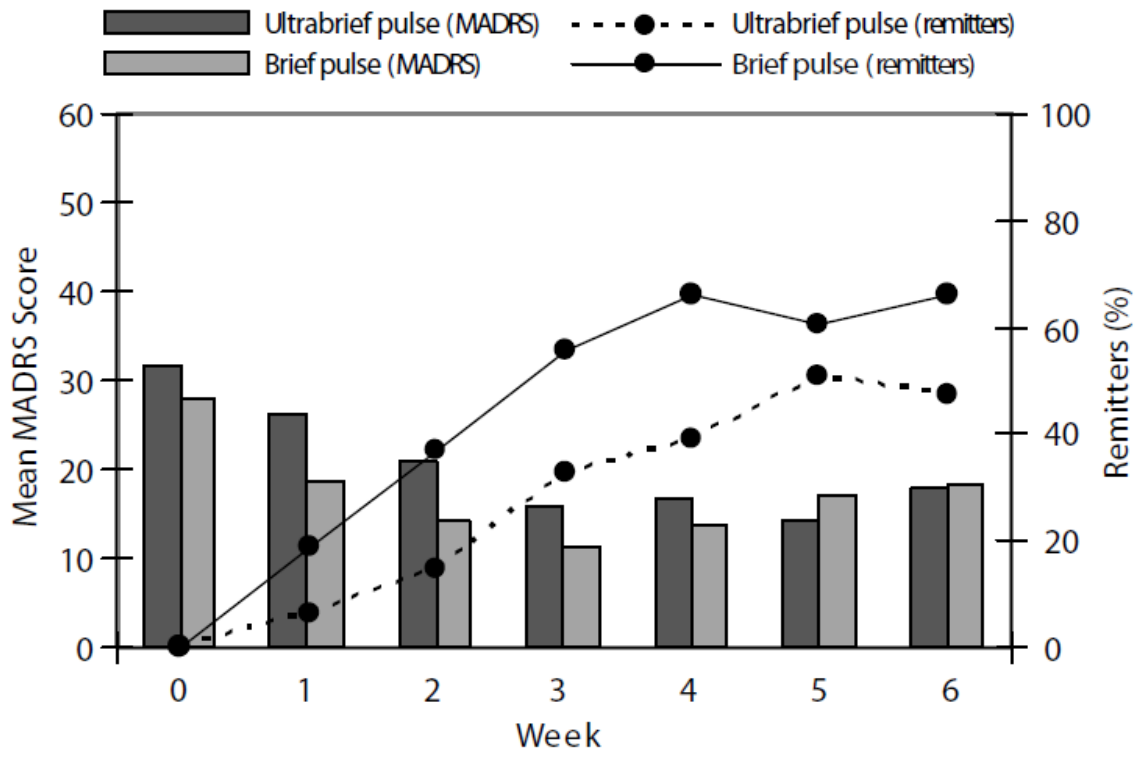


Figure 5 Scores on the Columbia University AMI. Retrograde amnesia for autographical events was assessed immediately after the end of the randomized and crossover phases and at 2- and 6-month follow-up, after completing all ECT. At each time point, analyses of covariance indicated that each of the ultrabrief ECT conditions resulted in less retrograde amnesia than any of the brief pulse conditions ($P < .05$). Thus, effects of pulse width on extent of retrograde amnesia persisted at least 6 months after completion of ECT.

Brief vs Ultrabrief Unilateral

Figure 2. MADRS Scores and Percentages of Remitters in the Brief Pulse (n = 38) and Ultrabrief Pulse (n = 49) Electroconvulsive Therapy Groups



Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Spaans et al 2013

Sienaert et al 2009

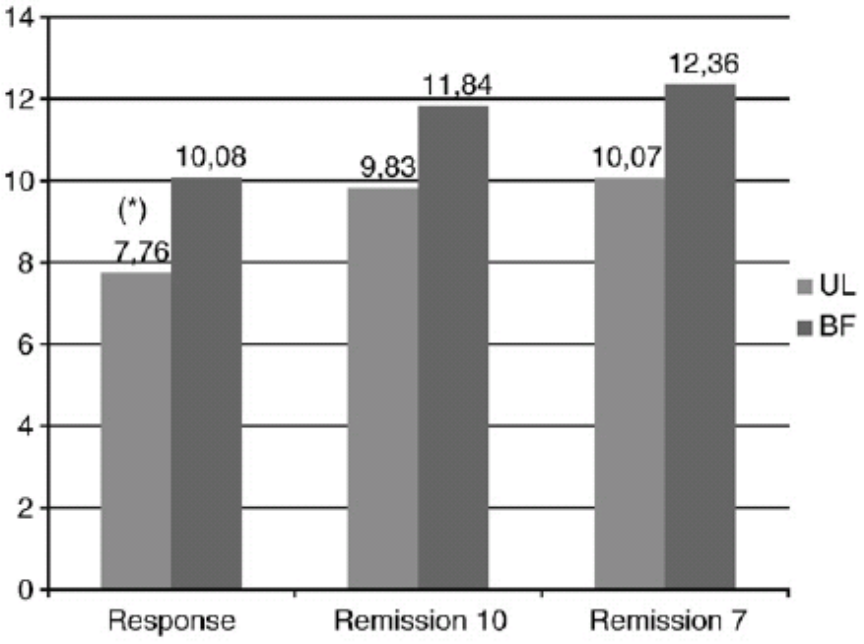


Fig. 2. Mean number of treatment sessions to achieve end-point criteria. UL: unilateral ECT; BF: Bifrontal ECT; (*) $t(38.2)=2.24$; $p<0.03$.

Table 2
Treatment parameters

Characteristic	Bifrontal N = 32 (50%)		Unilateral N = 32 (50%)		p
	N	%	*N*	%	
Methohexital	24	75.00	16	50.00	0.04
Etomidate	8	25.00	16	50.00	
	Mean	SD	Mean	SD	
Succinylcholine dose	63.5	11.82	64.06	13.22	.97
Methohexital dose	66.13	12.52	66.25	11.61	.97
Etomidate dose	12.75	1.83	13.37	2.90	.90
Seizure threshold (mC)	89.35	70.44	38.40	24.92	<.0001
Number titrations	1.87	0.95	1.28	0.58	.0052
Frequency (Hz)	46.90	28.85	65.77	28.20	.0015
Train duration (s)	7.60	0.68	7.98	0.09	.0005
Final treatment dose (mC)	213.71		311.55	206.74	.01
Motor seizure duration – first treatment	58.74	19.82	62.19	34.37	.63
Motor seizure duration – last treatment	41.17	12.56	37.07	10.24	.17
EEG seizure duration – first treatment	91.52	45.16	98.81	46.78	.53
EEG seizure duration – last treatment	58.79	16.52	55.37	14.96	.41
MMSE baseline	26.72	2.67	27.17	2.97	$F(1,56)=.76$
MMSE post 1	27.67	2.60	27.81	2.42	$p=.4733$
MMSE post 6	28.63	1.15	28.44	2.12	

BF 0,3 ms 1,5 x ST RR:78% REMR:34

UL 0,3 ms 6 x ST RR:78% REMR:44

A conclusion on the ultrabrief thing?

- Is Ultrabrief pulse 6 x ST UL ECT as effective as bilateral – with fewer side effects?
- Does Ultrabrief BL loose effectivity with decreasing PW ? Or is it the decreasing dose??
- More research.

Initial Dose

- Formula based (age, gender, electrode placement)
- Dosetitration

- Fixed high dose (unilateral)

Abrams: Response by stimulus dose.

Table 6–1 Brief-pulse unilateral ECT response by stimulus dose

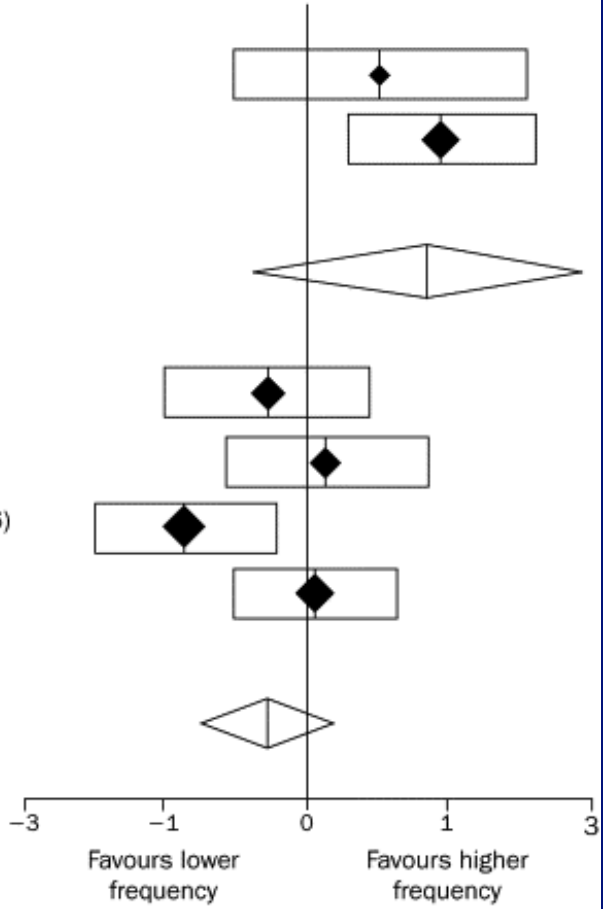
Author	Mean dose	Improvement (%)	Response rate (%)	Mean # ECTs	Dose method
Sackeim et al. (1993)	86 mC		17	9	1×
Letemendia et al. (1993)	107 mC	50		12	1×
Sackeim et al. (1987a)	113 mC	38*	28	9	1×
McCall et al. (2000)	136 mC		39	6	2.25×
Sackeim et al. (2000)	139 mC		35	10	1.5×
McCall et al. (1995)	151 mC	65		8	2.25×
Sackeim et al. (1993)	175 mC		43	9	2.5×
Ng et al. (2000)	188 mC	40		6	2.5×
Sackeim et al. (2000)	195 mC		45	9	2.5×
Abrams et al.. (1991)	378 mC	68	65	6	Fixed
Abrams, Swartz, and Vedak (1989)	378 mC	70		6	Fixed
McCall et al. (1995)	403 mC	69		6	Fixed
McCall et al. (2000)	403 mC		67	6	Fixed
Sackeim et al. (2000)	441 mC		80	8	6×
Pettinati et al. (1990)	476 mC	89		6	Age

Fixed = fixed dose; Age = age-based dose; (n)× = titration-based dose at (n) times threshold.

*Calculated from published figure.

1, 2 or 3 times weekly ?
UK-review Lancet 2003

Trial	Number of participants	Standardised effect size (95% CI)
Once a week *vs* three times a week		
Kellner 1992[65]	11	0·504 (−0·526 to 1·534)
Janakiramaiah 1998[66]	40	0·940 (0·287 to 1·593)
Pooled fixed effects		0·841 (0·311 to 1·370)
Pooled random effects		0·832 (−0·389 to 1·890)
Twice a week *vs* three times a week		
Gangadhar 1993[67]	30	−0·293 (−1·013 to 0·426)
Shapira 1998[68]	31	0·123 (−0·585 to 0·831)
Vieweg 1998[70]	46	−0·888 (−1·530 to −0·246)
Lerer 1995[69]	52	0·049 (−0·523 to 0·621)
Pooled fixed effects		−0·308 (−0·629 to 0·014)
Pooled random effects		−0·299 (−0·759 to 0·199)



1, 2 or 3 times weekly ?
Gangadhar 2010

Twice weekly seems to have the best balance between therapeutic outcome and adverse effects in the immediate treatment of **depression**

Increasing the frequency of ECT may result in more **rapid** improvement of depression, but increases **adverse cognitive** effects.

Very few data exist for comparing different frequencies during the immediate treatment of **other disorders.**

Lack of research evidence on the frequency of ECT administration during the **continuation and maintenance** phases

Pharmacological interventions

- Cardiovascular safety + airway secretion:
  - *atropine, glycopyrrolate, labetalol, esmolol, nitroglycerin*
- Gastrointestinal (nausa, reflux)
  - *ondansetron, citrate, famotidine, metoclopramide*
- Pain
  - *NSAIDs*
- Seizure modification
  - *Flumazenil, caffeine, theofylamine, midazolam, diazepam*

Pharmacological interventions 2

- Cognitive side effects:
  - *choline esterase inhibitors: galantamine, physostigmine*
  - *calcium blockers: nicardipine*
  - *pemoline, tryptophan, piracetam, naloxone*
  - *vasopressin, T3, ACTH, TRH,*
  - *”herbal”*

Anesthetics

- propofol
- methohexital, thiopental
- etomidate
- ketamine
- remifentanil

Bauer et al. 2009: Propofol vs Thiopental

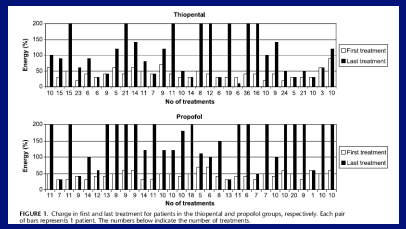


FIGURE 1. Charge in first and last treatment for patients in the thiopental and propofol groups, respectively. Each pair of bars represents 1 patient. The numbers below indicate the number of treatments.

TABLE 4. Seizure-Related Data

	Thiopental	Propofol	*P*
Cumulative EEG duration, s	451 ± 247	289 ±106	0.002
EEG duration per treatment, s	36.3 ± 13.2	25.7 ± 8.3	0.001
Visual seizures, cumulative, s	287 ± 182.8	150 ± 68.4	0.000
Visual seizures, per treatment, s	24.5 ± 13.0	13.5 ± 5.9	0.000
Restimulations (mean)	1.43 ± 2.25	2.19 ± 2.85	0.295
Restimulations, patients not receiving anticonvulsants	1	2.1	0.160
Total charge, mC	1300 ± 1641	1483 ±1150	0.099
Mean charge, mC	79.5 ± 50.7	109.8 ± 49.5	0.026

TABLE 6. Clinical Data

	Thiopental	Propofol	*P*
Remission*	14 (45%)	17 (55%)	0.781
Response*	6 (19.5%)	5 (16%)	
Nonresponder*	6 (19.5%)	4 (13%)	
Noncompleter*	5 (16%)	5 (16%)	
HDRS before ECT (number)†	25 (26)	27 (26)	0.62
BDI before ECT (number)†	21 (24)	21 (22)	0.89
HDRS, 6 treatments (number)†	15 (26)	13 (25)	0.21
BDI, 6 treatments (number)†	14 (23)	9 (24)	0.027
HDRS, end (number)†	11 (26)	9 (26)	0.19
BDI, end (number)†	8 (19)	6 (21)	0.29
MMSE (number)†	28.9 (24)	26.8 (25)	0.014
No. treatments†	13	10.2	0.27

*All patients.
†Completers.

Ketamine as Anesthesia for ECT Improved or faster?

- Okamoto 2010: K vs prop: Yes
- Kranaster 2011 K vs Thio: Yes (retrospective)

- Abdallah 2012: K vs K+Thio No (n=8)
- Järvenausta 2013: K+prop vs prop: No

Concomitant treatment with antidepressants ??
Sackeim et al. 2009

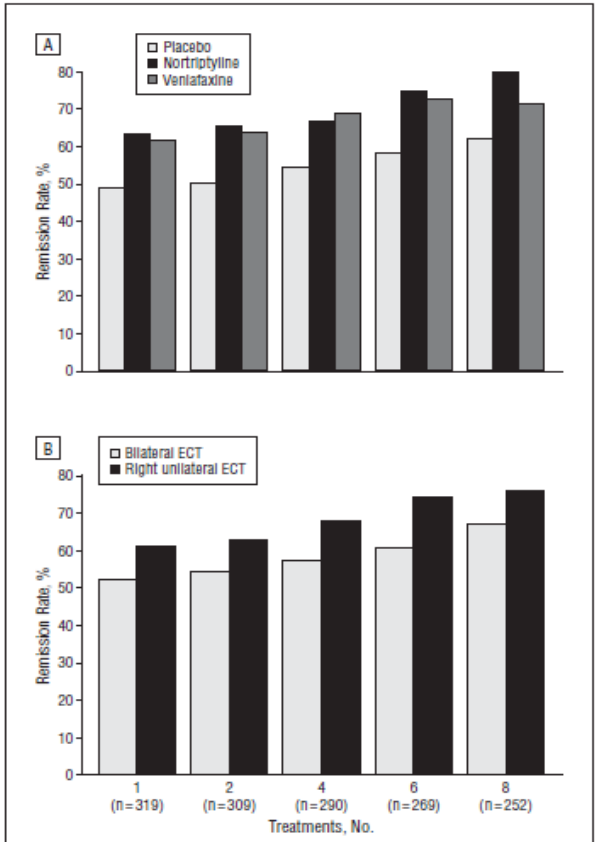


Figure 2. Remission rates for the pharmacological (A) and electroconvulsive therapy (ECT) electrode placement (B) conditions as a function of requiring a different number of treatments to be classified as a completer in the context of lack of remission. More stringent criteria result in an overall increase in remission rates, but have little effect on the differences among the pharmacological and ECT conditions.

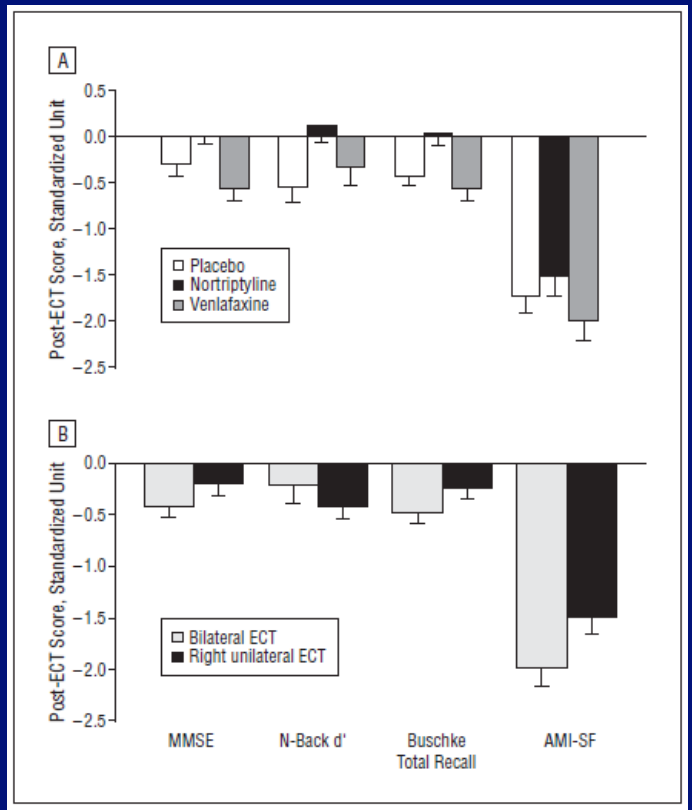


Figure 3. Mean post–electroconvulsive therapy (ECT) standard scores (with standard error) for the pharmacological (A) and ECT electrode placement (B) conditions on the 4 primary cognitive outcome measures. Nortriptyline had a significant advantage over venlafaxine on the modified Mini-Mental State Examination (MMSE) and Buschke Selective Reminding Test (SRT) and over placebo on the N-Back d′ measures. Right unilateral ECT had superior cognitive outcomes compared with bilateral ECT on the Buschke SRT and the Columbia University Autobiographical Memory Interview, Short Form (AMI-SF).

Maintenance Prudic et al. 2013

Older age was strongly associated with lower relapse risk
50% of the patients relapsed, 33.6% continued in remission 6 months after ECT, and 16.4% dropped out.

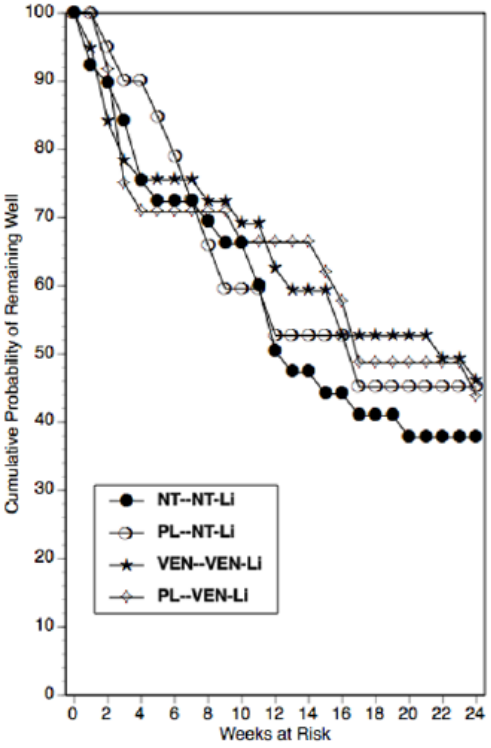


Figure 3.
Kaplan-Meier estimates of the proportion of patients who remained well during the continuation trial for patients randomized to the four treatment conditions: placebo (PL) or drug (NT or VEN) during ECT and, during continuation pharmacotherapy, nortriptyline and lithium (NT-Li) or venlafaxine and lithium (VEN-Li) as continuation pharmacotherapy.

Continuation ECT Kellner et al. 2006

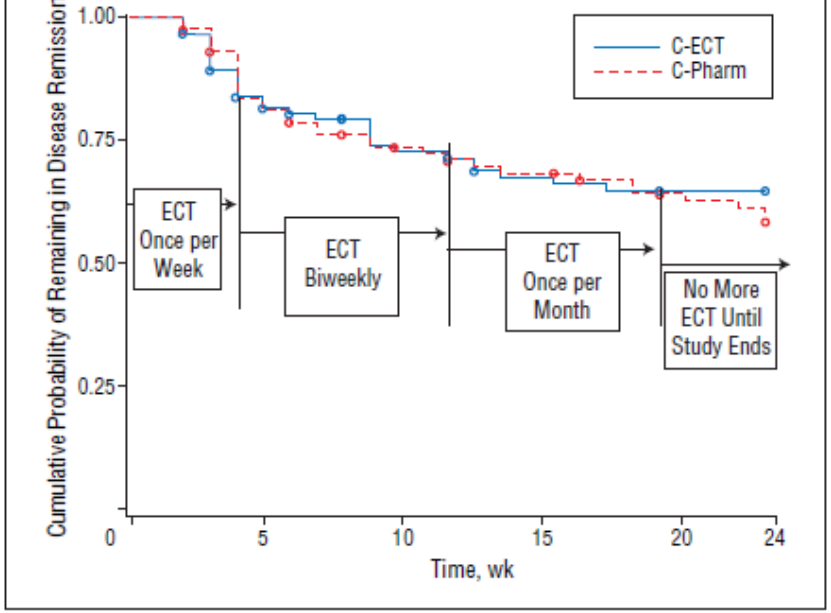


Figure 2. Kaplan-Meier curves showing proportion of patients who remained in disease remission (not disease relapse) during the continuation phase (phase 2). Log-rank test comparing distributions of time to relapse for C-ECT vs C-Pharm: $\chi^2=0.30$; $P=.59$. C-ECT indicates continuation electroconvulsive therapy; C-Pharm, combination of lithium carbonate plus nortriptyline hydrochloride.

Nordenskjöld et al 2013

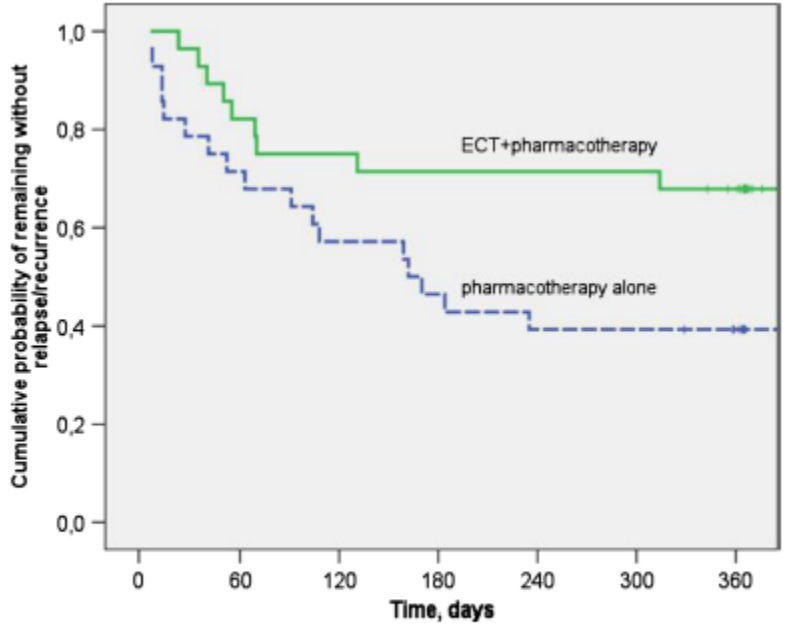


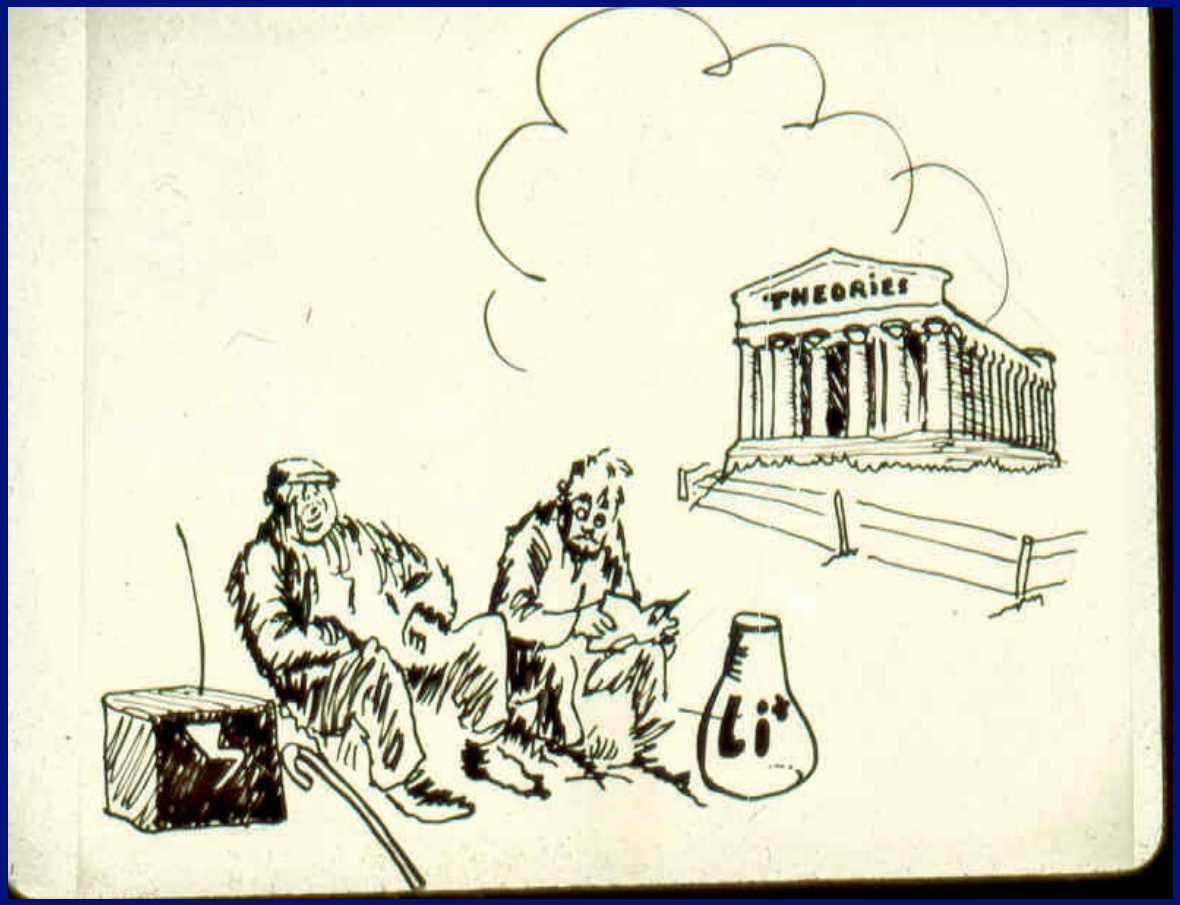
FIGURE 2. Kaplan-Meier function of the cumulative probability of remaining without relapse for patients treated with continuation ECT plus pharmacotherapy versus pharmacotherapy-alone in the intention-to-treat sample.

Continuation / Maintenance

- Jelovac, Kolhus & McLoughlin 2013:
  - "Maintenance of well-being following successful ECT needs to be improved"

Other forms of ”Brain stimulation”

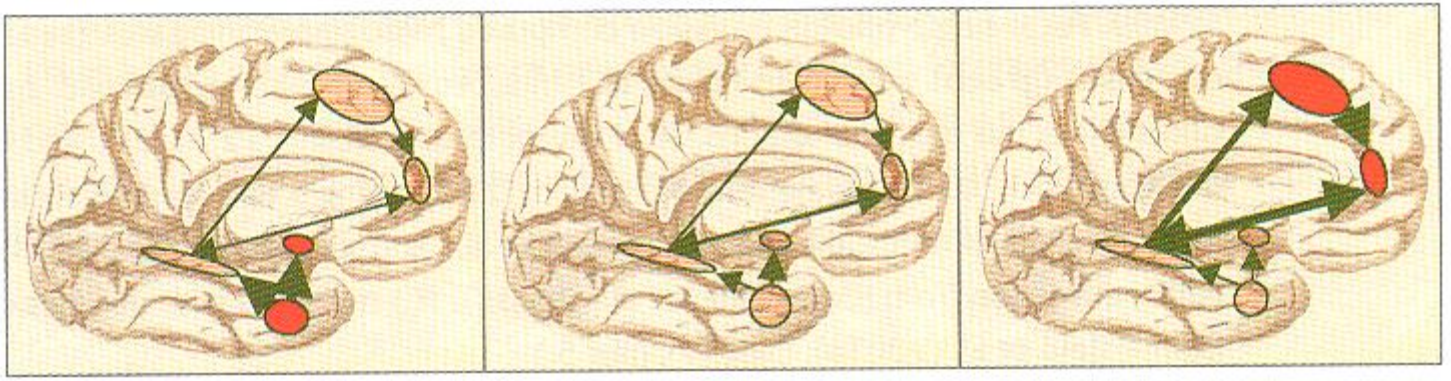
ECT: how does it work?



Bolwig:

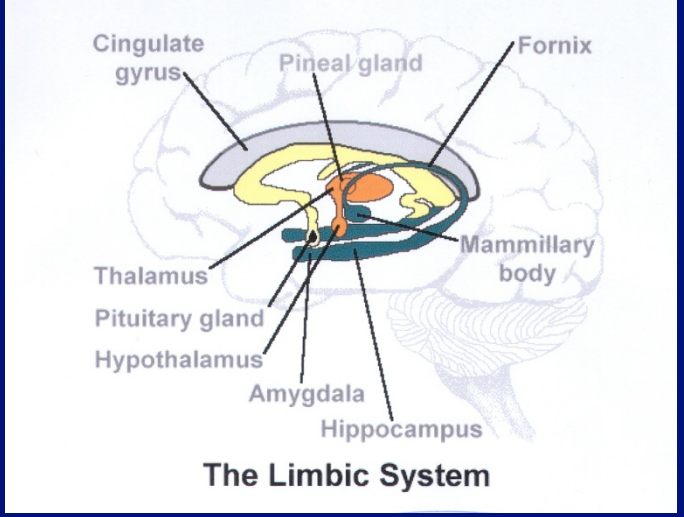
ECT : ***"old and effective - poor in theoretical foundation"***

Resetting ?

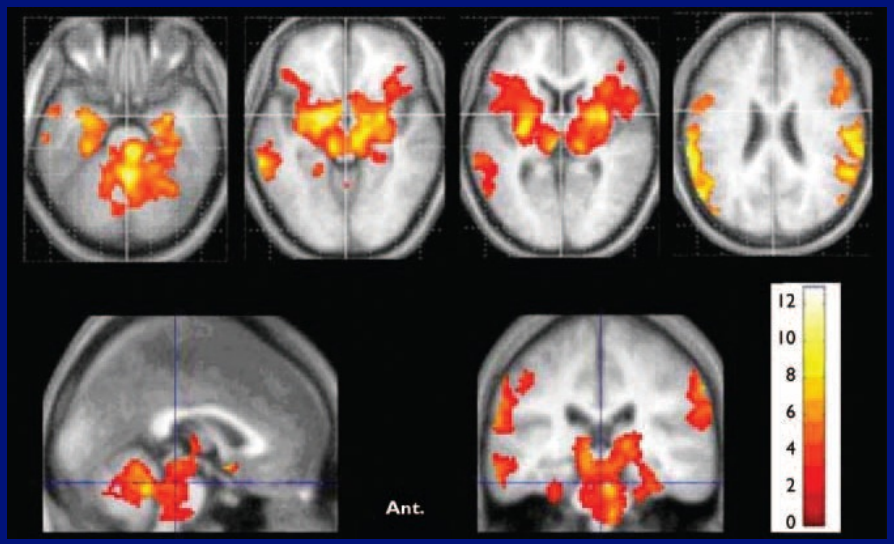


Sketch (hypothetical) of imbalanced activity within a neuronal circuit. Clinical syndromes may result from distinct patterns of dysregulated (= imbalanced) neuronal circuitry, in other words, overactivated as well as underactivated regions contribute to a complex constellation of symptoms (e.g., manic, depressive, catatonic, and psychotic symptoms). Color intensity and thickness of arrows indicate disordered activity. (See Chapter 4.)

Diencephalon



- HPA axis:
- Prolactin mm ↑ during ECT
- DST normalized following ECT
- Sezures must probably involve diencefalon



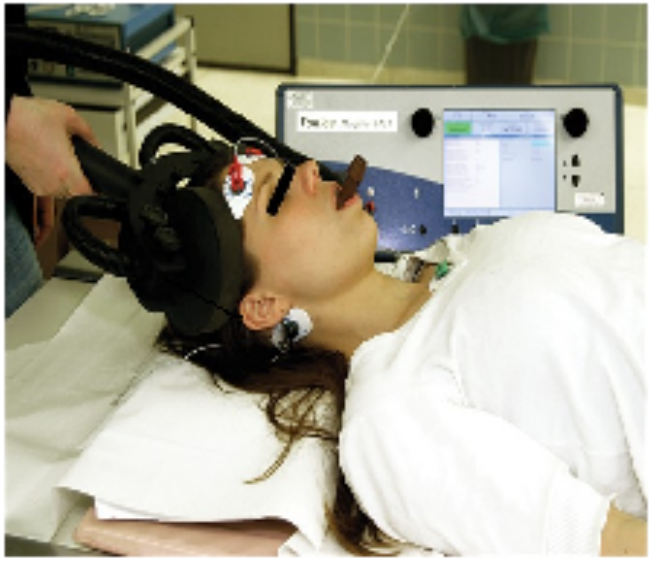
Fink M 1986
Ambrams R 1976

Takano 2007

A varieties of brain stimulations

- ”MST” Magnetic Seizure Therapy
- ”rTMS” repetitive Transcranial Magnetic Stimulation
- ”DBS” Deep Brain Stimulation
- ”PEMF” Transcranial low voltage pulsed electromagnetic fields
- ”tDCS” Transcranial Direct Current Stimulation
- ”VNS” Vagal Nerve Stimulation

Magnetic Seizure Therapy



Courtesy of Dr. Sarah Kayser

Magnetic seizure therapy for treatment-resistant depression yielded success with potentially fewer cognitive side effects, researchers said.

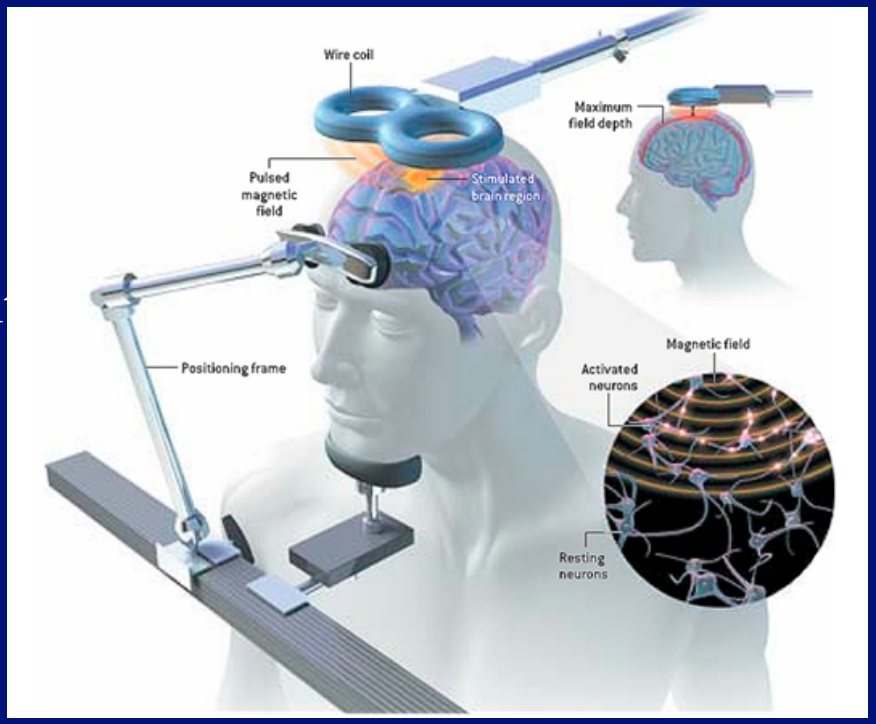
"For treatment-resistant depression, electroconvulsive therapy [ECT] is often the treatment of last resort. It has been applied for 75 years and is effective, but has cognitive side effects, relapse rates as high as 50%, and it carries a stigma," said Dr. Sarah Kayser of the University Hospital of Bonn (Germany), who presented the findings.

Magnetic seizure therapy [MST], performed under general anesthesia, is a more focal form of convulsive therapy that uses a strong

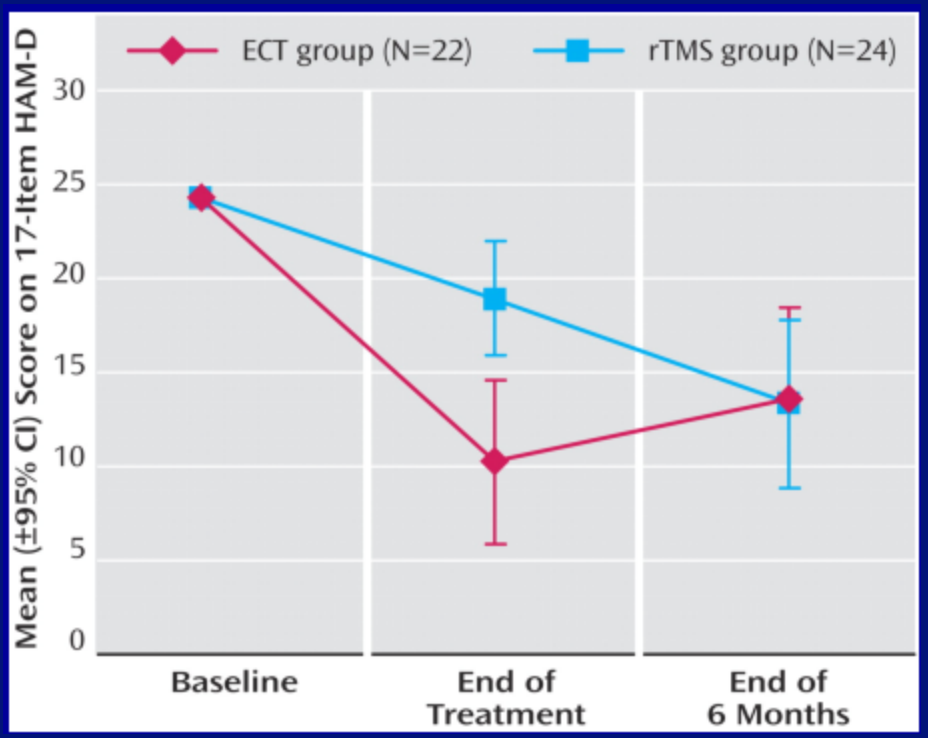
- Kayser S, Bewernick BH, Grubert C, Hadrysiewicz BL, Axmacher N,
- Schlaepfer TE: Psychiatr Res 2011, 45:569-76. RCT 10/10 pts.
- Fittzgerald et al 2013: 13 pts Open label
- Pulse Width < 0.1 ms

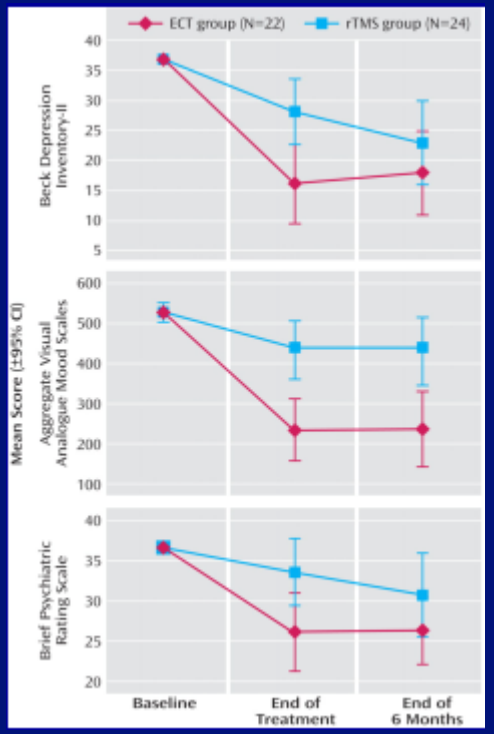
rTMS

- rTMS is used in neurophysiology for stimulation of cortex.
- rTMS treatment mosty used for treatment resistent depression.
- Many clinical studies with different applicationforms and stimulus parameters



rTMS vs ECT





From: A Randomized, Controlled Trial With 6-Month Follow-Up of Repetitive Transcranial Magnetic Stimulation and Electroconvulsive Therapy for Severe Depression. Am J Psychiatry 2007 164:73-81

Cochrane 2009 om rTMS

A U T H O R S ' C O N C L U S I O N S

Implications for practice:

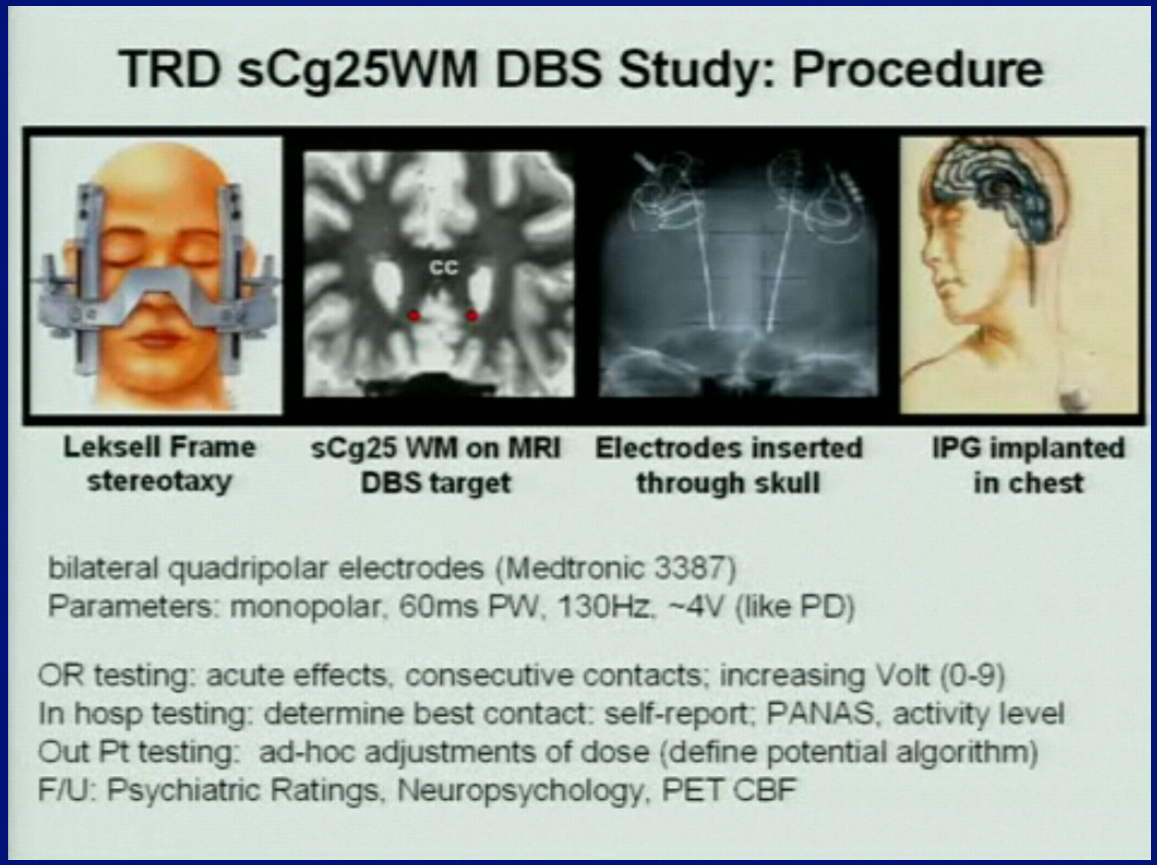
The information in this review suggests that there is no strong evidence for a possible efficacy of transcranial magnetic stimulation for the treatment of depression, although these results do not exclude the possibility of benefit.

rTMS

Lepping P Acta Psychiatrica Scand 2014:
A systematic review :

Conclusion
"Whilst rTMS appears to be efficacious ….
the clinical relevance of its efficacy is doubtful"

Deep Brain Stimulation (DBS)



Used Routinely for Parkinsonism and Dystonia treatment.

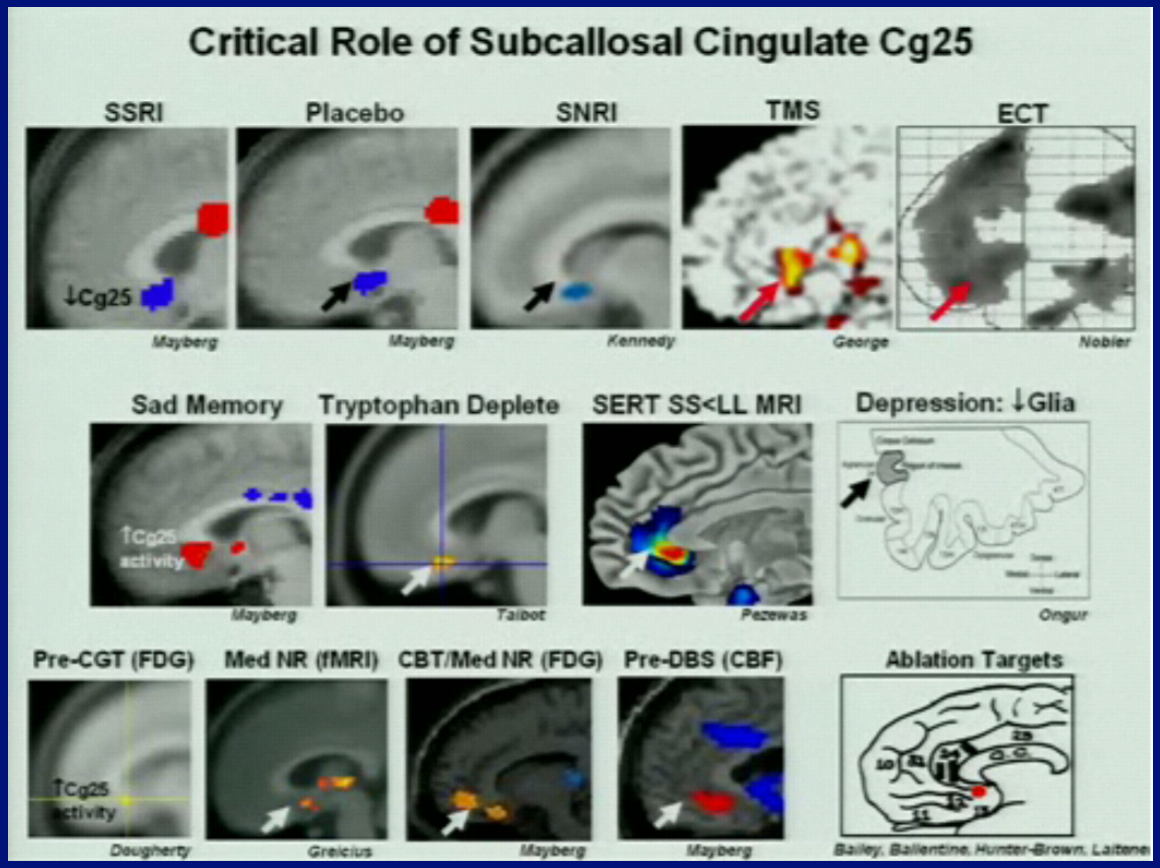
Thomas Insel - Director of the NIMH om DBS:

- “the same kind of approach that has worked so well in Parkinson’s disease may work equally well—or even better—in depression.”

Thomas Insel - Director of the NIMH 2:

- However, researchers currently use different anatomical targets for DBS, and they have demonstrated varying degrees of success

Mayberg: Cg25



Pulsed Electromagnetic Fields PEMF

- Involves applying low intensity electromagnetic fields to the brain via a series of scalp coils.
- Unlike transcranial direct current stimulation, targeted pulsed electromagnetic uses electromagnetic fields rather than direct electrical current to stimulate cortical neurons.
- Unlike transcranial magnetic stimulation, the electromagnetic fields are relatively static and not strong enough to actually depolarize cortical neurons

“

PEMF

PEMF used in bone healing, revascularization in orthopedics

Psychiatry:one dobbel-blinded RCT: 30 min daily for 5 weeks

“Martiny K, Lunde M, Bech P. Transcranial low voltage Pulsed Electromagnetic Fields in Patients with Treatment-resistant Depression. Biol Psychiatry. 2010 Jul 15;68(2):163-169.

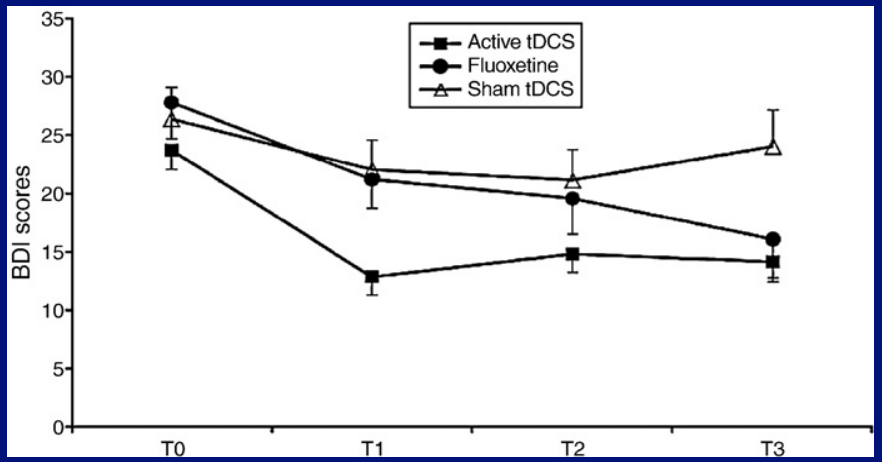
PEMF Effekt

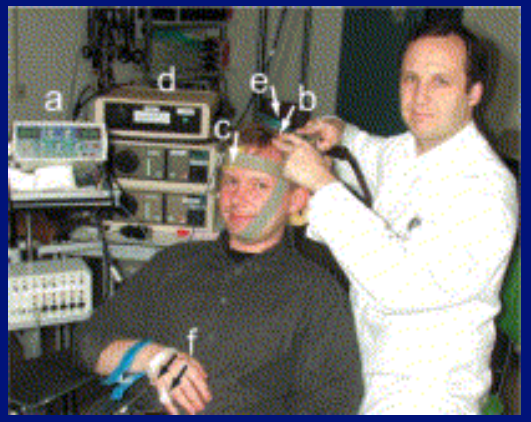
Uge	**HAM-D_{17}**	
Gruppe	Activ PEMF (N=25)	Sham PEMF (N=25)
Baseline	**21.1 (4.1)**	**20.9 (3.3)**
Uge 1	**17.0 (2.4)****	**19.0 (2.3)**
uge 2	**15.5 (2.3)****	**18.2 (2.3)**
uge 3	**14.0 (3.1)****	**17.5 (3.1)**
uge 4	**12.5 (4.3)****	**16.7 (4.3)**
uge 5	**11.0 (5.7)****	**16.0 (5.6)**

Needs to be replicated in another setting !!!

Transcranial Direct Current Stimulation (tDCS)

- DC 1-2 mA applied directly to the scull
- Up to 20 min per session daily in weeks





Martin DM, Alonzo A, Ho KA, Player M, Mitchell PB, Sachdev P, Loo CK. Continuation transcranial direct current stimulation for the prevention of relapse in major depression. J Affect Disord. 2012 Nov 9.

Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A (2009): Treatment ofdepression with transcranial direct current stimulation (tDCS): A review. *Exp Neurol* 219:14 –19.

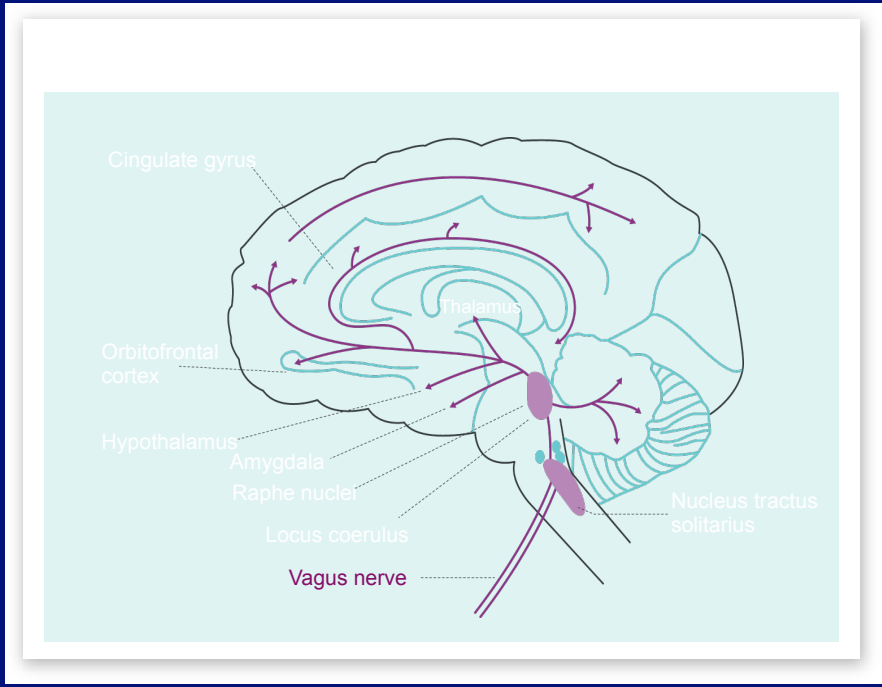
Transcranial Direct Current Stimulation (tDCS)

- Based on a small number of open and sham-controlled studies, transcranial direct current stimulation may have antidepressant effects in depressed patients

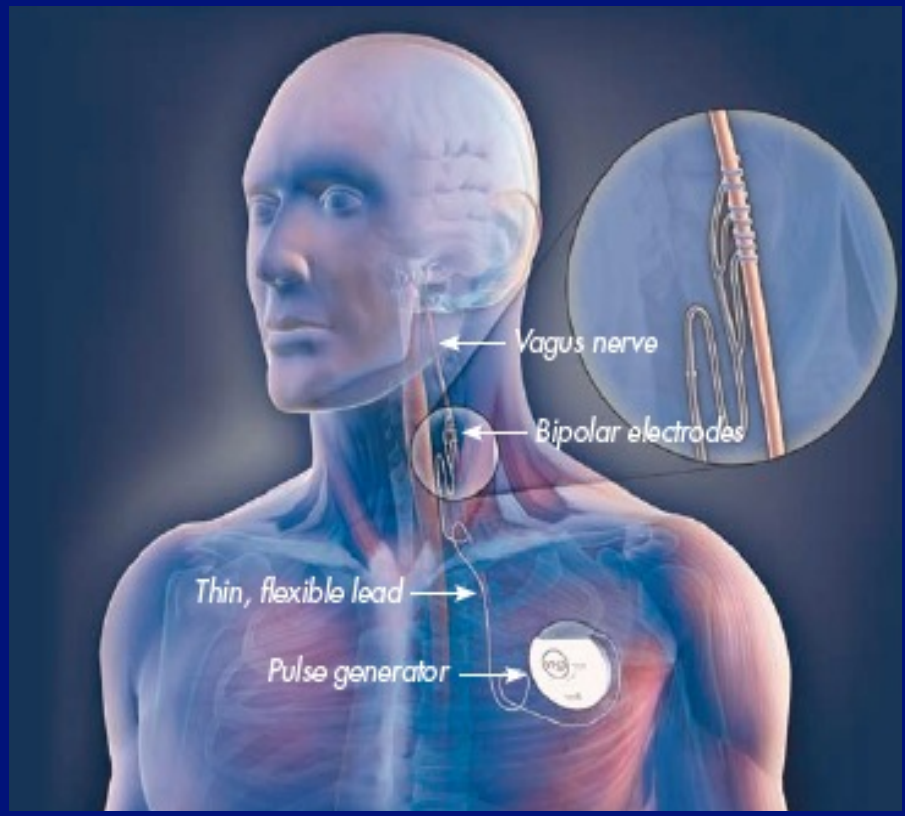
- Also studied in Schizophrenia and addiction

Berlim MT, Van den Eynde F, Daskalakis ZJ. Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: A systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. J Psychiatr Res. 2012 Oct 18.

VNS Therapy

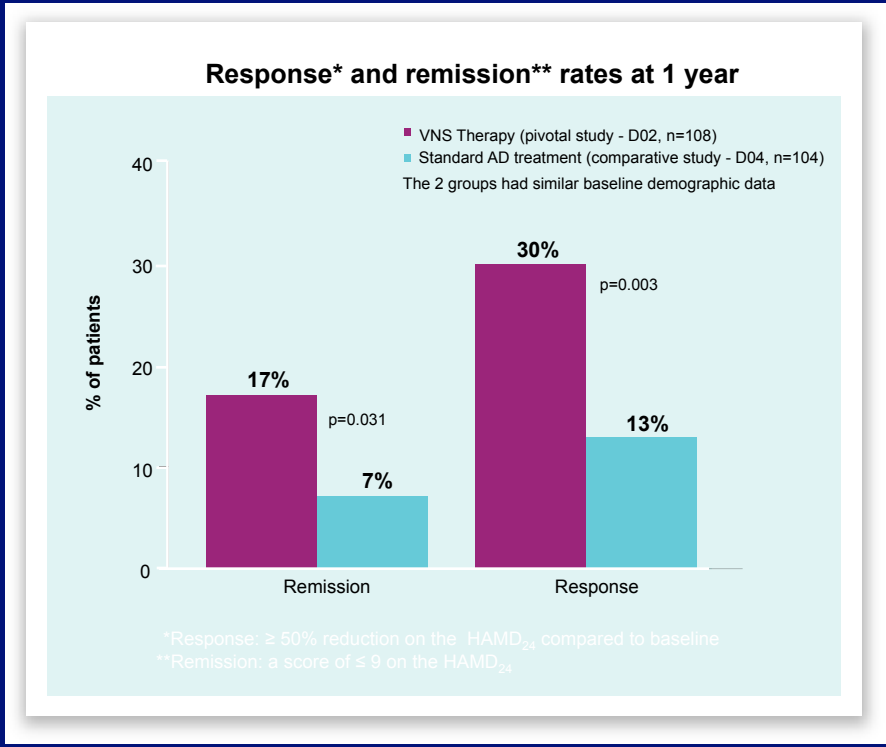


- Activity of noradrenergic and serotonergic neurons in nucleus coeruleus og dorsale raphe nuclei increased



Implanted pace-maker like pulse generator and stimulation electrodes on left VN 80% afferents.

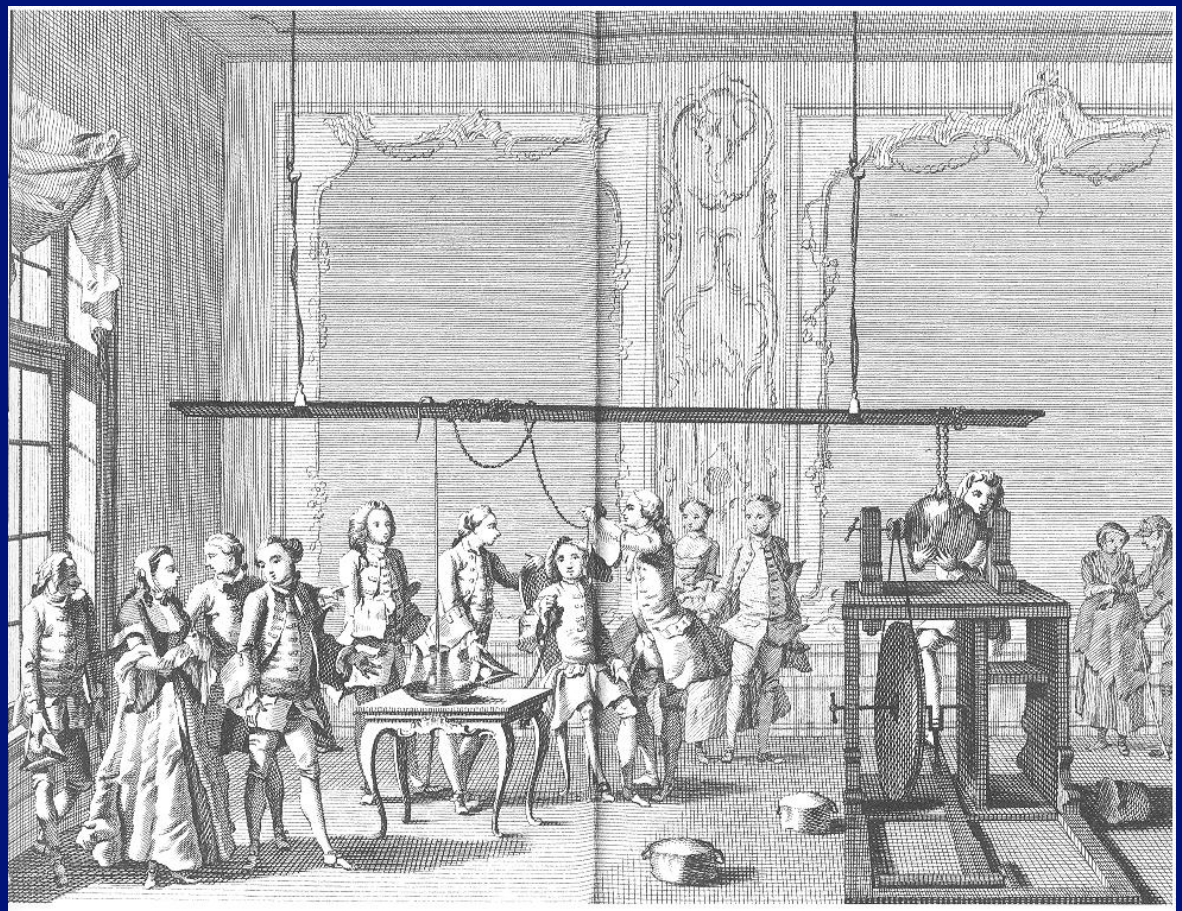
VNS Therapy
Additional efficacy



- A comparison of VNS Therapy and standard antidepressant treatments, show statistically significant better results for VNS Therapy[1]
- Adding VNS Therapy is associated with a greater antidepressive benefit[1]

1. **George** *et al*., Biological Psychiatry, 2005.

Ikke ECT historie



En elektrisermaskine udnyttet til helbredelse af forskellige sygdomme, i København bl.a. af Kratzenstein. Tegning af Peter Cramer (1726–1782); kobberstik af Jonas Haas (ca. 1720–1775). L. Spengler 1754. KB.

Christensen DC 2009

Ikke ECT historie

Kat. 55 *Professor Jacobson elektrifiserer den berømte Maler Munch…*, 1908

Blæk på papir, 137 x 212 mm

Munch-museet, Oslo, inv.nr. MM T 1976