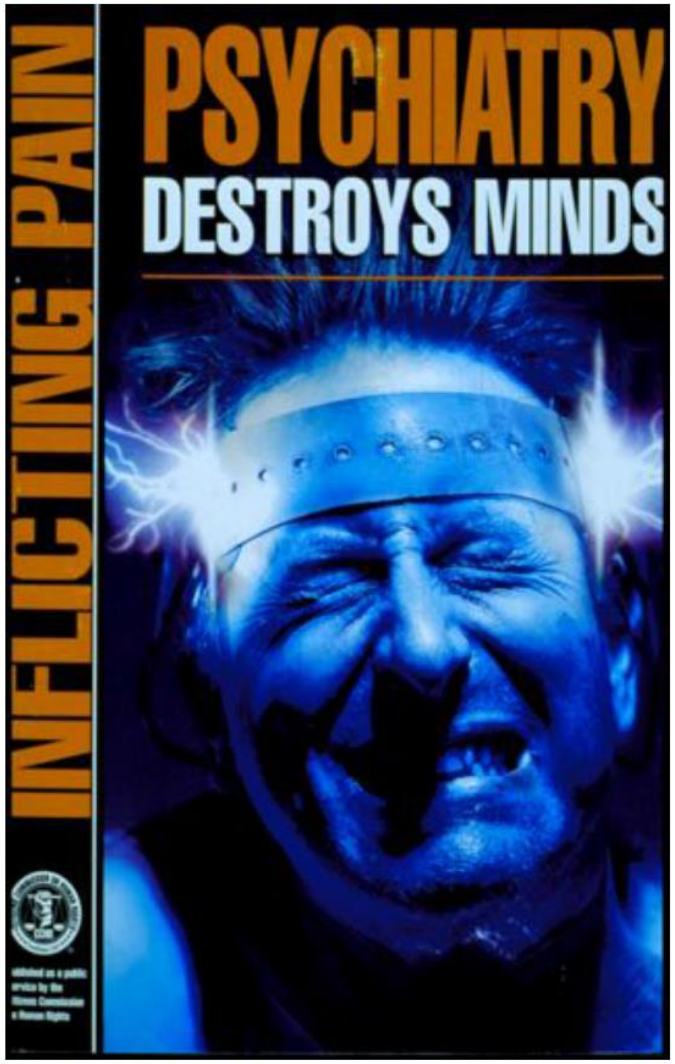
Zentralinstitut
für Seelische
Gesundheit

Safety of ECT at the Neuronal Level

Malmö, 26.5.2023

Alexander Sartorius

Why are we talking about safety at the neuronal level ?



Obviously, the „sledge hammer“ metaphor is wrong, but problems could be finer grained, since:

- we do observe cognitive side effects

- repeated (non-ECT) epileptic grand mal seizures lead to gliosis (i.e. neuronal death)

- we do apply high voltages and high currents

- most people would have a bad gut feeling about answering to „are you 100% sure that it‘s safe for the brain, i.e. at a neuronal level?“

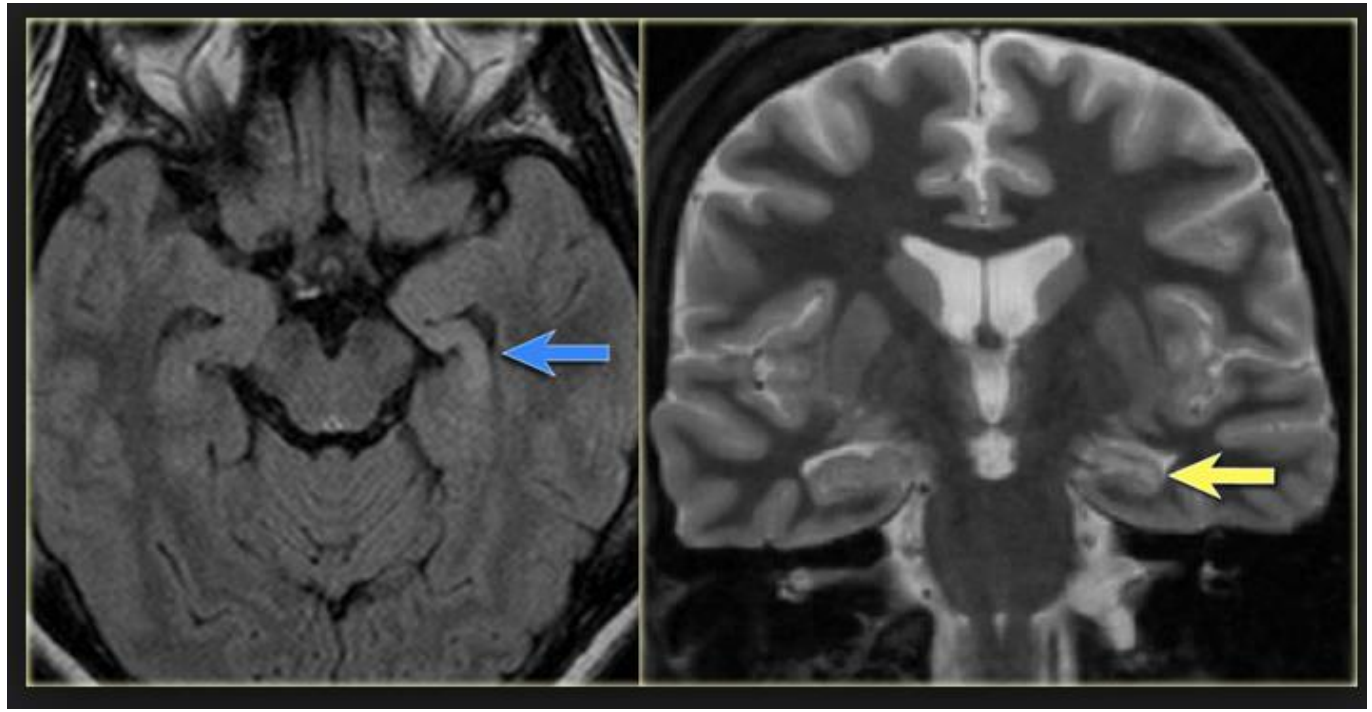
Why should it be safe?

Overview:

- oxygen
- NSE, S100 (marker of neuronal death)
- Abeta 42 (marker of Alzheimer‘s disease)
- immune system (inflammatory marker)
- BDNF (neuronal growth hormone)
- Klotho (anti-aging hormone)
- high voltage

- final thoughts

oxygen

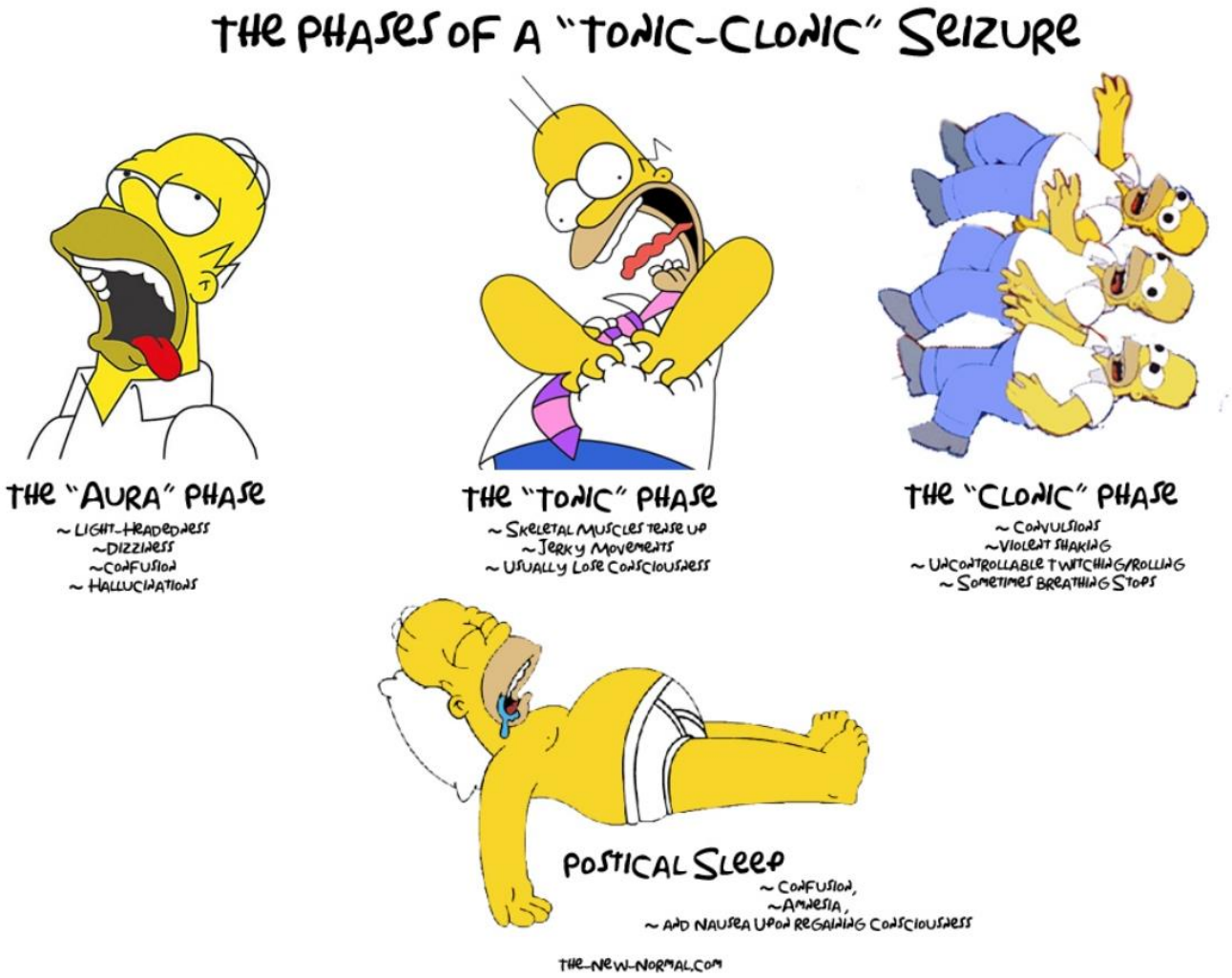


35-year-old patient
with refractory temporal lobe epilepsy.

MR shows subtle hyperintensity of the left hippocampus on the axial FLAIR (blue arrow) and atrophy of the left hippocampus on coronal images (yellow arrow).

Radiology Assistant

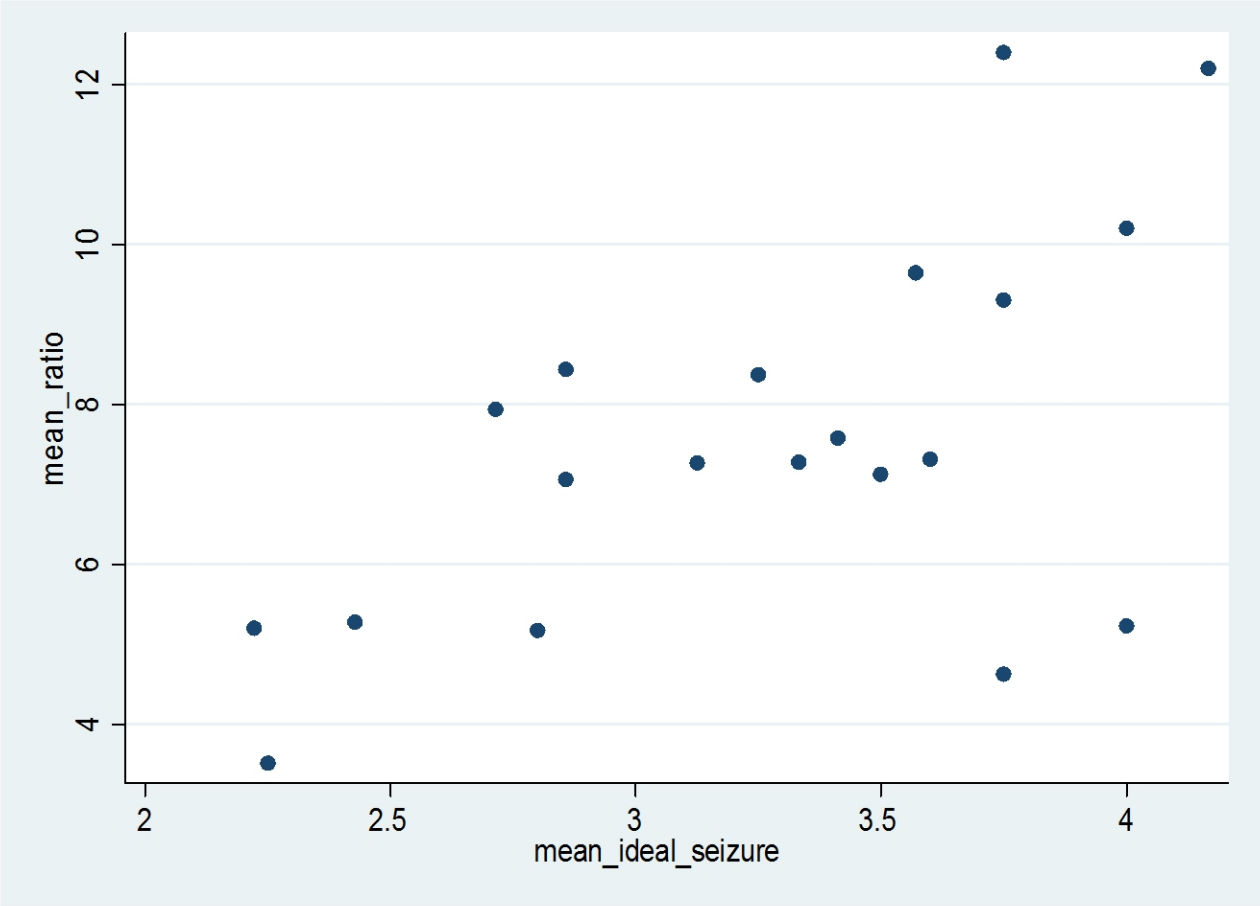
oxygen



What is the main difference between ECT and a grand mal seizure ?

oxygen

O_2/
CO_2



New Evidence for Seizure Quality Improvement by Hyperoxia and Mild Hypocapnia.
Aksay SS, Bumb JM, Janke C, Hoyer C, Kranaster L, Sartorius A.
J ECT. 2014 Mar 12.

oxygen

Charlie Kellner: “The green gas is the good one !”

- O_2 makes the procedure safe

- O_2 lowers seizure threshold

Why should it be safe?

Overview:

- oxygen ✓
- NSE, S100
- Abeta 42
- immune system
- BDNF
- Klotho
- high voltage

NSE and S100

“brain damage markers”

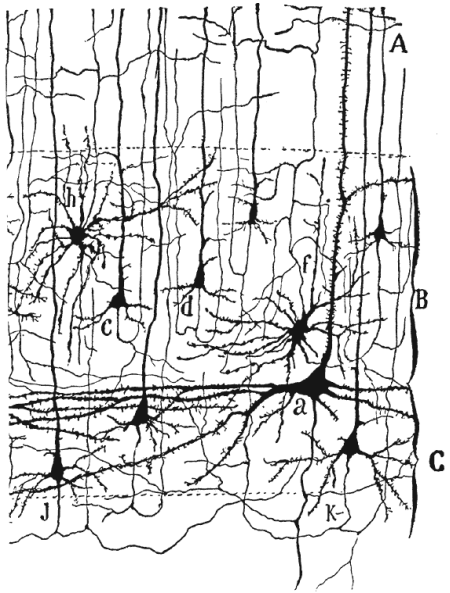
S100B is a glial cell protein with higher levels reflecting neuronal distress.

Neuron-specific enolase (NSE) detects even diffuse, small microstructural brain changes.

NSE and S100: no evidence for ECT induced increase

Arts B, Peters M, Ponds R, Honig A, Menheere P, van Os J. S100 and impact of ECT on depression and cognition. J ECT. 2006 Sep;22(3):206-12.	maybe, but small n
Agelink MW, Andrich J, Postert T, Würzinger U, Zeit T, Klotz P, Przuntek H. Relation between electroconvulsive therapy, cognitive side effects, neuron specific enolase, and protein S-100. J Neurol Neurosurg Psychiatry. 2001 Sep;71(3):394-6	Ø
Kranaster L, Janke C, Mindt S, Neumaier M, Sartorius A. Protein S-100 and neuron-specific enolase serum levels remain unaffected by electroconvulsive therapy in patients with depression. J Neural Transm (Vienna). 2014 Nov;121(11):1411-5.	Ø
Carlier A, Boers K, Veerhuis R, Bouckaert F, Sienaert P, Eikelenboom P, Vandenbulcke M, Stek ML, van Exel E, Dols A, Rhebergen D. S100 calcium-binding protein B in older patients with depression treated with electroconvulsive therapy. Psychoneuroendocrinology. 2019 Dec;110:104414.	Ø
Gbyl K, Jørgensen NR, Videbech P. Serum S100B protein after electroconvulsive therapy in patients with depression. Acta Neuropsychiatr. 2022 Oct;34(5):269-275.	Ø

Histopathology? This is truely neuronal level !



Long term use of M-ECT

British Journal of Psychiatry (1985), **147**, 203–204

1,250 Electroconvulsive Treatments without Evidence of Brain Injury

*SELECTED STAFF, UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE

Since its introduction in the late 1930s, electroconvulsive therapy (ECT) has been an important yet controversial treatment of psychiatric disorders. In spite of being effective in selected circumstances, it has been questioned as an inducer of central nervous system (CNS) damage (Calloway *et al*, 1977). Animal studies have demonstrated brain injury from electroconvulsive applications (Friedberg, 1977) though the technique utilised was not the same as ECT employed in current psychiatric practice (Frankel, 1977). ECT results in transient memory deficits, but correlation to CNS damage or permanent memory dysfunction has not been confirmed (Fink, 1977, 1982; Frankel, 1977; Frith, 1983; Menken *et al*, 1979; Squire, 1977; Weeks *et al*, 1980). The medical community is concerned about these treatments, in spite of the lack of any consensus that they produce brain damage.

This report presents a post-mortem brain study of a patient who received over 1,250 ECTs during a 26-year period. The neuropathological examination was normal.

Neuropathological Evaluation of an 84-Year-Old Man After 422 Electroconvulsive Therapy Treatments

Danielle Anderson, MD, Robert Wollmann, MD, PhD,† and Stephen H. Dinwiddie, MD‡*

Abstract: Concern remains among many that electroconvulsive therapy (ECT) causes "brain damage." This ambiguous term presumably refers to lesions that could, in principle, be observed either grossly or microscopically in postmortem studies, and the assertion that it occurs appears to be based largely on old reports with dubious relevance to modern practice. Fortunately, using modern technique, ECT is so safe that mortality around the time of treatment is extraordinarily rare, and as a result, there has been little opportunity for postmortem examination of individuals who had recently had ECT. We report a case in which postmortem brain examination was performed roughly a month after the patient's last treatment.

Key Words: electroconvulsive therapy, neuropathology

(*J ECT* 2013;00: 00–00)

suicide attempt and resulted in a 2-year psychiatric hospitalization. He had a second lengthy hospitalization at age 66 years; in between the hospitalizations, he was noted to have had "periods of elation and overactivity," but it was not until he was 68 years old that he was hospitalized for treatment of a psychotic manic episode.

Treatment with haloperidol led to development of neuroleptic malignant syndrome, which was medically treated. Subsequent treatment with lithium carbonate was not well tolerated; valproate treatment led to bone marrow suppression, and a later trial of olanzapine again resulted in neuroleptic malignant syndrome.

His first episode of classic catatonic stupor occurred at the age of 74 years. This resolved promptly with his first course of ECT, after which he was lost to follow-up for 9 months. He returned to treatment following a suicide attempt. The next

MR imaging ?
- a preview:

„ It is another very important finding of our study that **no longitudinal GM decreases due to an ECT treatment** were detected in our whole brain analysis. This adds further evidence to hypothesis that ECT enables and/or restores plasticity **falsifying older ideas of ECT induced “brain damaging”**.“

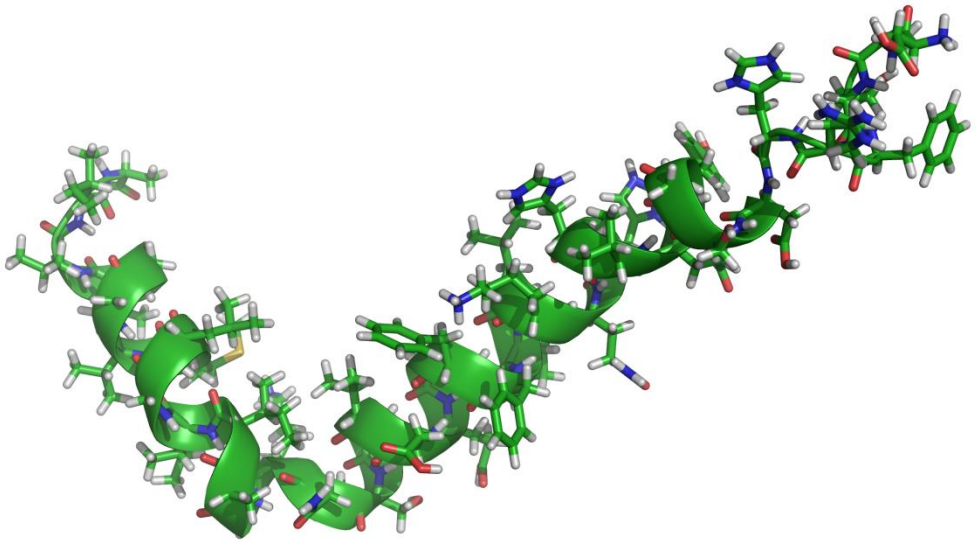
Sartorius A, Demirakca T, Böhringer A, Clemm von Hohenberg C, Aksay SS, Bumb JM, Kranaster L, Ende G. Electroconvulsive therapy increases temporal gray matter volume and cortical thickness. Eur Neuropsychopharmacol. 2016 Mar;26(3):506-17.

Why should it be safe?

Overview:

- oxygen ✓
- NSE, S100 ✓
- Abeta 42
- immune system
- BDNF
- Klotho
- high voltage

$A_{\beta}42$



- Aβ is formed after sequential cleavage of the amyloid precursor protein (APP)
- The most common isoforms are Aβ40 and Aβ42
- The Aβ40 form is the more common of the two,
- but **Aβ42** is the more fibrillogenic and is thus associated with disease states.

$A_{\beta}42$ (low n)

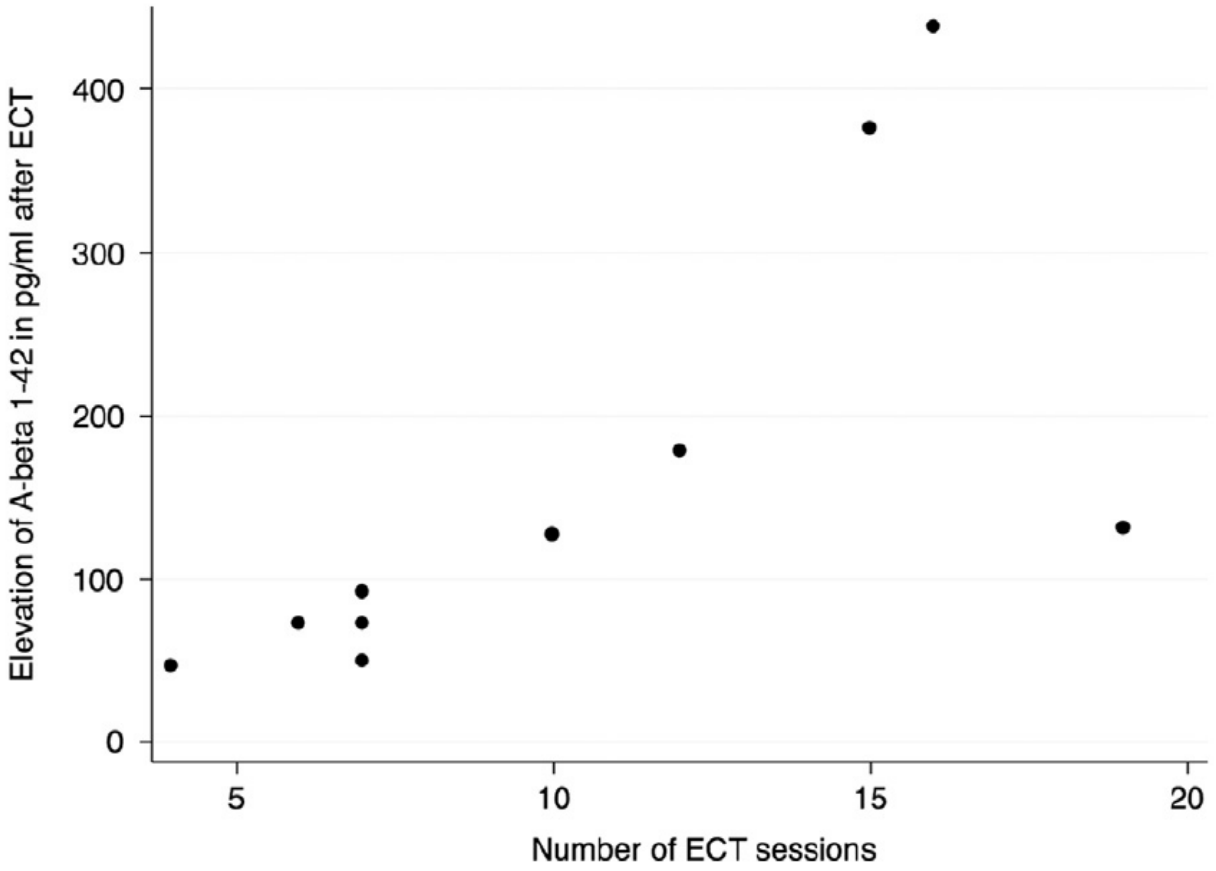


Figure 1 The number of ECT sessions of each patient positively correlated with the increase of $A\beta_{1\text{-}42}$ in the CSF (Coef: 19.5; $r^2=0.50$; $p=0.023$) in the patients who responded to the treatment.

A_{β} brain accumulation (n=1)

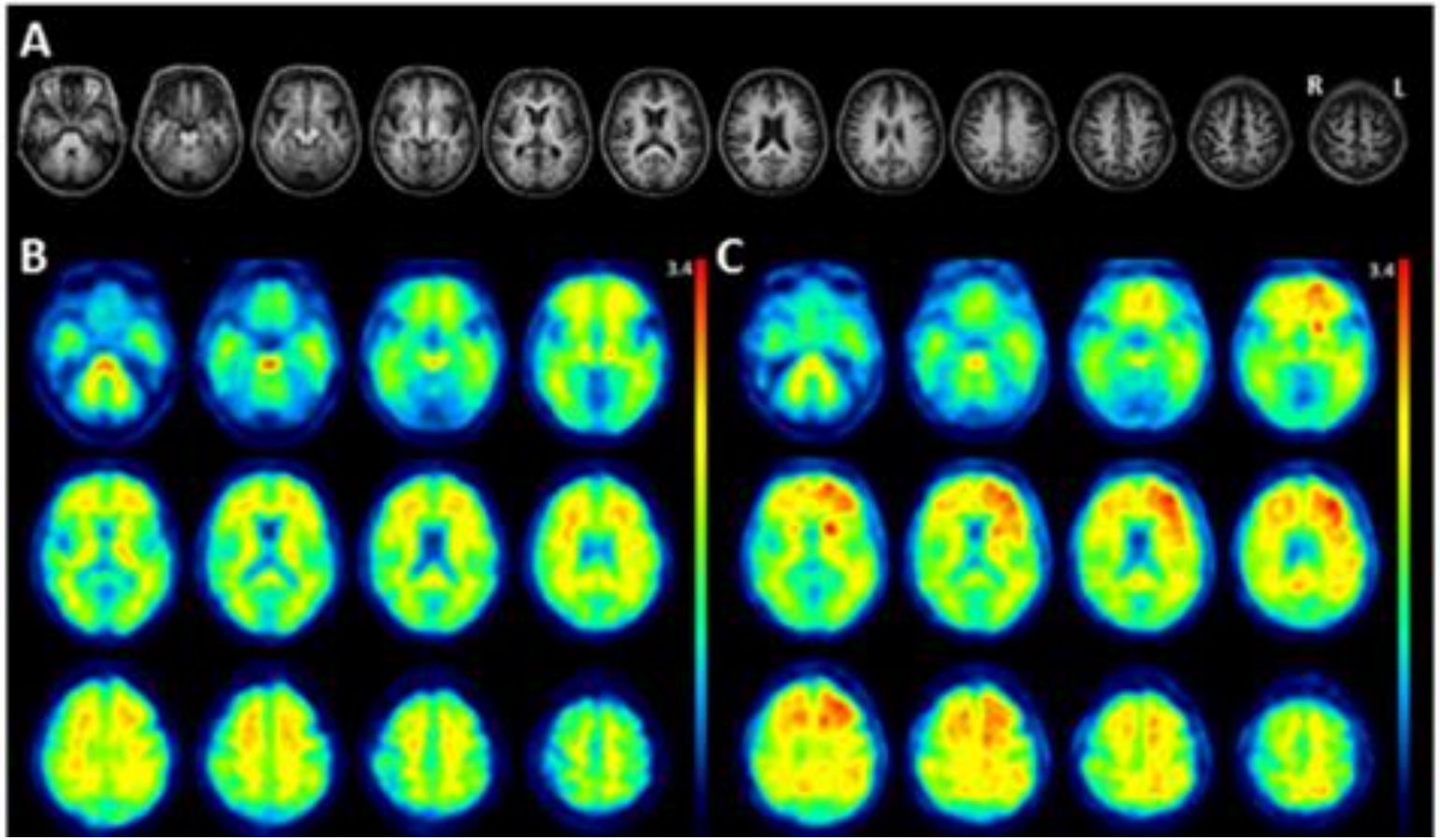


Figure 1. Neuroimaging results. **(A)** Structural magnetic resonance imaging. **(B)** ^{18}F-Flutemetamol scan performed before electroconvulsive therapy (ECT). **(C)** Carbon-11-labeled Pittsburgh compound B (^{11}C-PIB) scan performed 20 months after ECT. Color code in panels **(B)** and **(C)** represents standardized uptake value ratio. **(D)** Voxelwise *Z*-map of the ^{18}F-flutemetamol scan performed before ECT shown in panel **(B)**. **(E)** Voxelwise *Z*-map of the ^{11}C-PIB scan performed after ECT shown in panel **(C)**. Color code in panels **(D)** and **(E)** correspond to *Z*-values. All images are displayed in axial plane, radiologic convention (left side of scan corresponds with right side of brain).

Vandenbulcke M, Bouckaert F, De Winter FL, Koole M, Adamczuk K, Vandenberghe R, Emsell L, Van Laere K. Asymmetric Amyloid Deposition in the Brain Following Unilateral Electroconvulsive Therapy. Biol Psychiatry. 2017 Jan 15;81(2):e11-e13.

Dementia (non-neuronal and populational level)

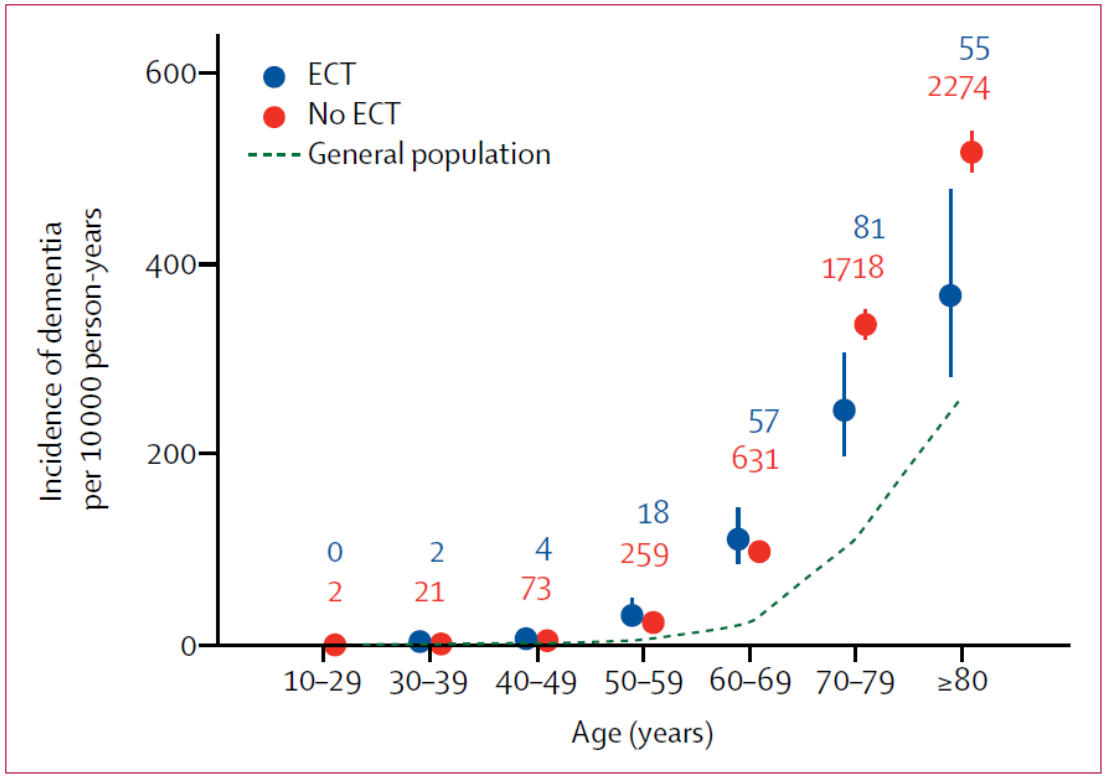
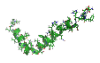


Figure 2: **Incidence of dementia in relation to electroconvulsive therapy (ECT)**
Data (incidence per 10 000 person-years [95% CI]) are from different age groups for 168 015 patients with affective disorders and in the Danish general population. The blue circles (received ECT) and red circles (did not receive ECT) represent incidence rates of dementia. The smaller numbers above the circles give the number of incident cases of dementia in 5901 patients treated with ECT and in 162 114 patients not treated with ECT. The dashed green line represents the number of cases of incident dementia in the general Danish population.

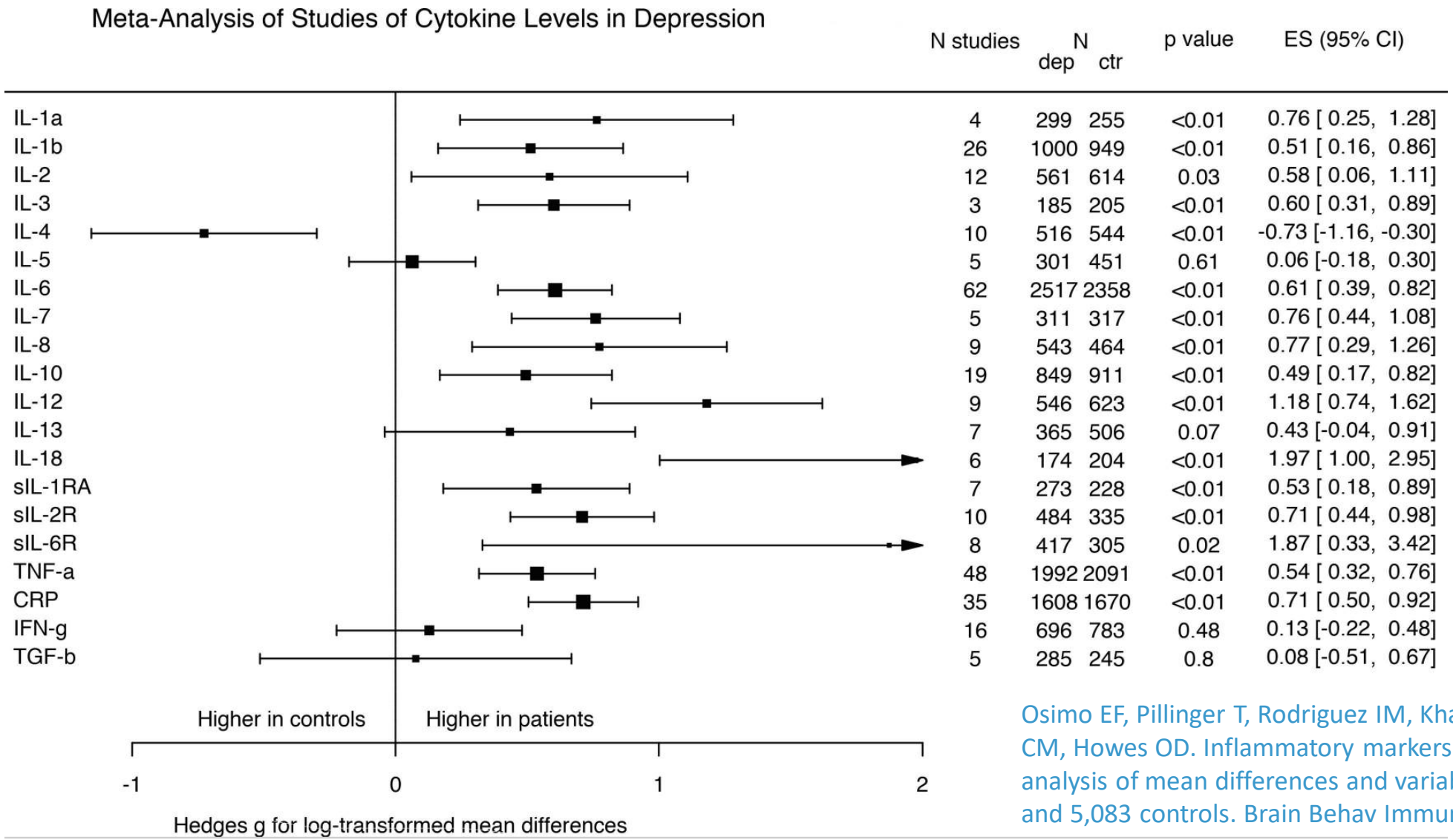
Electroconvulsive therapy and risk of dementia in patients with affective disorders: a cohort study.
Osler M, Rozing MP, Christensen GT, Andersen PK, Jørgensen MB. Lancet Psychiatry. 2018 Apr;5(4):348-356.

Why should it be safe?

Overview:

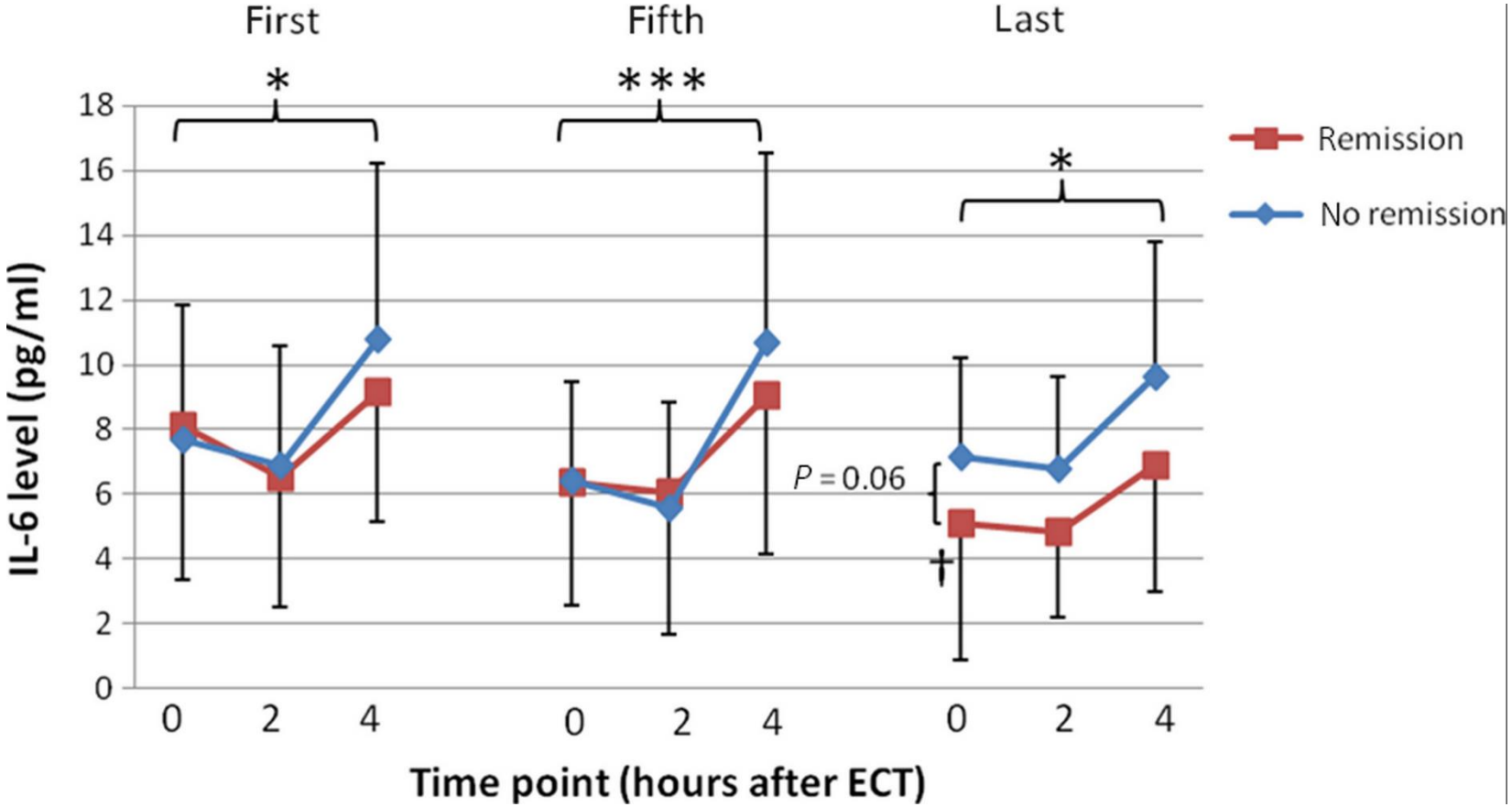
- oxygen ✓
- NSE, S100 ✓
- Abeta 42 
- immune system
- BDNF
- Klotho
- high voltage

Depression: immune system / inflammation



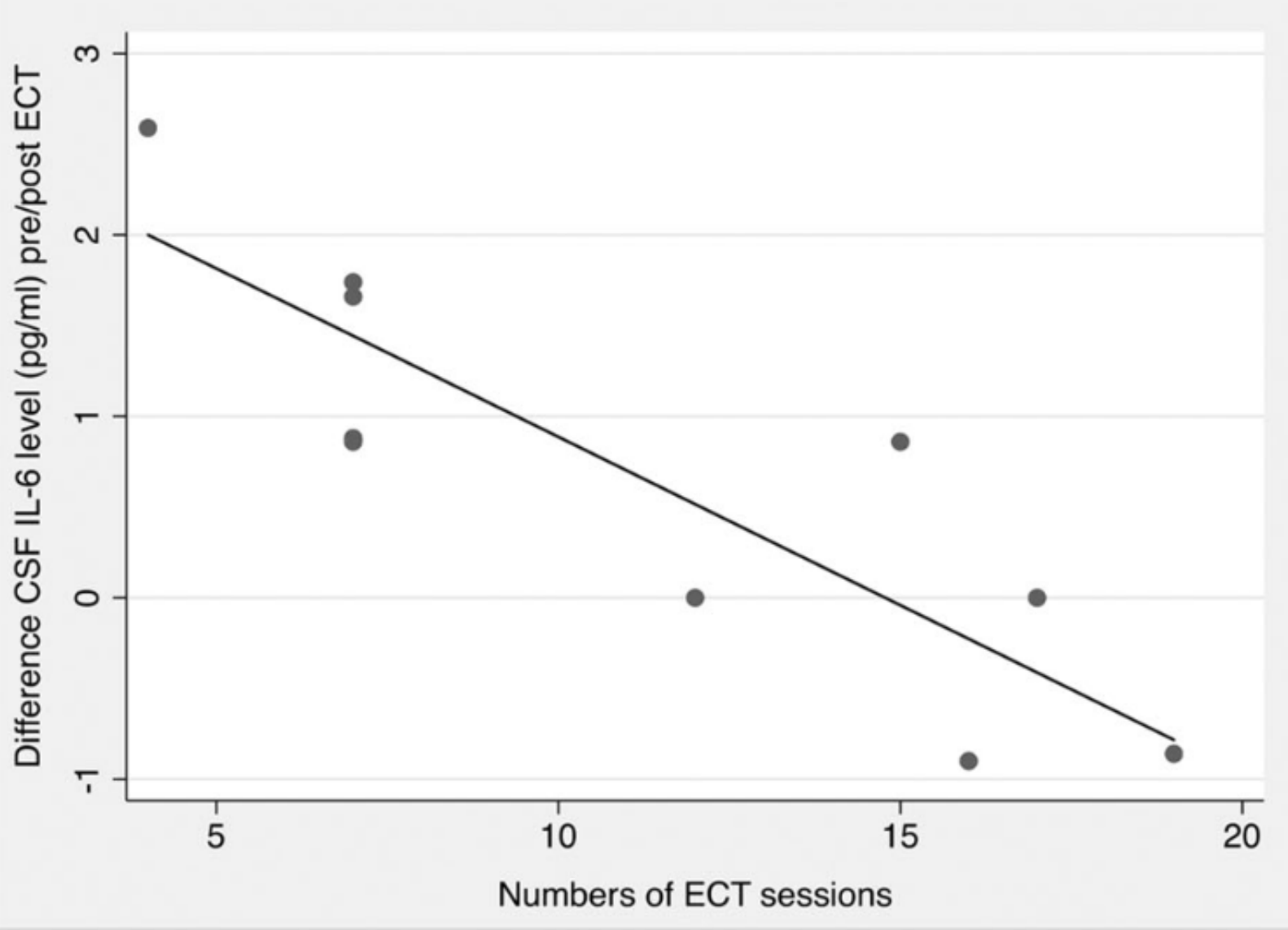
Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Howes OD. Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav Immun. 2020 Jul;87:901-909.

ECT: immune system / inflammation: IL-6



Järventausta K, Sorri A, Kampman O, Björkqvist M, Tuohimaa K, Hämäläinen M, Moilanen E, Leinonen E, Peltola J, Lehtimäki K. Changes in interleukin-6 levels during electroconvulsive therapy may reflect the therapeutic response in major depression. Acta Psychiatr Scand. 2017 Jan;135(1):87-92.

immune system / inflammation: IL-6 in CSF



Mindt S, Neumaier M, Hoyer C, Sartorius A, Kranaster L. Cytokine-mediated cellular immune activation in electroconvulsive therapy: A CSF study in patients with treatment-resistant depression. World J Biol Psychiatry. 2020 Feb;21(2):139-147.

immune system / inflammation: ECT: negative studies

Ryan KM, McLoughlin DM. Peripheral blood inflammatory markers in depression: Response to electroconvulsive therapy and relationship with cognitive performance. Psychiatry Res. 2022 Sep;315:114725. DOI: 10.1016/j.psychres.2022.114725

Carlier A, Rhebergen D, Veerhuis R, Schouws S, Oudega ML, Eikelenboom P, Bouckaert F, Sienaert P, Obbels J, Stek ML, van Exel E, Dols A. Inflammation and Cognitive Functioning in Depressed Older Adults Treated With Electroconvulsive Therapy: A Prospective Cohort Study. J Clin Psychiatry. 2021 Aug 10;82(5):20m13631. doi: 10.4088/JCP.20m13631. PMID: 34383393.

Why should it be safe?

Overview:

- oxygen ✓
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- immune system ✓ (inflammatory marker)
- BDNF (neuronal growth hormone)
- Klotho (anti-aging hormone)
- high voltage

BDNF (neuronal growth hormone): Rise within the brain with ECT

Table 1 Covariate influence (ANCOVA) of tissue BDNF on serum BDNF.

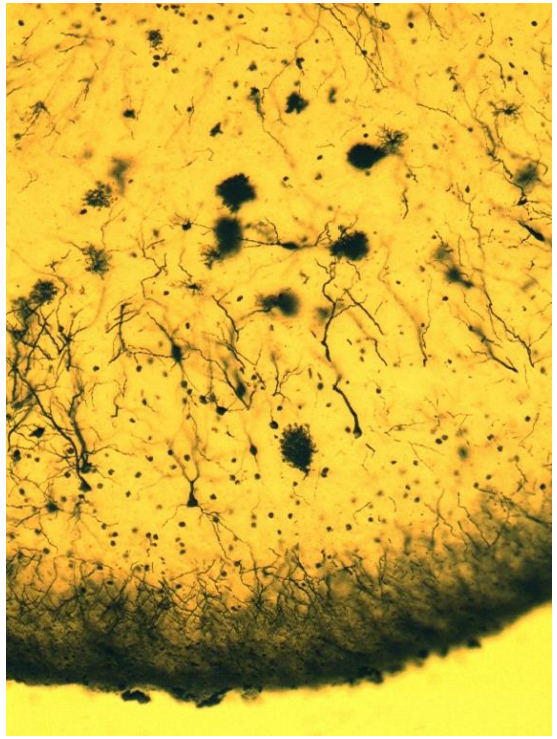
Serum BDNF level	F (df)	p
number of ECS sessions (factor)	7.54 (2)	0.0007
brain region (factor)	9.69 (1)	0.002
time (factor)	5.32 (1)	0.02
tissue BDNF (covariate)	7.11 (1)	0.0085

Serum BDNF (dependent variable) ANCOVA with number of ECS sessions, brain regions (PFC and hippocampus) and time (two factor levels, i.e., ≤3 days and ≥1 week) as factors and tissue BDNF level as a covariate. Number of observations is 172. The ANCOVA model reveals an R^2 of 0.12, dropping tissue BDNF from the model leads to a smaller explained variance ($R^2 = 0.08$), in other words: introducing tissue BDNF as a covariate increases the explained variance

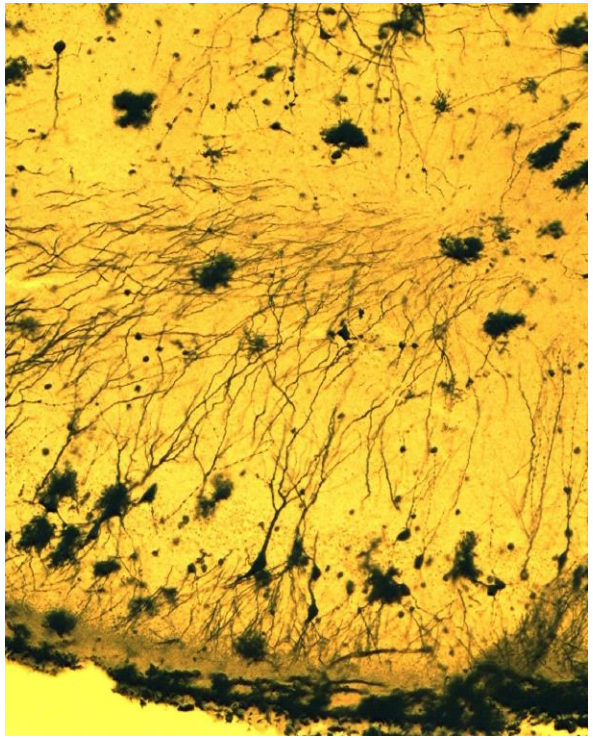
Sartorius A, Hellweg R, Litzke J, Vogt M, Dormann C, Vollmayr B, Danker-Hopfe H, Gass P.
Correlations and discrepancies between serum and brain tissue levels of neurotrophins after electroconvulsive treatment in rats.
Pharmacopsychiatry. 2009 Nov;42(6):270-6.

BDNF (neuronal growth hormone): Cell Growth with ECT

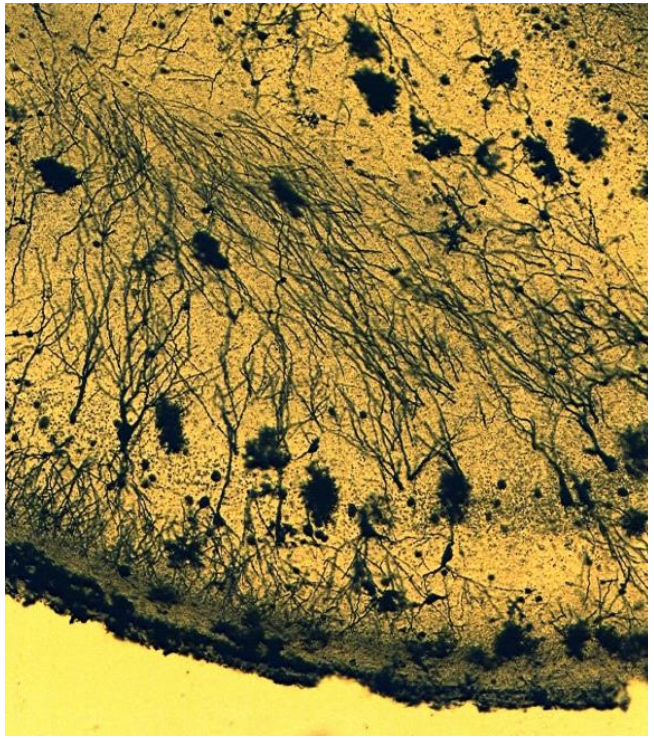
Hippocampal pyramidal cells (rat) with dendritic arborization



6x Sham



6x 10 mC



6x 40 mC

Smitha JS, Roopa R, Khaleel N, Kutty BM, Andrade C. Images in electroconvulsive therapy: electroconvulsive shocks dose-dependently increase dendritic arborization in the CA1 region of the rat hippocampus. J ECT. 2014 Sep;30(3):191-2.

BDNF (neuronal growth hormone): Lower in Depression

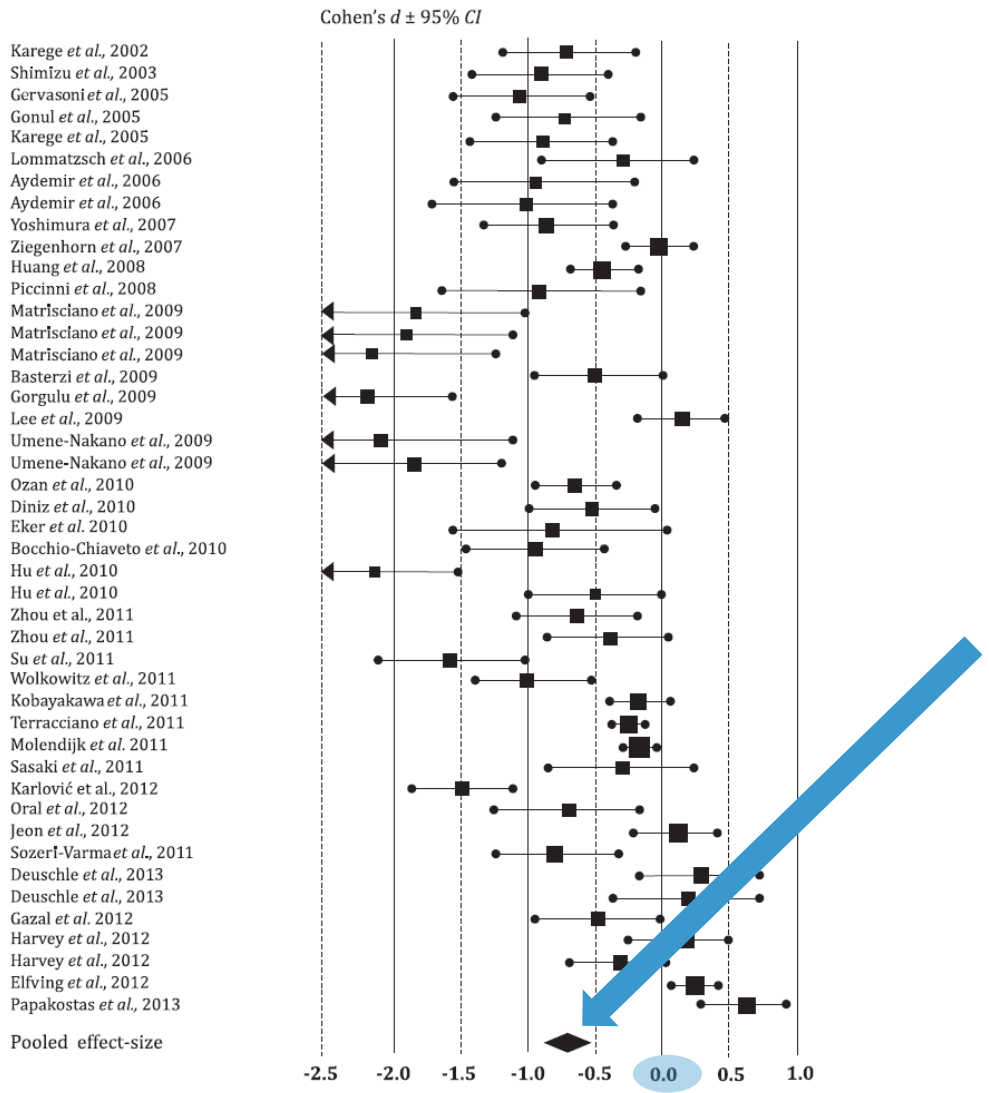


Figure 2. Forrest plot for random-effect meta-analysis on differences in serum BDNF concentrations between healthy control subjects and antidepressant-free depressed patients. The sizes of the squares are proportional to sample size.

Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N=9484).
Molendijk ML, Spinhoven P, Polak M, Bus BA, Penninx BW, Elzinga BM.
Mol Psychiatry. 2014 Jul;19(7):791-800

BDNF (neuronal growth hormone): Rise with ECT in Serum

Study or Subgroup	after ECT Mean	SD	Total	before ECT Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bilgen, 2014	2.71	0.38	30	1.99	0.51	30	11.8%	1.58 [1.00, 2.16]
Bocchio-Chiavetto, 2006	32.3	7.76	23	27.64	9.13	23	11.8%	0.54 [-0.05, 1.13]
Bumb, 2014	3	1.1	20	2.59	1.1	20	11.4%	0.37 [-0.26, 0.99]
Gedge, 2012	12.29	3.47	11	9.95	6.41	11	9.2%	0.44 [-0.41, 1.28]
Haghighi, 2013	0.38	0.3	20	0.15	0.17	20	11.1%	0.92 [0.27, 1.58]
Hu, 2010	7.9	3.42	28	5.66	2.07	28	12.2%	0.78 [0.24, 1.33]
Lin, 2013	3.65	2.01	47	3.65	2.26	47	13.6%	0.00 [-0.40, 0.40]
Salehi, 2016	0.33	0.23	20	0.15	0.17	20	11.1%	0.87 [0.22, 1.52]
Stelzhammer, 2012	12.97	10.21	8	20.33	5.46	8	7.6%	-0.85 [-1.89, 0.19]
Total (95% CI)			**207**			**207**	**100.0%**	**0.56 [0.17, 0.96]**

Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 29.33$, df = 8 (P = 0.0003); $I^2 = 73\%$
Test for overall effect: Z = 2.77 (P = 0.006)

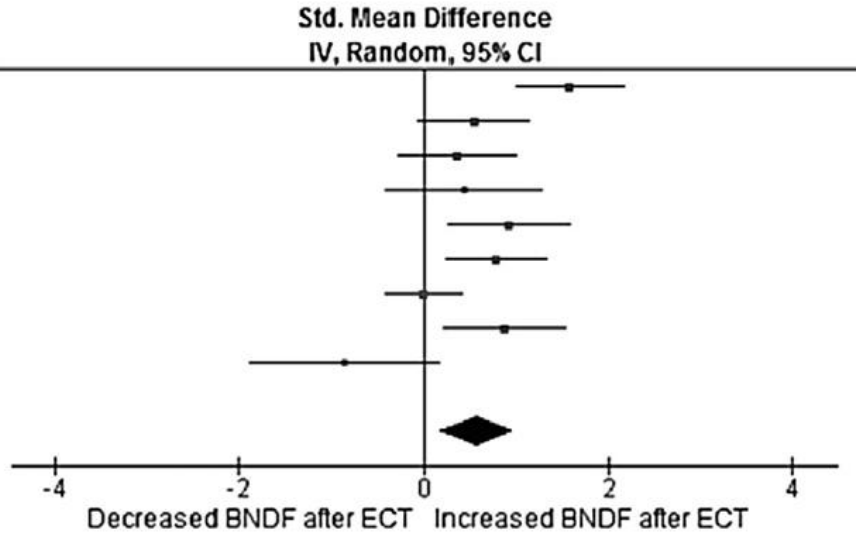


Fig. 2. Forest plot. **Abbreviations**: BDNF, brain-derived neurotrophic fator; CI, confidence interval; ECT, electroconvulsive therapy.

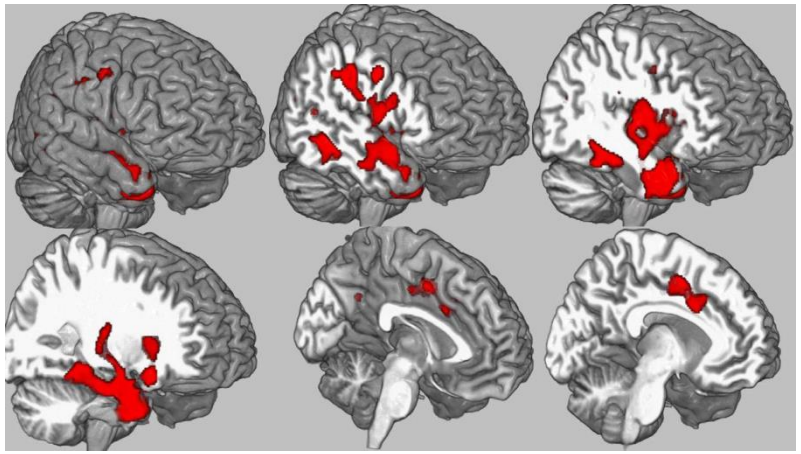
Increased BDNF levels after electroconvulsive therapy in patients with major depressive disorder: A meta-analysis study.
Rocha RB, Dondossola ER, Grande AJ, Colonetti T, Ceretta LB4, Passos IC, Quevedo J, da Rosa MI.
J Psychiatr Res. 2016 Dec;83:47-53.

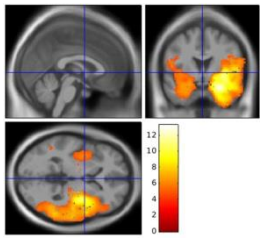
BDNF (neuronal growth hormone): Rise with ECT in CSF

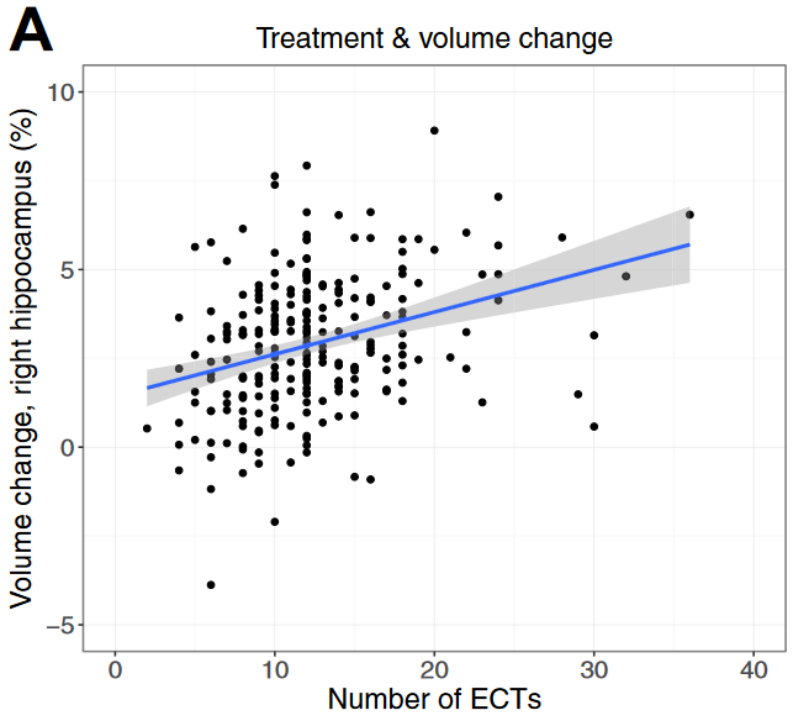
					BDNF CSF Levels in pg/mL		
No.	**Age**	**Sex**	**No. ECT**	**Clinical Outcome**	**Baseline**	**After ECT**	**Change (%)**
1	29	M	16	Response	10	88	78 (774)
2	72	F	12	Response	199	316	117 (59)
3	72	F	4	Response	78	350	272 (346)
4	72	F	7	Response	287	427	140 (49)
5	73	M	15	Response	160	550	390 (242)
6	73	F	7	Response	159	111	−48 (−30)
7	83	M	19	Response	162	170	8 (5)
8	57	F	7	Nonresponse	296	270	−26 (−8)
9	58	M	17	Nonresponse	7	102	95 (1282)

Mindt S, Neumaier M, Hellweg R, Sartorius A, Kranaster L. Brain-Derived Neurotrophic Factor in the Cerebrospinal Fluid Increases During Electroconvulsive Therapy in Patients With Depression: A Preliminary Report. J ECT. 2020 Sep;36(3):193-197.

BDNF (neuronal growth hormone): GM Growth with ECT







Sartorius A, Demirakca T, Böhringer A, Clemm von Hohenberg C, Aksay SS, Bumb JM, Kranaster L, Ende G.
Electroconvulsive therapy increases temporal gray matter volume and cortical thickness.
Eur Neuropsychopharmacol. 2016 Mar;26(3):506-17

Electroconvulsive therapy induced gray matter increase is not necessarily correlated with clinical data in depressed patients.
Sartorius A, Demirakca T, Böhringer A, Clemm von Hohenberg C, Aksay SS, Bumb JM, Kranaster L, Nickl-Jockschat T, Grözinger M, Thomann PA, Wolf RC, Zwanzger P, Dannlowski U, Redlich R, Zavorotnyy M, Zöllner R, Methfessel I, Besse M, Zilles D, Ende G.
Brain Stimul. 2019 Mar - Apr;12(2):335-343.

Volume of the Human Hippocampus and Clinical Response Following Electroconvulsive Therapy.
Oltedal L, Narr KL, Abbott C, Anand A, Argyelan M, Bartsch H, Dannlowski U, Dols A, van Eijndhoven P, Emsell L, Erchinger VJ, Espinoza R, Hahn T, Hanson LG, Hellemann G, Jorgensen MB, Kessler U, Oudega ML, Paulson OB, Redlich R, Sienaert P, Stek ML, Tendolkar I, Vandenbulcke M, Oedegaard KJ, Dale AM
Biol Psychiatry. 2018 May 29.

Why should it be safe?

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- oxygen ✓
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- high voltage

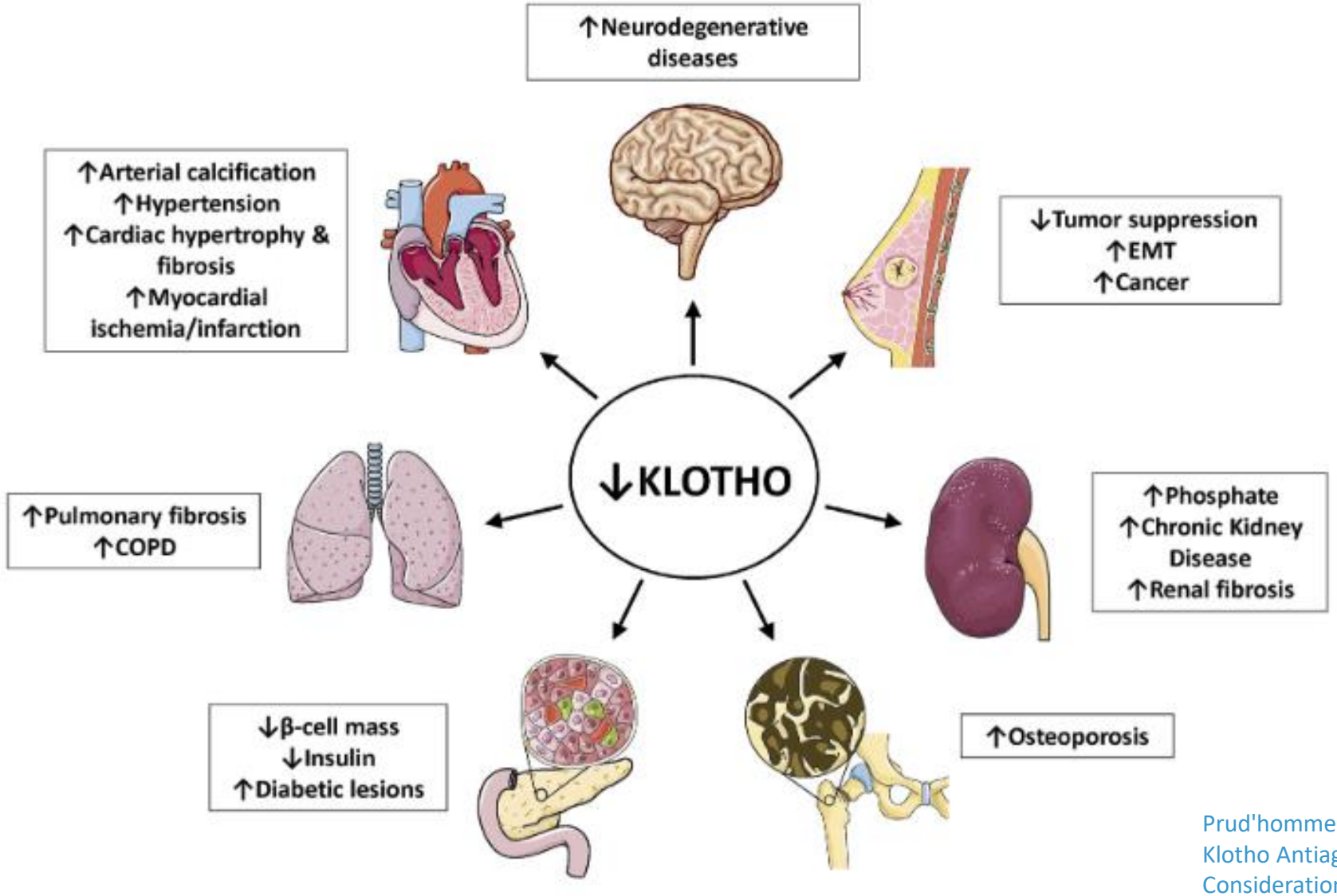
Klotho

Klotho (Κλωθώ) is one of the Three Fates
who spin (Klotho),
draw out (Lachesis)
and cut (Atropos) the thread of Life in Greek mythology.

atropa bella donna (latin)

Tollkirsche (german)
Atropa (engl.)
Galnebær (dansk)
Belladonnor (svenskt)
Belladonnat (suomalainen)

Klotho – an Antiaging Protein



Prud'homme GJ, Kurt M, Wang Q. Pathobiology of the Klotho Antiaging Protein and Therapeutic Considerations. Front Aging. 2022 Jul 12;3:931331.

Klotho – an Antiaging Protein: CSF changes with ECT

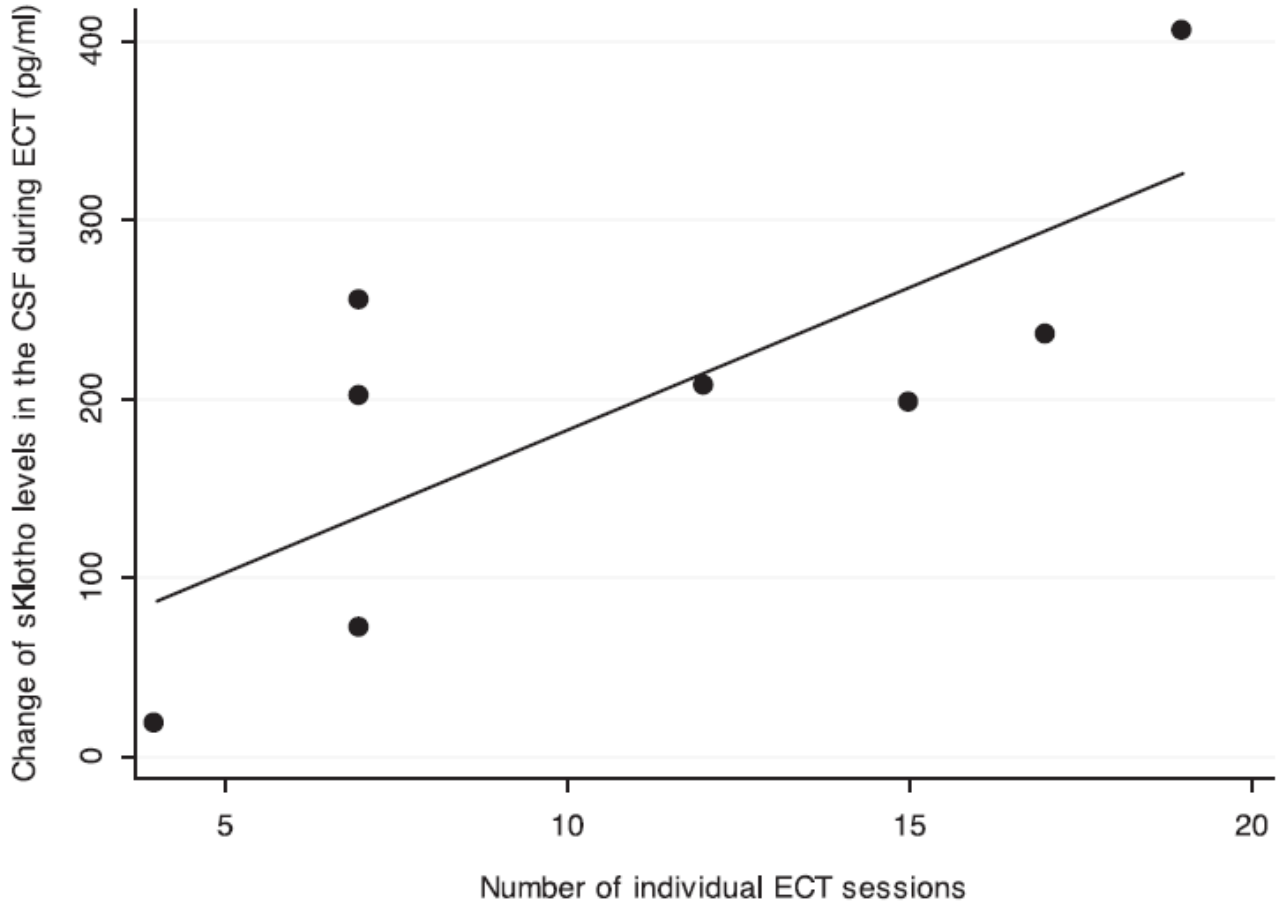


Figure 1 Correlation between the increase of sKlotho levels in the CSF during ECT and the individual performed ECT sessions ($F1, 6) = 7.84$, $p = 0.031$).

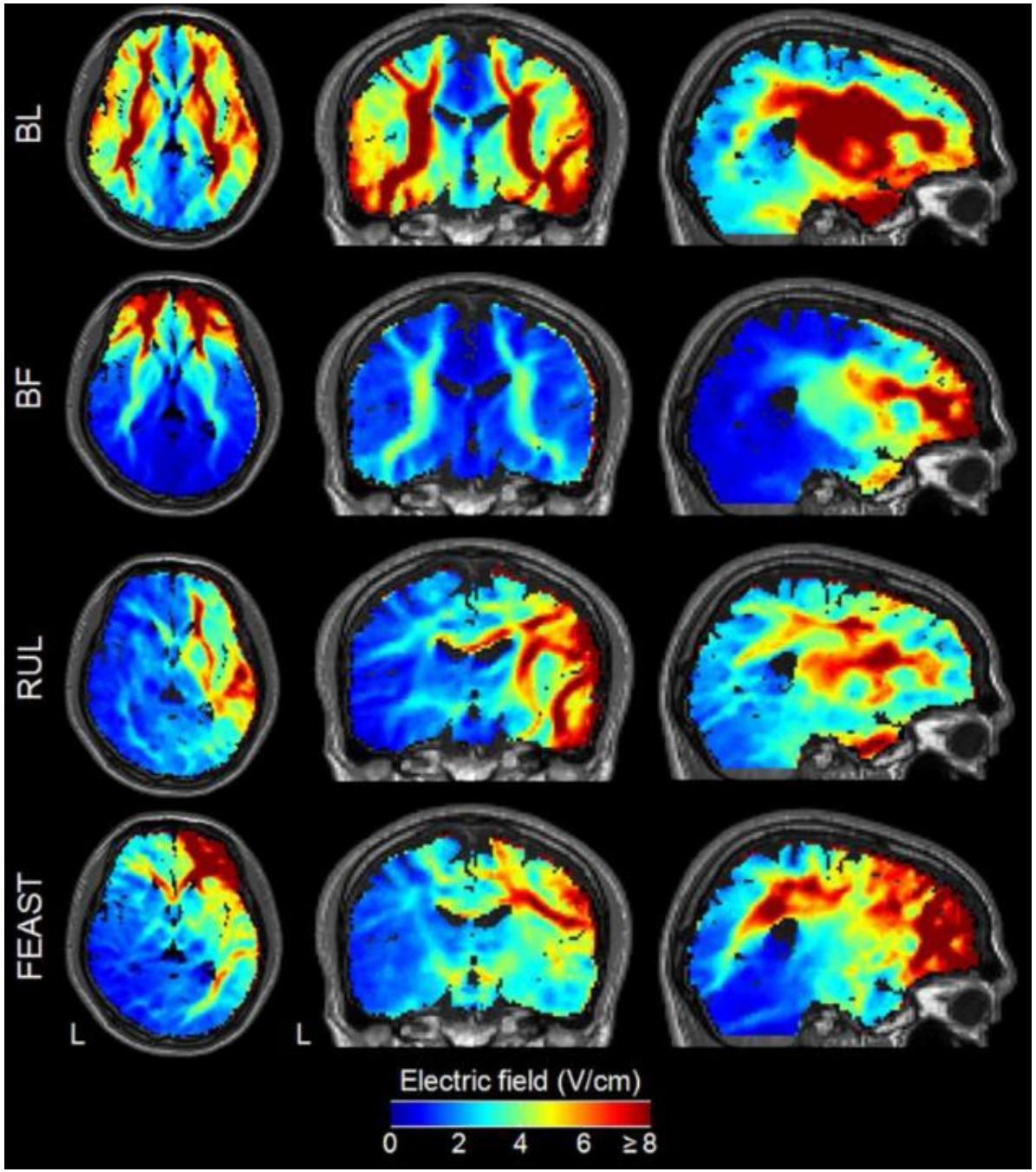
Electroconvulsive therapy enhances the anti-ageing hormone Klotho in the cerebrospinal fluid of geriatric patients with major depression.
Hoyer C, Sartorius A, Aksay SS, Bumb JM, Janke C, Thiel M, Haffner D, Leifheit-Nestler M, Kranaster L.
Eur Neuropsychopharmacol. 2018 Mar;28(3):428-435.

Why should it be safe?

Overview:

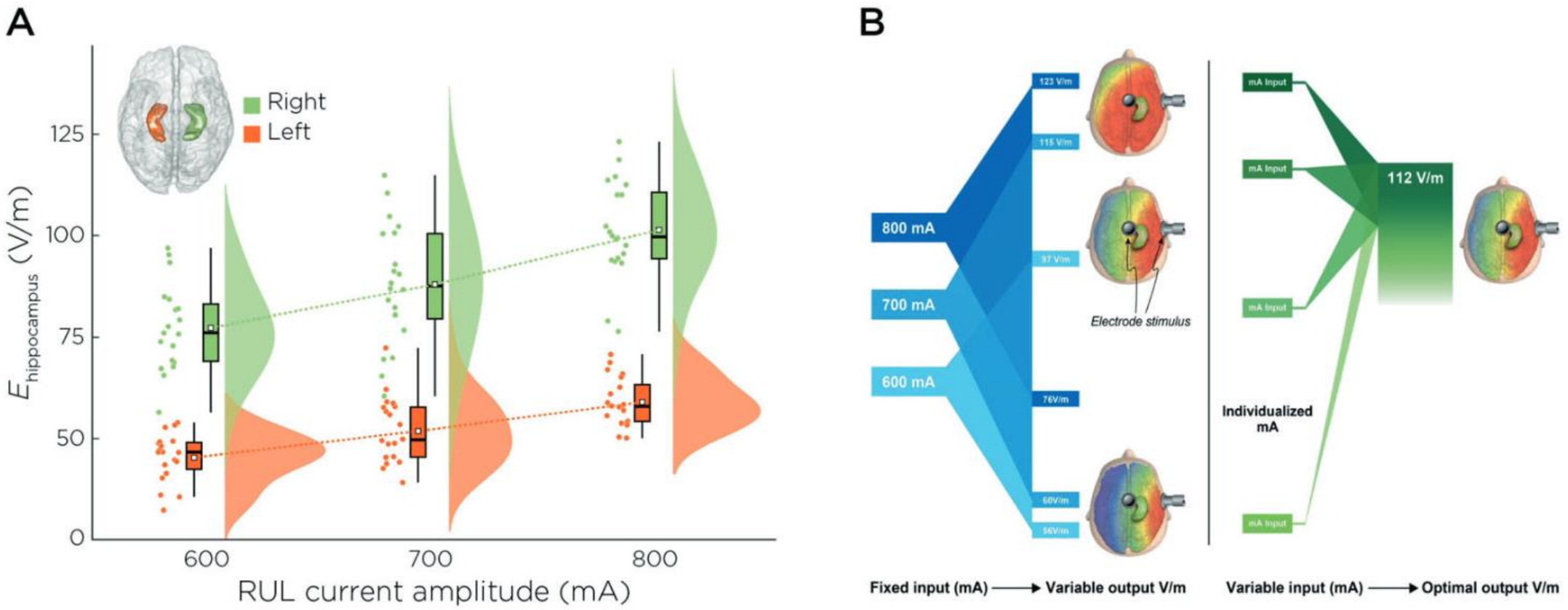
- oxygen ✓
- NSE, S100 ✓ (marker of neuronal death)
- Abeta 42  (marker of Alzheimer‘s disease)
- immune system ✓ (inflammatory marker)
- BDNF ✓ (neuronal growth hormone)
- Klotho ✓ (anti-aging hormone)
- high voltage

High voltage



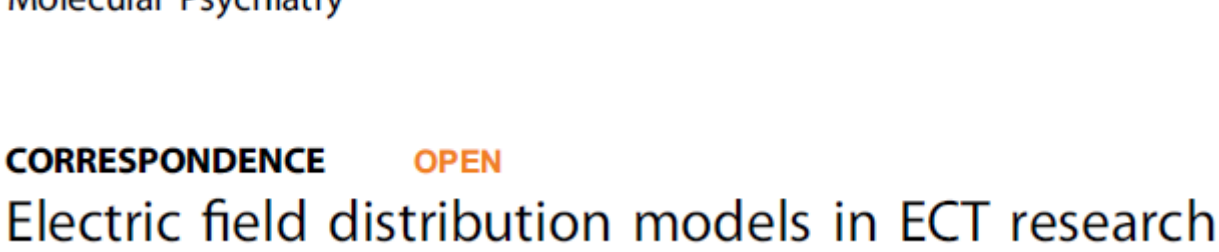
Lee WH, Deng ZD, Kim TS, Laine AF, Lisanby SH, Peterchev AV. Regional electric field induced by electroconvulsive therapy in a realistic finite element head model: influence of white matter anisotropic conductivity. Neuroimage. 2012 Feb 1;59(3):2110-23. doi: 10.1016/j.neuroimage.2011.10.029.

High voltage



Deng ZD, Argyelan M, Miller J, Quinn DK, Lloyd M, Jones TR, Upston J, Erhardt E, McClintock SM, Abbott CC. Electroconvulsive therapy, electric field, neuroplasticity, and clinical outcomes. Mol Psychiatry. 2022 Mar;27(3):1676-1682.

High voltage



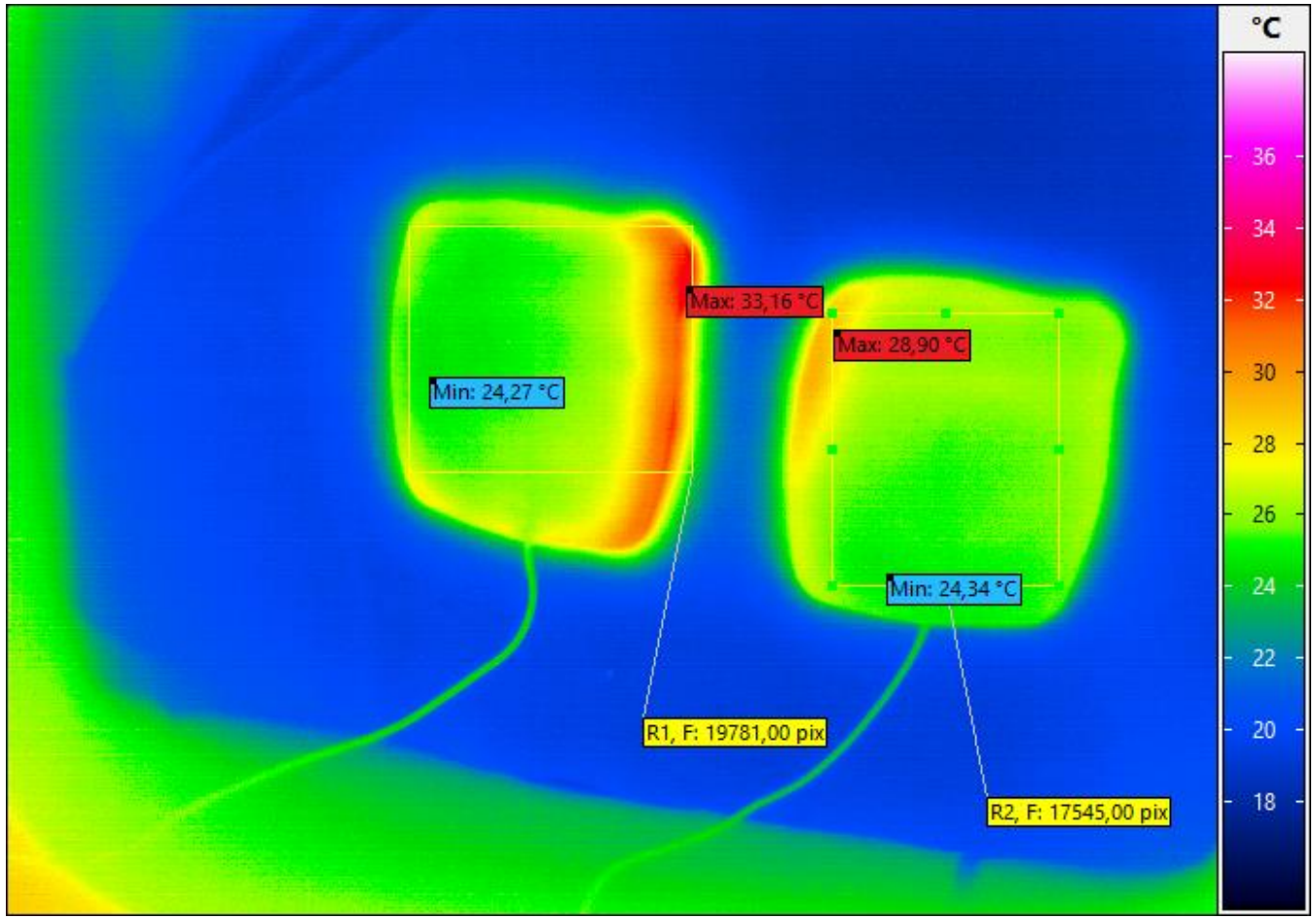
Problems with ECT E-field models in SEVERAL high ranking publications:

- *direct current is a wrong assumption*
- *knowledge about inductivity and capacity is necessary for EVERY brain voxel (missing)*
- *inductivity and capacity are strongly frequency dependent (not known, not included)*
- *“dosing” leads to frequency changes (not included)*
- *“electrical breakdown” was never implicated (since it’s 0.9A not 0.9mA)*
- *waveform was not taken into account (e.g. pulse versus sine)*
- *direction dependency -like in white matter tracts- was not implicated*

Sartorius A. Electric field distribution models in ECT research. Mol Psychiatry. 2022 Sep;27(9):3571-3572.

High voltage

What do we have: max. 400V and 0.9A, but ms pulses!



average temperature increase of 1°C per 100 joules

$W = U \times I \times t = U \times Q$

e.g.: *= 200V x 504mC (that's 100%)*
= 200V x 0.504C
= 100.8 joules => 1°C

That's comparable to a cMRI scan induced temperature rise

Swartz C, Mirkovich D, Dietze D. Temperatures and Voltages From the Electroconvulsive Therapy Stimulus. J ECT. 2023 Mar 30.

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- immune system ✓ (inflammatory marker)
- BDNF ✓ (neuronal growth hormone)
- Klotho ✓ (anti-aging hormone)
- high voltage ✓

- final thoughts

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Suna Su
Aksay

Sebastian Karl

Laura
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Jan Malte
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and

Jessica Mächnich

Franziska Putschögl
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Thank you for your attention

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