ECT for Melancholia, Psychotic Depression and TRD: Effect on the Brain?

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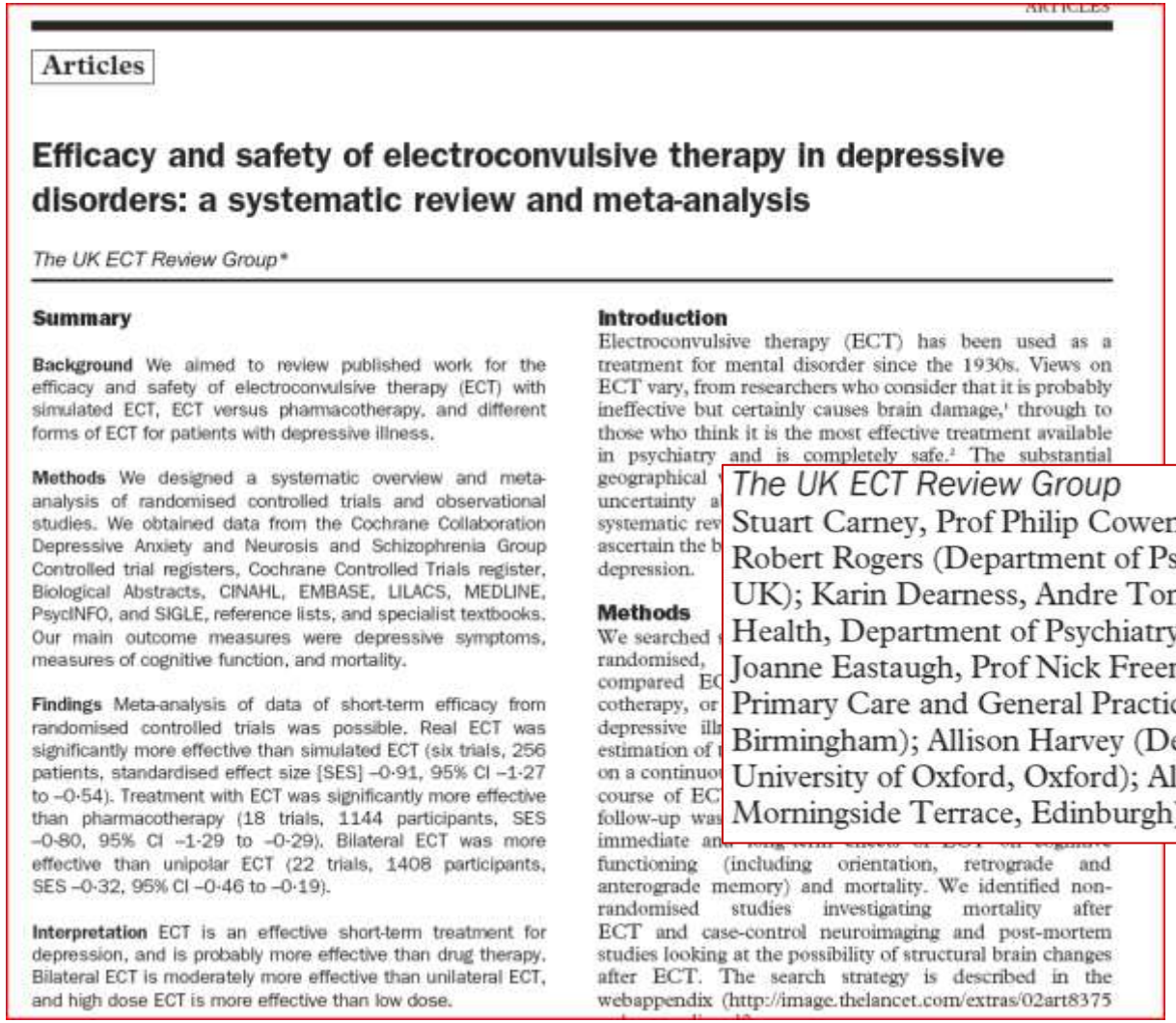
Disclosures

- No involvement in pharmaceutical industry of any kind
- Not member of any advisory boards
- Not a shareholder in any pharmaceutical company

Outline

- Clinical predictors for effect of ECT in depressed patients
- Biological predictors of effect
- Does ECT damage the brain – what is the evidence?
- How does ECT work? Two recent hypotheses
- Our own study of severely depressed patients treated with ECT

The effect of ECT: Lancet 2003 Mar 8;361(9360):799-808.



Articles

Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis

*The UK ECT Review Group**

Summary

Background We aimed to review published work for the efficacy and safety of electroconvulsive therapy (ECT) with simulated ECT, ECT versus pharmacotherapy, and different forms of ECT for patients with depressive illness.

Methods We designed a systematic overview and meta-analysis of randomised controlled trials and observational studies. We obtained data from the Cochrane Collaboration Depressive Anxiety and Neurosis and Schizophrenia Group Controlled trial registers, Cochrane Controlled Trials register, Biological Abstracts, CINAHL, EMBASE, LILACS, MEDLINE, PsycINFO, and SIGLE, reference lists, and specialist textbooks. Our main outcome measures were depressive symptoms, measures of cognitive function, and mortality.

Findings Meta-analysis of data of short-term efficacy from randomised controlled trials was possible. Real ECT was significantly more effective than simulated ECT (six trials, 256 patients, standardised effect size [SES] –0·91, 95% CI –1·27 to –0·54). Treatment with ECT was significantly more effective than pharmacotherapy (18 trials, 1144 participants, SES –0·80, 95% CI –1·29 to –0·29). Bilateral ECT was more effective than unipolar ECT (22 trials, 1408 participants, SES –0·32, 95% CI –0·46 to –0·19).

Interpretation ECT is an effective short-term treatment for depression, and is probably more effective than drug therapy. Bilateral ECT is moderately more effective than unilateral ECT, and high dose ECT is more effective than low dose.

Introduction

Electroconvulsive therapy (ECT) has been used as a treatment for mental disorder since the 1930s. Views on ECT vary, from researchers who consider that it is probably ineffective but certainly causes brain damage,[1] through to those who think it is the most effective treatment available in psychiatry and is completely safe.[2] The substantial geographical
uncertainty a
systematic rev
ascertain the b
depression.

Methods

We searched
randomised,
compared EC
cotherapy, or
depressive ill
estimation of
on a continuo
course of EC
follow-up wa
immediate an
functioning (including orientation, retrograde and anterograde memory) and mortality. We identified non-randomised studies investigating mortality after ECT and case-control neuroimaging and post-mortem studies looking at the possibility of structural brain changes after ECT. The search strategy is described in the webappendix (http://image.thelancet.com/extras/02art8375

The UK ECT Review Group

Stuart Carney, Prof Philip Cowen, Prof John Geddes, Prof Guy Goodwin, Robert Rogers (Department of Psychiatry, University of Oxford, Oxford, UK); Karin Dearness, Andre Tomlin (Centre for Evidence Based Mental Health, Department of Psychiatry, University of Oxford, Oxford); Joanne Eastaugh, Prof Nick Freemantle, Helen Lester (Department of Primary Care and General Practice, University of Birmingham, Birmingham); Allison Harvey (Department of Experimental Psychology, University of Oxford, Oxford); Allan Scott (Royal Edinburgh Hospital, Morningside Terrace, Edinburgh)

ECT versus sham ECT (N=256) Lancet 2003

Trial	Number of participants	Standardised effect size (95% CI)
Wilson 1963	12	–1·078 (–2·289 to 0·133)
West 1981	25	–1·255 (–2·170 to –0·341)
Lambourn 1978	40	–0·170 (–0·940 to 0·600)
Freeman 1978	40	–0·629 (–1·264 to 0·006)
Gregory 1985	69	–1·418 (–2·012 to –0·824)
Johnstone 1980	70	–0·739 (–1·253 to –0·224)
Pooled fixed effects		–0·911 (–1·180 to –0·645)
Pooled random effects		–0·908 (–1·270 to –0·537)

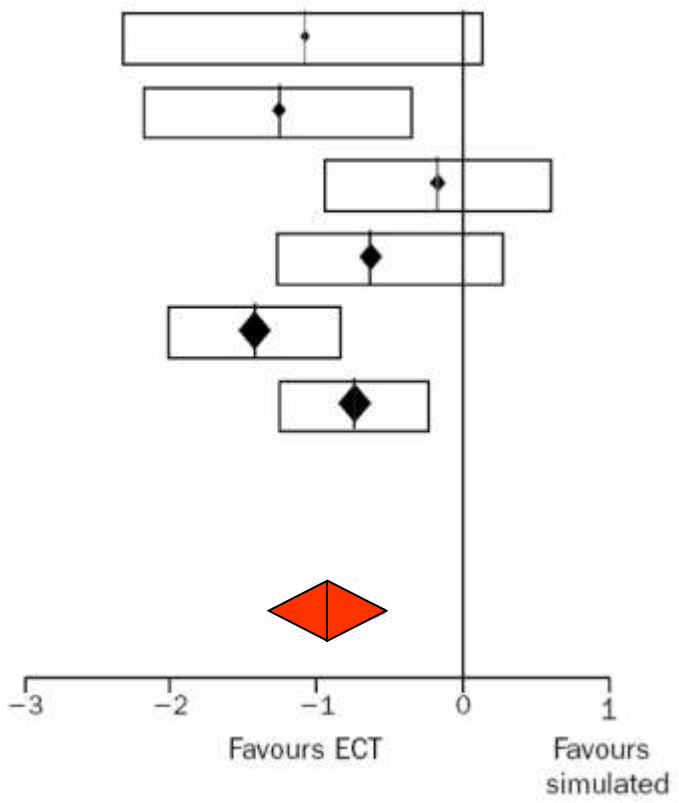


Figure 1: **Effect of ECT versus simulated ECT on depressive symptoms**

UK ECT Review group. Lancet 2003

ECT versus psychopharmacological treatment (N=760)

Trial	Number of participants	Standardised effect size (95% CI)
Steiner 1978	12	0·369 (–0·840 to 1·578)
Wilson 1963	12	–0·513 (–1·663 to 0·637)
Davidson 1978	19	–1·389 (–2·449 to –0·328)
McDonald 1966	22	–0·930 (–1·813 to –0·047)
Gangadhar 1982	32	1·287 (0·406 to 2·169)
MacSweeney 1975	27	–0·714 (–1·492 to 0·065)
Dinan 1989	30	–0·196 (–0·926 to 0·534)
Janakiramaiah 2000	30	–1·095 (–1·863 to –0·328)
Folkerts 1997	40	–1·336 (–2·032 to –0·640)
Herrington 1974	43	–1·497 (–2·174 to –0·821)
Stanley 1962	47	–1·342 (–2·047 to –0·638)
Medical Research Council 1965	204	–0·559 (–0·883 to –0·234)
Greenblatt 1964	242	–1·683 (–2·020 to –1·346)
Pooled fixed effects		–1·010 (–1·170 to –0·856)
Pooled random effects		–0·802 (–1·290 to –0·289)

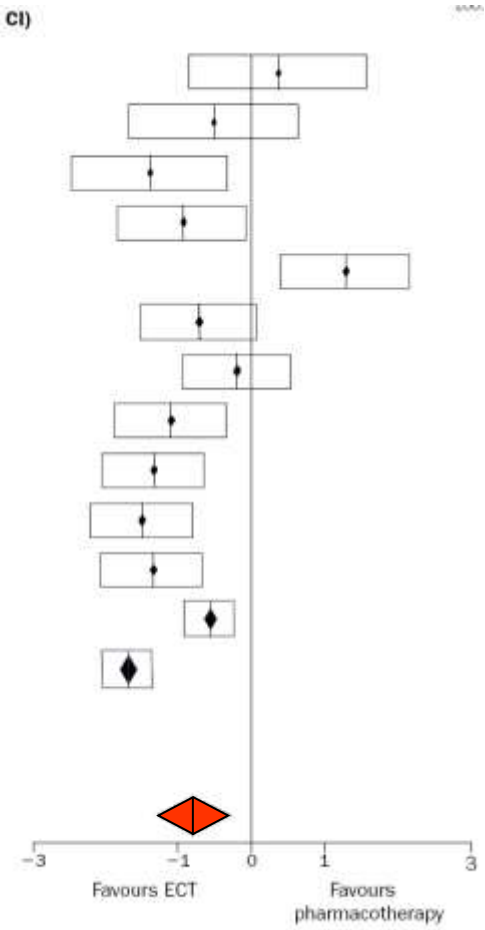
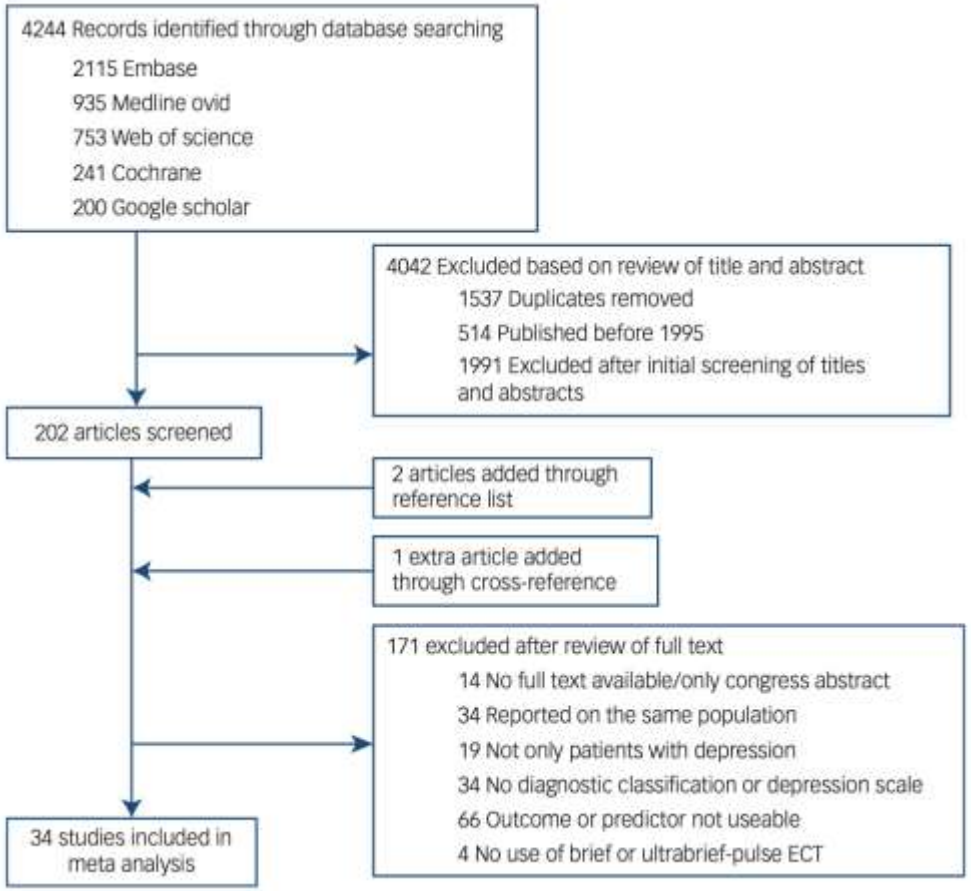


Figure 3: **Effect of ECT versus pharmacotherapy on depressive symptoms**

UK ECT Review group. Lancet 2003

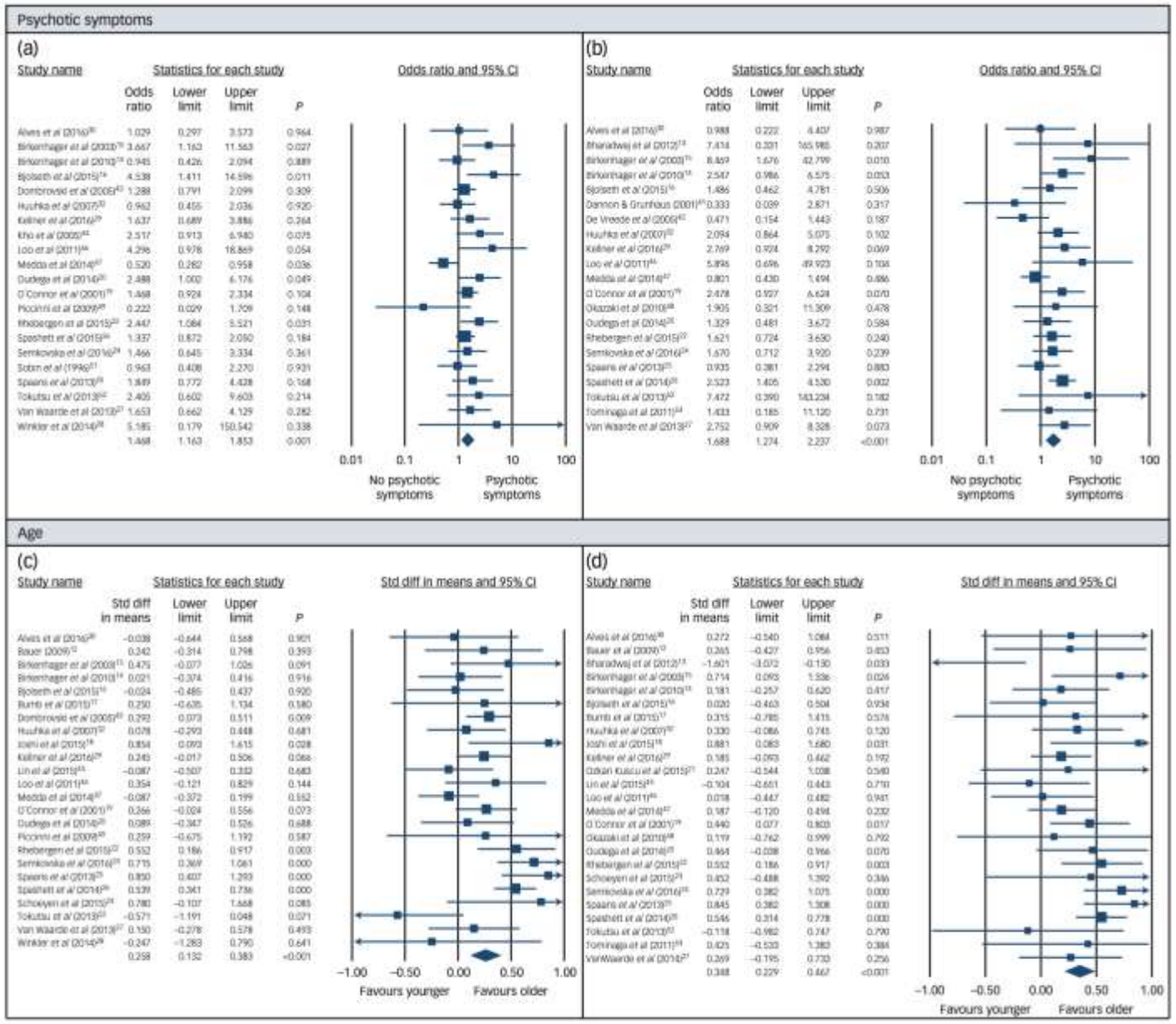
Clinical predictors for effect of ECT in depressed patients (Diermen et al 2018)



1. Studies assessing the effect of brief- or ultrabrief-pulse ECT on depression severity, published in or after 1995, articles are written in English
2. Adults (>18 years of age) with uni- or bipolar depression (confirmed by RDC, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5 or ICD-10 criteria)
3. Presence of psychotic or melancholic symptoms was confirmed by a structured diagnostic or clinical interview
4. Classification of patients as ‘responder/non-responder’ or ‘remitter/non-remitter’ based on scores on valid clinician rated depression scales (Hamilton Rating Scale for Depression or Montgomery–Åsberg Depression Rating Scale

Included 34 studies reporting on 3276 patients

Remission Responce

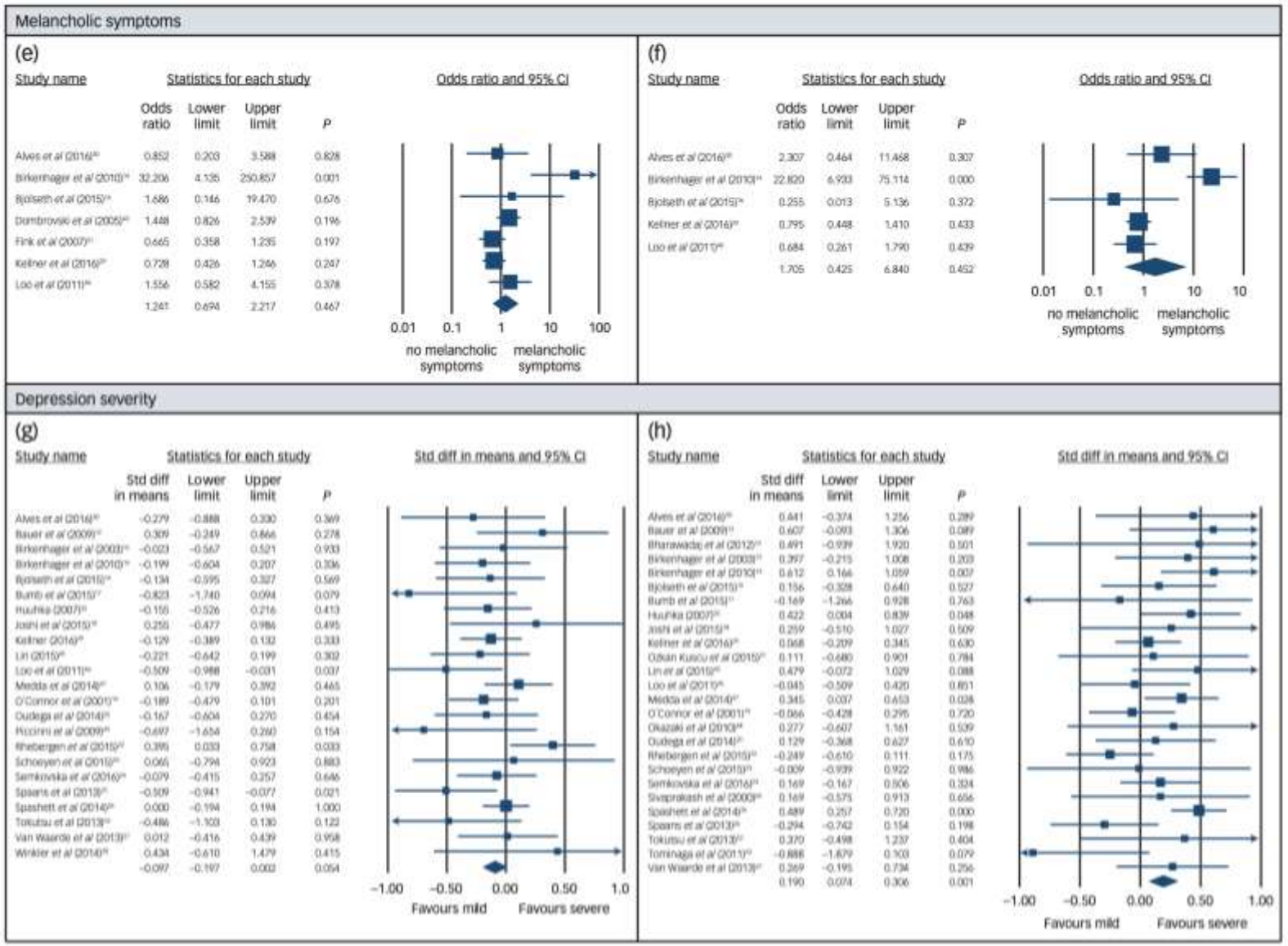


Presence of psychotic symptoms
OR of 1.69 ($P < 0.001$) for response
and 1.47 ($P = 0.001$) for remission

The SMD for older age was 0.35 ($P < 0.001$)
for response analysis, and
0.26 ($P < 0.001$) for remission

Diermen et al 2018

Remission Responce



Melancholic features of MDD:

- Loss of pleasure in all or most daily activities
- Lack of reactivity to positive events
- Early awakening (>2 hours)
- Symptoms of MDD worse in the morning
- Psychomotor retardation or agitation
- Loss of appetite
- Significant weight loss
- Reduced libido

Severity of depression and response:
SMD 0.19, P=0.001.
Depression severity was not associated with remission.

Diermen et al 2018

Conclusion about prognostic signs & symptoms

Depression	Correlation	Evidence
Age	+++	Metanalysis
Gender	0	++
Psychotic depression	+++	Metanalysis
Melancholic features	0	Metanalysis
Suicide risk	+++	++
Duration of episode	÷ ÷	+++
Severity of episode	++	Metanalysis
Diagnosis	UD=BD	Metanalysis
Early responce	++	+++

Diermen et al. 2018
Bahji et al. 2018
Haq et al. 2015
Dierckx et al. 2012
Heinen et al. 2010

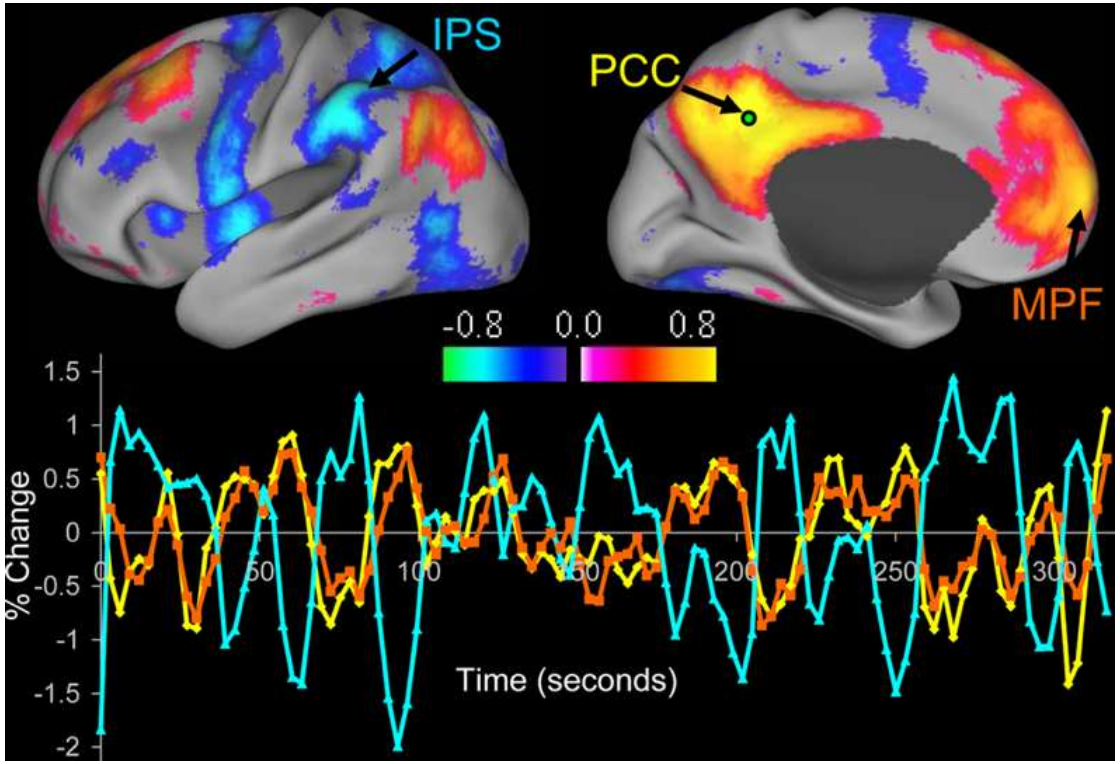
Effect in ECT in cases of treatment resistance

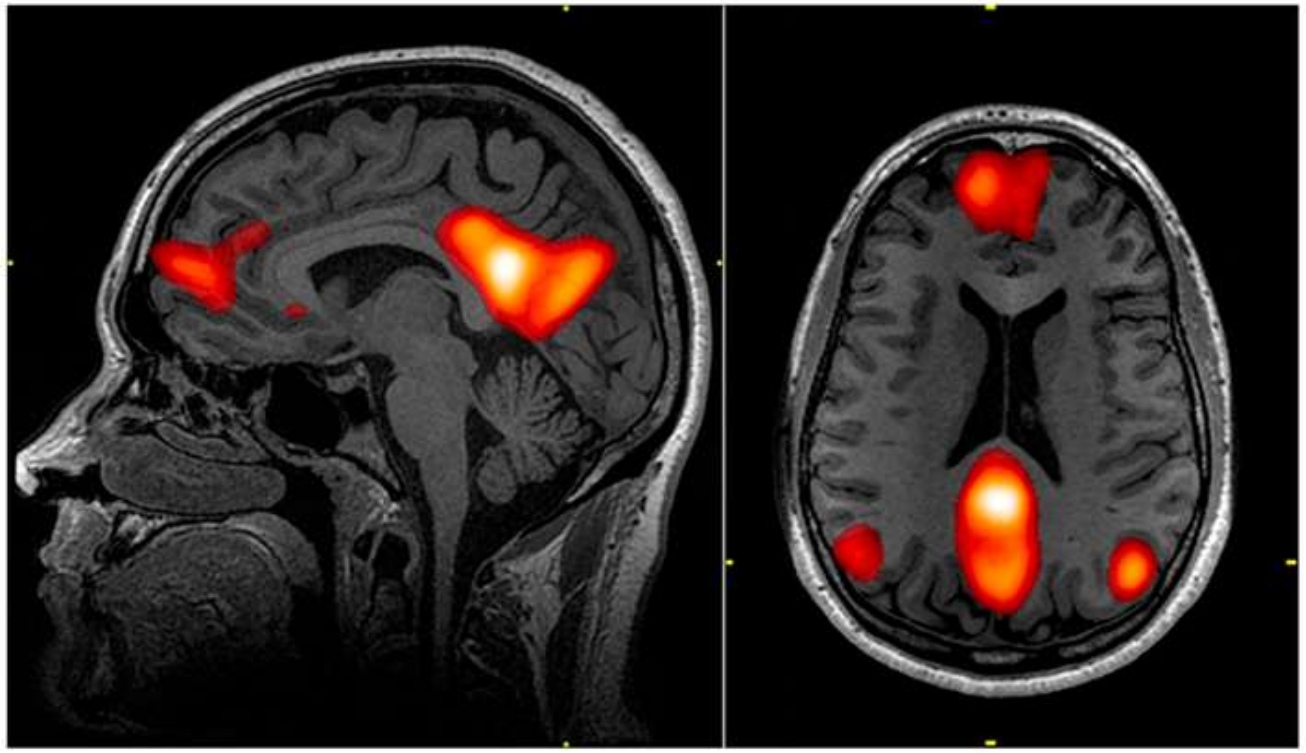
- Response rate 58% for patients with medication failure and 70% for those without (Haq et al. 2015)

Any Biological predictors for effect?

- Neurotrophic factors
  - Brain Derived Neurotrophic Factor
- Resting state connectivity
- Neurotransmittors
  - Serotonin, Catecholamines, Glutamate
- Genetic predictors, gene expression
  - DRD2, DRD3, COMT…

Resting state connectivity (fMRI)



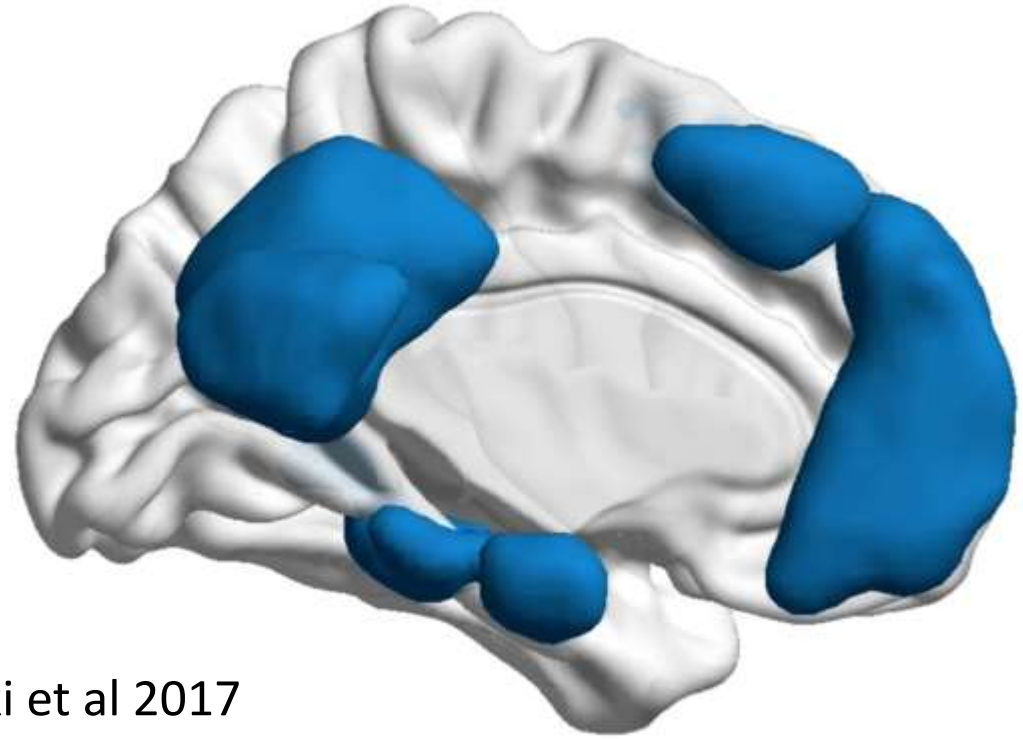


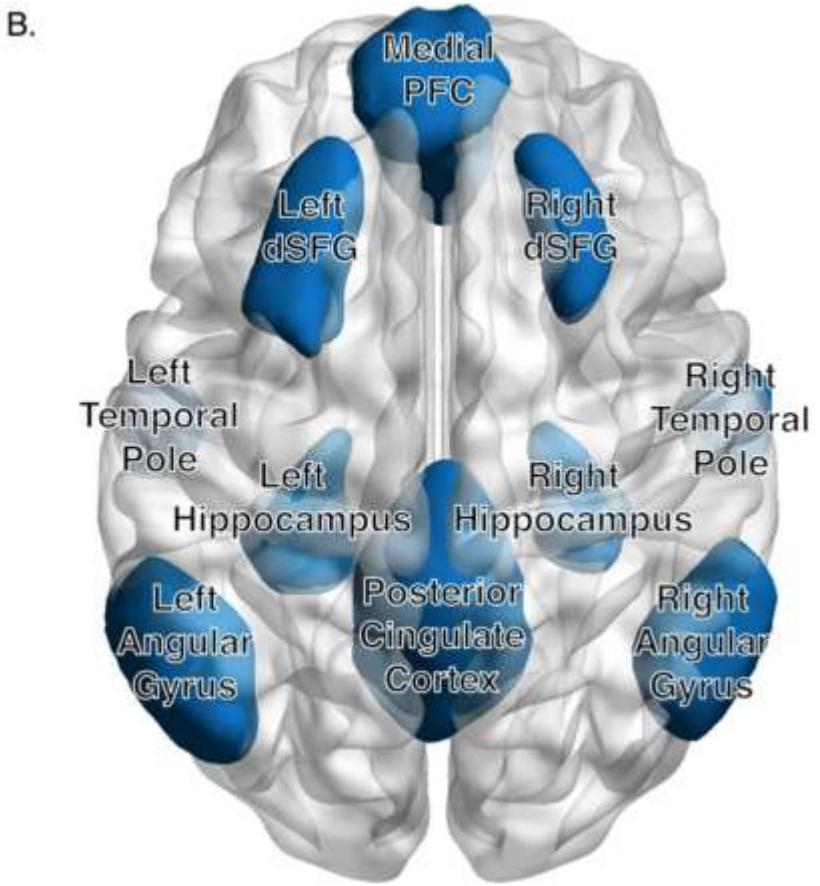
Raichle 2001: **The Default mode network**
Medial prefrontal cortex,
posterior cingulate cortex,
precuneus, inferior parietal lobules
medial temporal regions

Active when relaxing, daydreaming

Sheline et al 2010
Mulders et al. 2015
Zhao et al 2019

Activity in The Default mode network is increased in depression





Brakowski et al 2017
Zhiliang et al 2020
Dini et al 2021

Can Resting State Connectivity predict effect?

- Some studies have shown reduced resting state connectivity in DMN after ECT

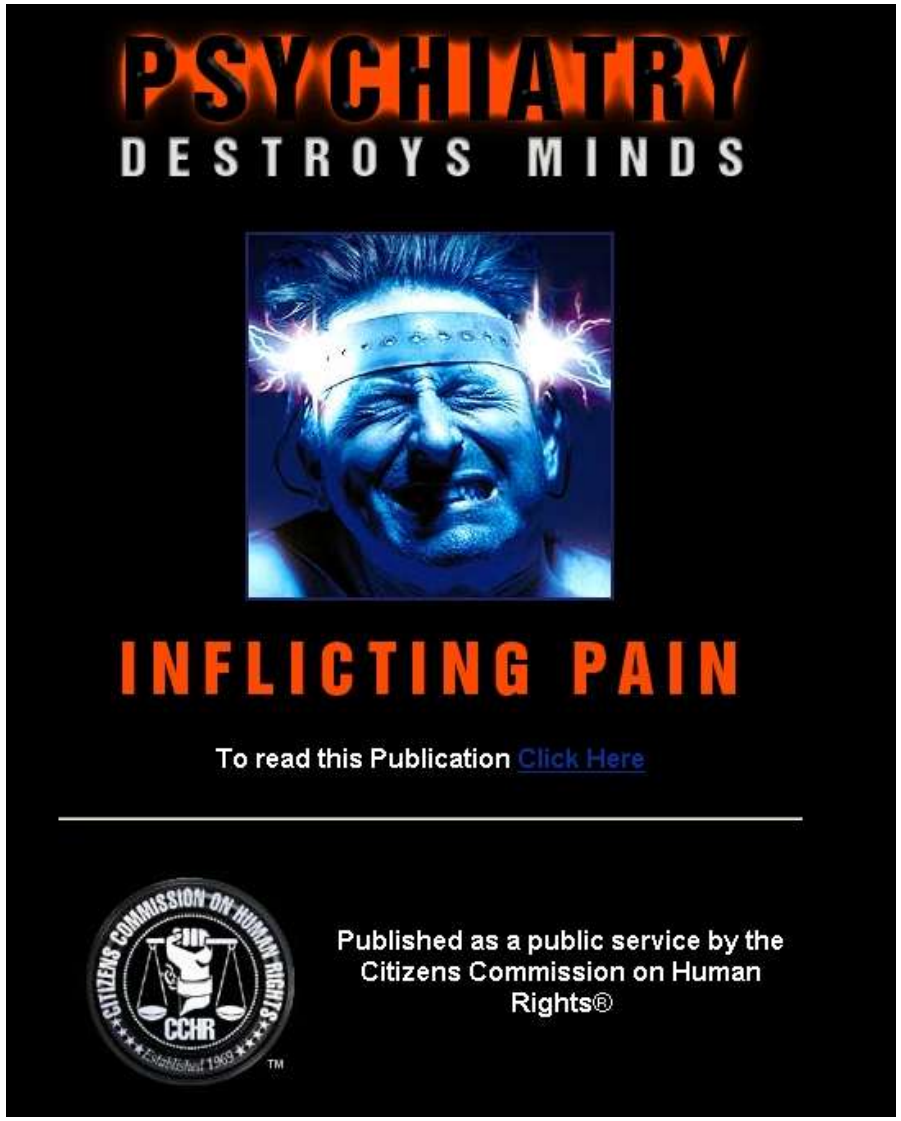
Brakowski et al 2017
Zhiliang et al 2020
Dini et al 2021

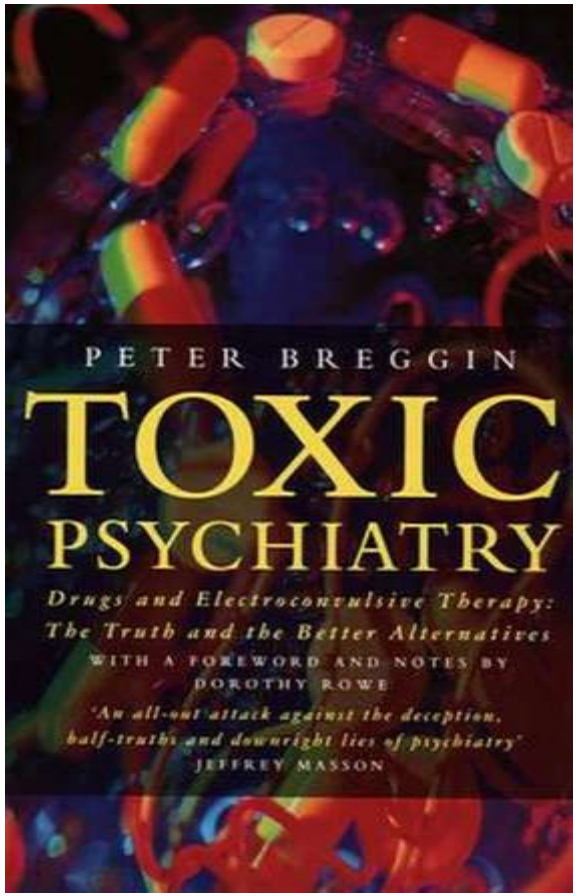
Does ECT damage the brain?

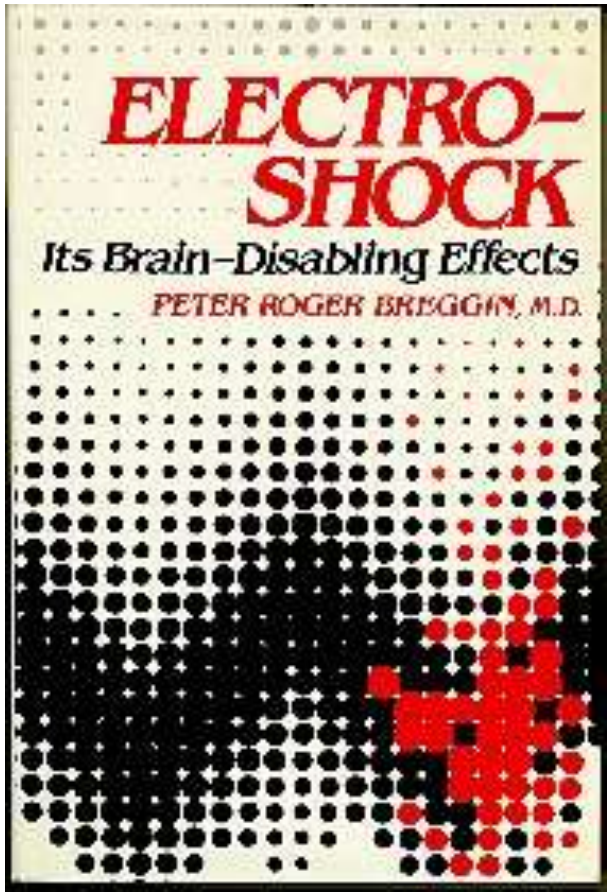
Why shouldn’t it damage the brain?

- Difficult to treat epilepsy
- Generalized seizure:
  - Huge muscular workload = large consumption of oxygen
  - Respiration arrest
- The application of the current

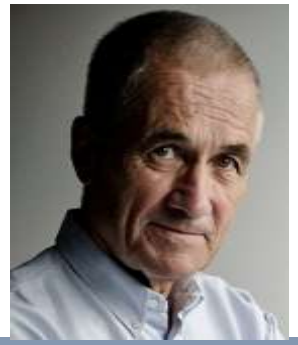
- Many patients (and doctors) fear brain damage







Danish: ”Medborgernes Menneskerettigheds kommission”



Peter Gøtzsche

Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2018: 1–16
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DOI: 10.1111/acps.12884

ACTA PSYCHIATRICA SCANDINAVICA

Review

Electroconvulsive therapy increases brain volume in major depression: a systematic review and meta-analysis

Gbyl K, Videbech P. Electroconvulsive therapy increases brain volume in major depression: a systematic review and meta-analysis

Objective: The main purpose of this review was to synthesise evidence on ECT's effects on brain's structure.
Method: A systematic literature review of longitudinal studies of depressed patients treated with ECT using magnetic resonance imaging (MRI) and meta-analysis of ECT's effect on hippocampal volume.
Results: Thirty-two studies with 467 patients and 285 controls were included. The MRI studies did not find any evidence of ECT-related brain damage. All but one of the newer MRI volumetric studies found ECT-induced volume increases in certain brain areas, most consistently in hippocampus. Meta-analysis of effect of ECT on hippocampal volume yielded pooled effect size: $g = 0.39$ (95% CI = 0.18–0.61) for the right hippocampus and $g = 0.31$ (95% CI = 0.09–0.53) for the left. The DTI studies point to an ECT-induced increase in the integrity of white matter pathways in the frontal and temporal lobes. The results of correlations between volume increases and treatment efficacy were inconsistent.
Conclusion: The MRI studies do not support the hypothesis that ECT causes brain damage; on the contrary, the treatment induces volume increases in fronto-limbic areas. Further studies should explore the relationship between these increases and treatment effect and cognitive side effects.

K. Gbyl, P. Videbech

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Key words: electroconvulsive therapy; magnetic resonance imaging; diffusion tensor imaging; depressive disorder, major

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Accepted for publication March 8, 2018

Dr. Krzysztof Gbyl

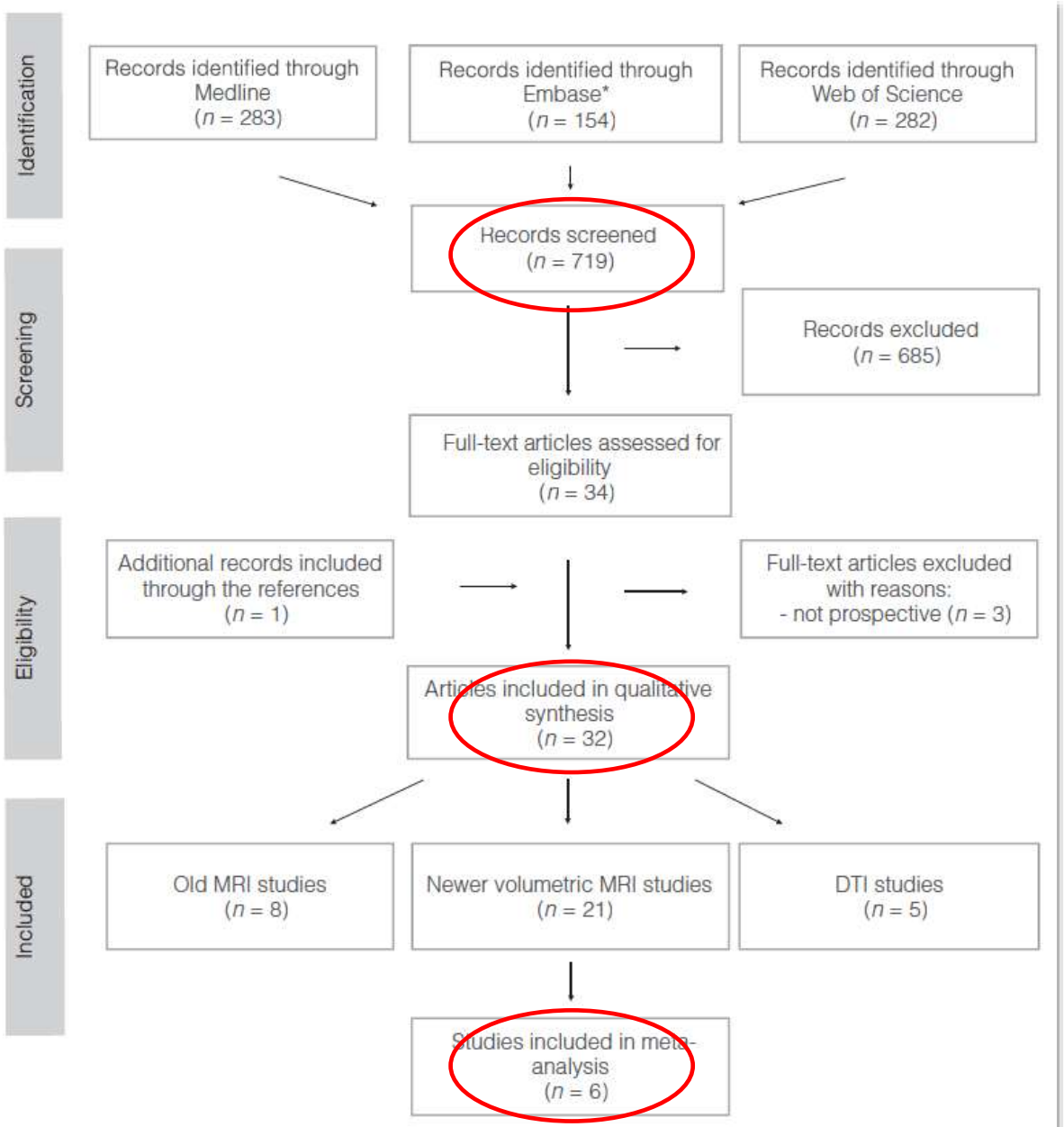
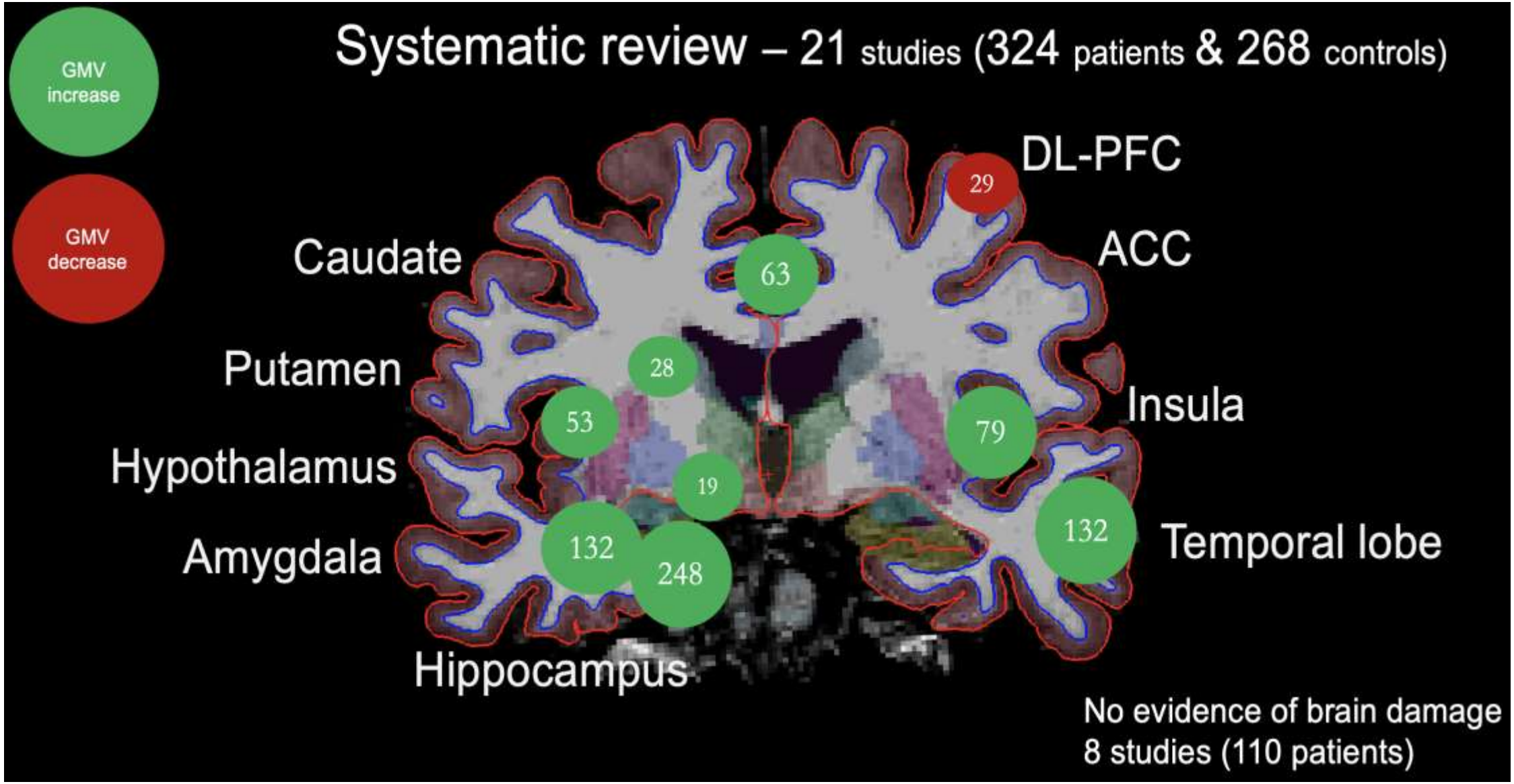


Fig. 1. Flowchart illustrating the study selection. *After excluding Medline records.

Results

- 32 MRI studies including 467 patients and 285 matched healthy controls
- No study comparing before vs. after ECT using MRI showed signs of atrophy



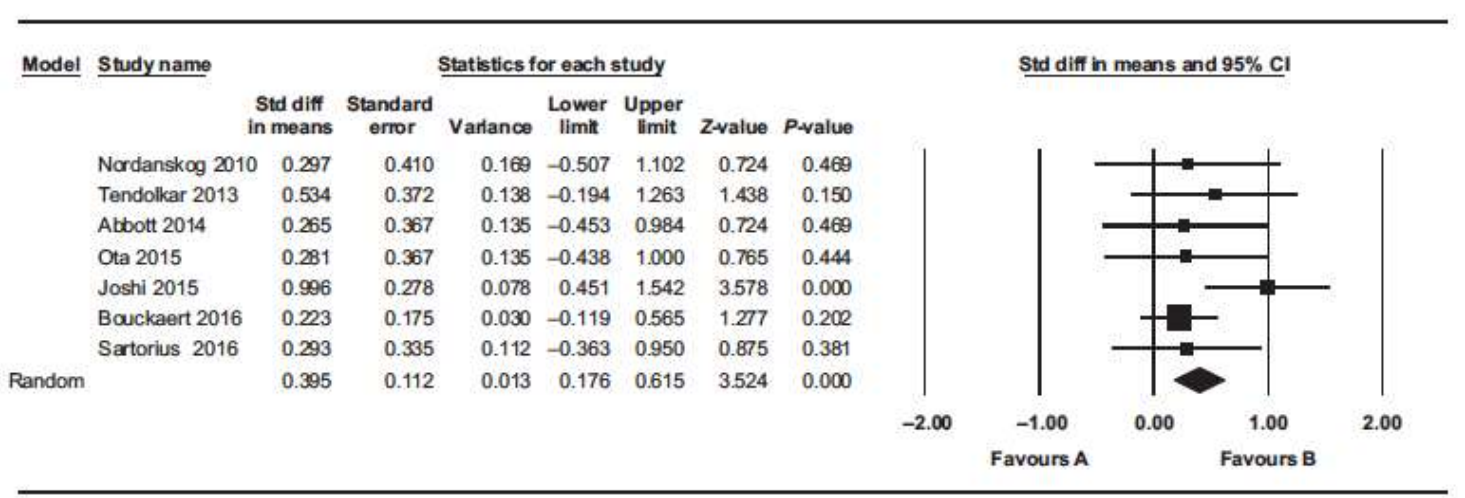
Gbyl & Videbech 2018

Metaanalyses of the volume of hippocampus

Why are the hippocampus Interesting?

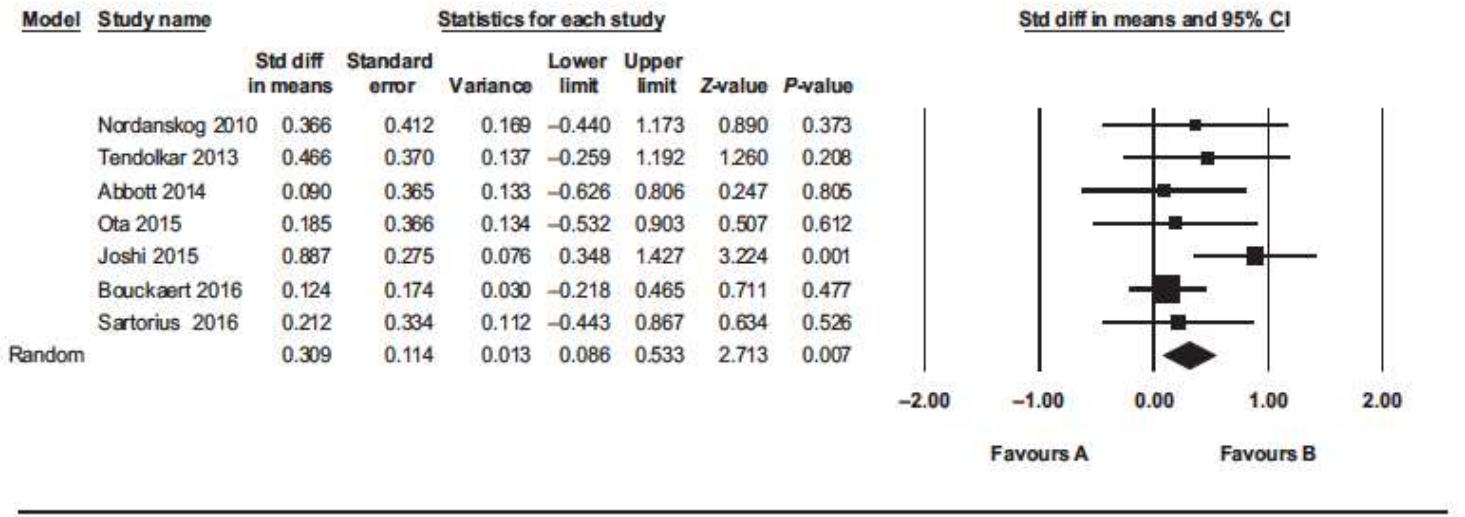
- Very vulnerable to hypoxia
- Important for memory consolidation
- Involved in depression

Gbyl & Videbech 2018



Model	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
	Nordanskog 2010	0.297	0.410	0.169	−0.507	1.102	0.724	0.469
	Tendolkar 2013	0.534	0.372	0.138	−0.194	1.263	1.438	0.150
	Abbott 2014	0.265	0.367	0.135	−0.453	0.984	0.724	0.469
	Ota 2015	0.281	0.367	0.135	−0.438	1.000	0.765	0.444
	Joshi 2015	0.996	0.278	0.078	0.451	1.542	3.578	0.000
	Bouckaert 2016	0.223	0.175	0.030	−0.119	0.565	1.277	0.202
	Sartorius 2016	0.293	0.335	0.112	−0.363	0.950	0.875	0.381
Random		0.395	0.112	0.013	0.176	0.615	3.524	0.000

Fig. 2. Meta-analysis of the volume change of the right hippocampus following a series of ECT.



Model	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
	Nordanskog 2010	0.366	0.412	0.169	−0.440	1.173	0.890	0.373
	Tendolkar 2013	0.466	0.370	0.137	−0.259	1.192	1.260	0.208
	Abbott 2014	0.090	0.365	0.133	−0.626	0.806	0.247	0.805
	Ota 2015	0.185	0.366	0.134	−0.532	0.903	0.507	0.612
	Joshi 2015	0.887	0.275	0.076	0.348	1.427	3.224	0.001
	Bouckaert 2016	0.124	0.174	0.030	−0.218	0.465	0.711	0.477
	Sartorius 2016	0.212	0.334	0.112	−0.443	0.867	0.634	0.526
Random		0.309	0.114	0.013	0.086	0.533	2.713	0.007

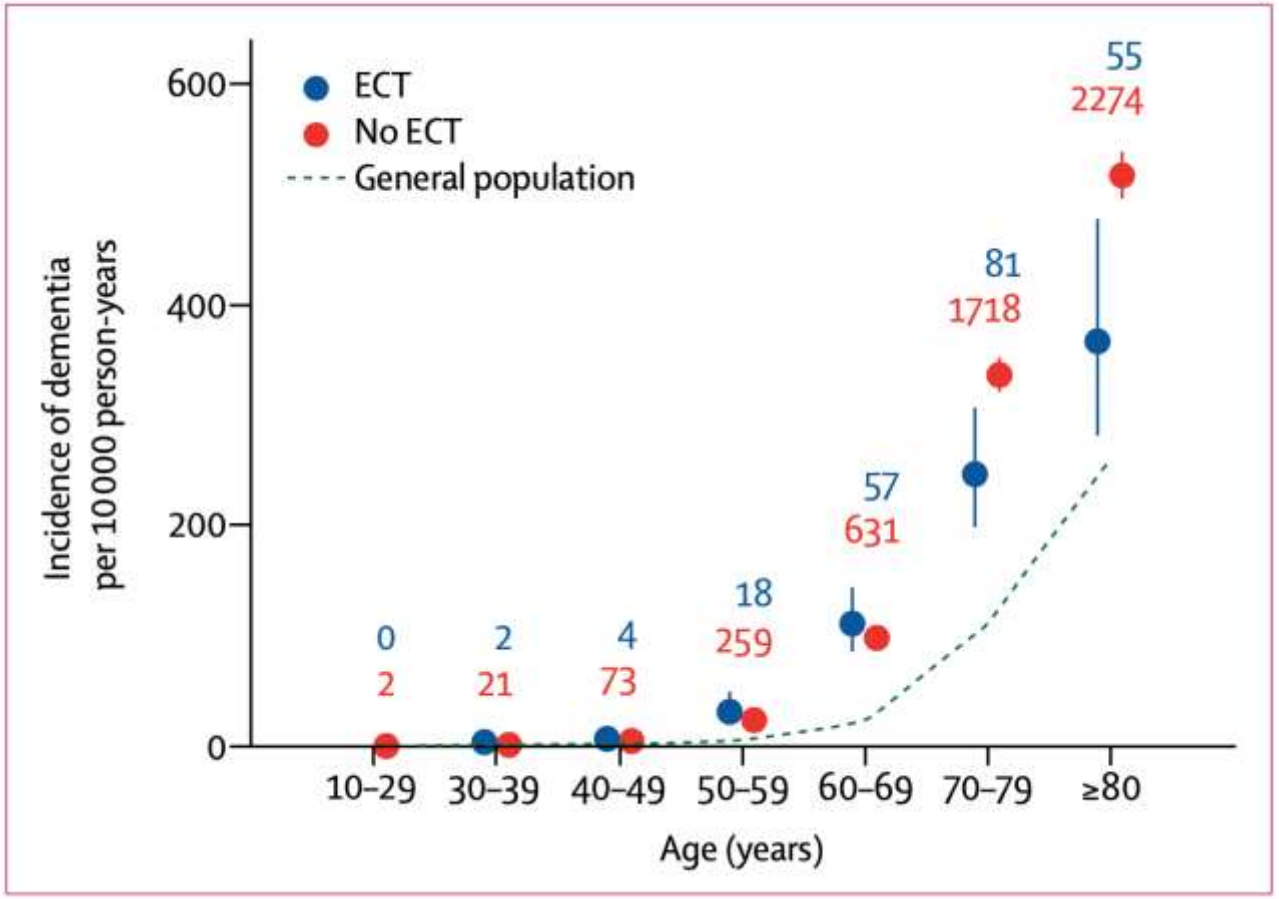
Fig. 3. Meta-analysis of the volume change of the left hippocampus following a series of ECT.

Is ECT followed by later development of dementia?

- Depression itself doubles the risk of dementia (Saczynski 2010, Dinez 2013, Mourao 2016)
- Severe depression => increased likelihood of ECT
- We would thus expect increased prevalence of dementia in patients receiving ECT

Studies of ECT and dementia (I)

- Chu et al. 2018: 994 ECT-patients and 2982 psychiatric controls (age and gender matched)
  - Ca. 50 % with schizophrenia
  - Followed for 10 years
  - Prevalence of dementia: 5.0 % among patients, 4.5 % among controls
- Osler et al. 2018: Cohort of 168.015 ptt of which 5901 was treated with ECT
  - Followed in 5 year
  - Dementia in controls: 3.1 % in ECT patients: 3.6 %
  - Controlled for age, mortality, social conditions, clincal variables



Studies of ECT and dementia (II)

ORIGINAL STUDY

Long-Term Risk of Developing Dementia After Electroconvulsive Therapy for Affective Disorders

Simon Hjerrild, MD, PhD, Johnny Kahlert, MSc, PhD,† Poul-Erik Buchholtz, MD,* Raben Rosenberg, MD, DMSc,‡ and Poul Videbech, MD, DMSc§*

Objectives: Severe depression is associated with an increased risk of de- administered neuropsychological tests and processing speed, working memory, anterograde memory, and some aspects of exec-

2021

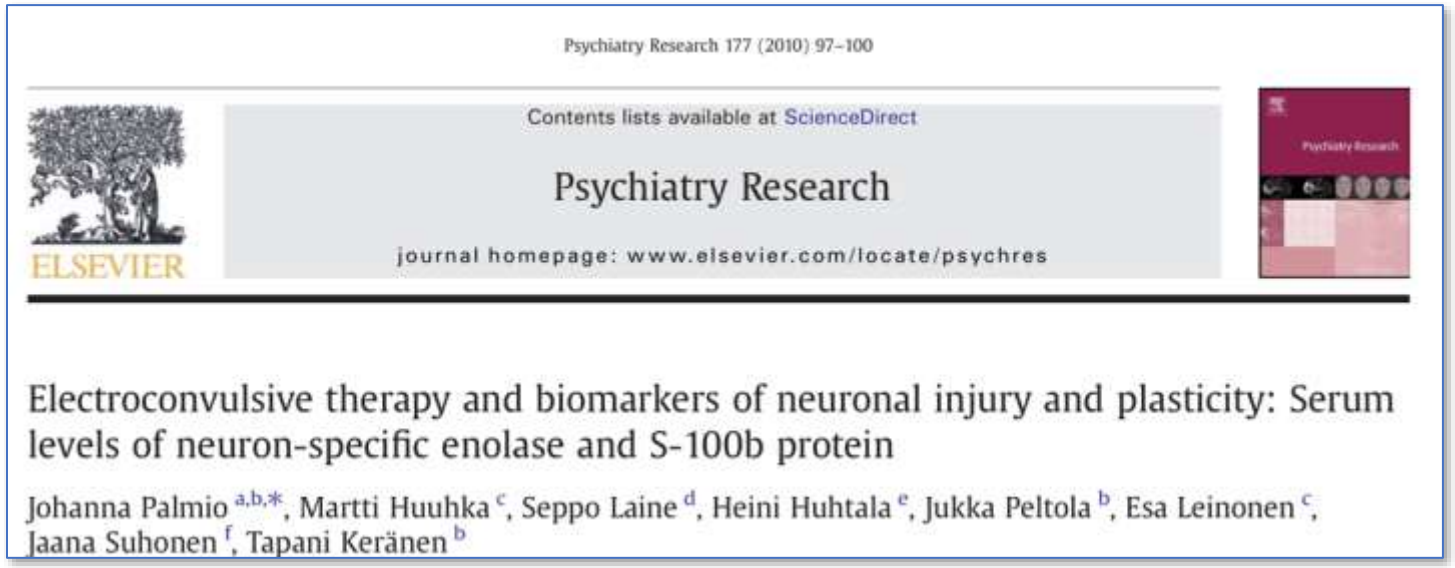
Hjerrild et al. 2021

- 1089 consecutive in-patients with affective disorders, receiving ECT during 1982 to 2000
- 3011 in-patients with affective disorders not treated with ECT
- 108,867 individuals randomly selected from the background population
- Followed for 18 years (median value)
- Matched on sex, age, and the non-ECT cohort was further matched according to diagnoses and admission period and hospital
- Dementia diagnoses from the national patient health registry
- Analyses adjusted for disease severity, somatic, and psychiatric comorbidities

Hjerrild et al. 2021

- Difference between the ECT and the non-ECT cohort:
  - In the ECT cohort: 30% had psychotic depression and 28 % severe depression
  - In the non-ECT cohort: 13% had psychotic depression and 13 % severe depression
- The cumulative incidence of dementia
  - 13.45% (10.75–16.46%) in the ECT cohort
  - 10.53% (8.5–12.81%) in the non-ECT cohort
  - 8.43% (8.17–8.7%) in the background cohort

Specific lab-tests



Psychiatry Research 177 (2010) 97–100

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Electroconvulsive therapy and biomarkers of neuronal injury and plasticity: Serum levels of neuron-specific enolase and S-100b protein

Johanna Palmio [a,b,*], Martti Huuhka [c], Seppo Laine [d], Heini Huhtala [e], Jukka Peltola [b], Esa Leinonen [c], Jaana Suhonen [f], Tapani Keränen [b]

- S100B – Glia activation increase seen in cranial trauma
- Neuron specific enolase (NSE) – sign of neuron death
- Most studies does not show any increase after ECT
- Gbyl et al. in publication

Gbyl & Videbech 2018

ECT – Electroconvulsive therapy

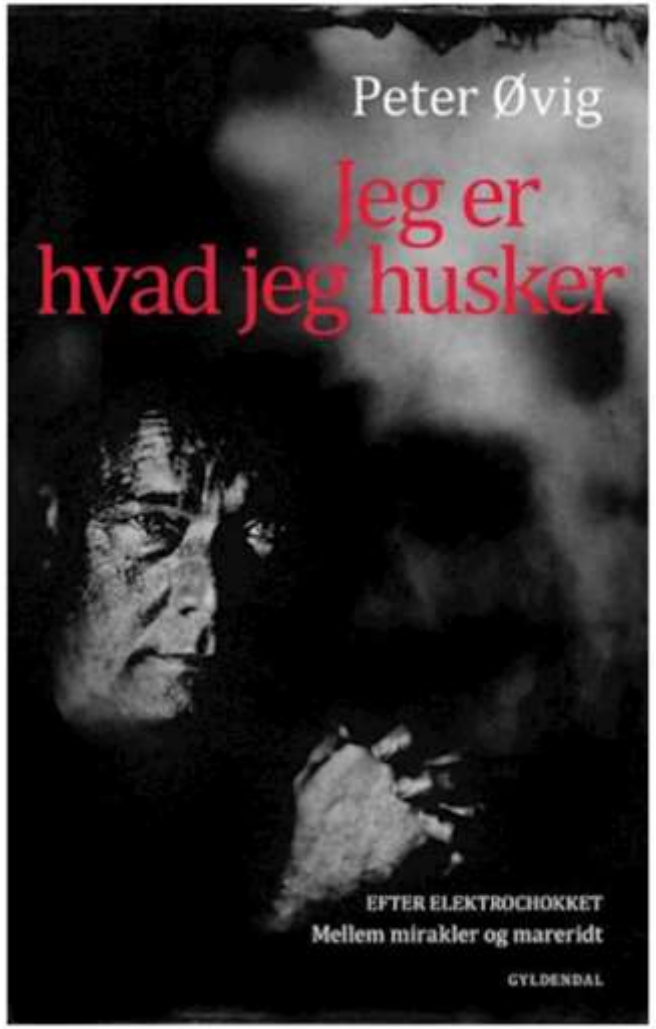
- Used for 80 years
- Highly effective
- Fast acting
- Safe (mortality, dementia)

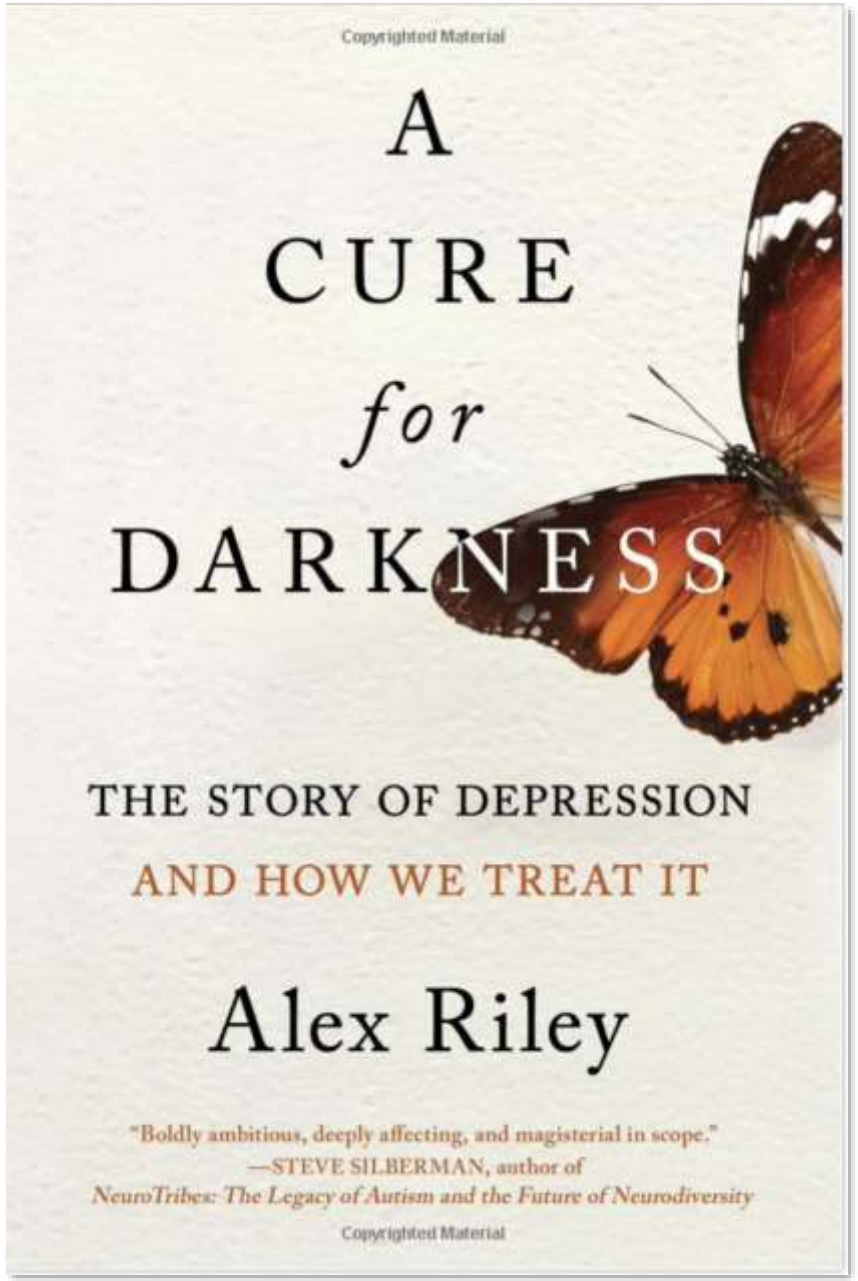
The mechanism of action is unclear

Geddes J et al. Lancet 2003
Kellner CH Acta Psych Scand 2019
Tørring N Acta Psych Scand 2017
Sackeim,HA. JAMA Psychat 2017

A clearer idea of the mechanism may improve ECT-practice

- Making ECT even more effective with fewer side effects
- Finding better biomarkers of response
- Reducing prejudice and stigma

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NeuroTribes: The Legacy of Autism and the Future of Neurodiversity
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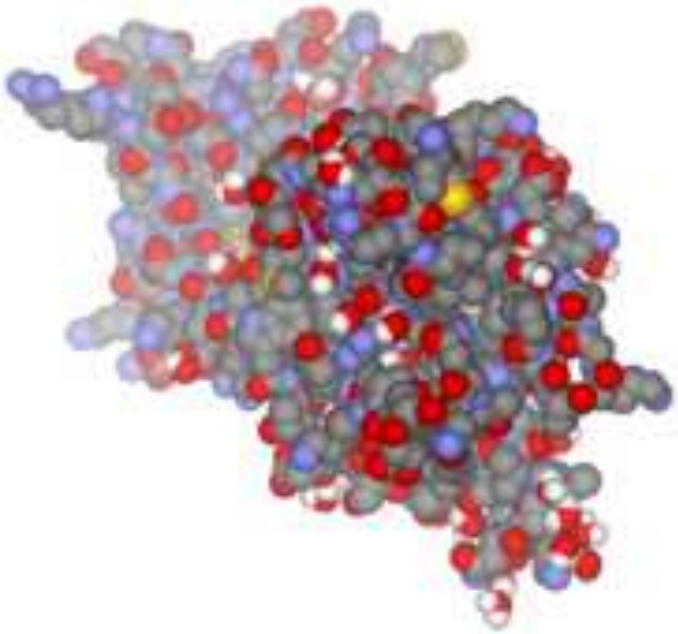
Neurotrophic hypothesis (I)

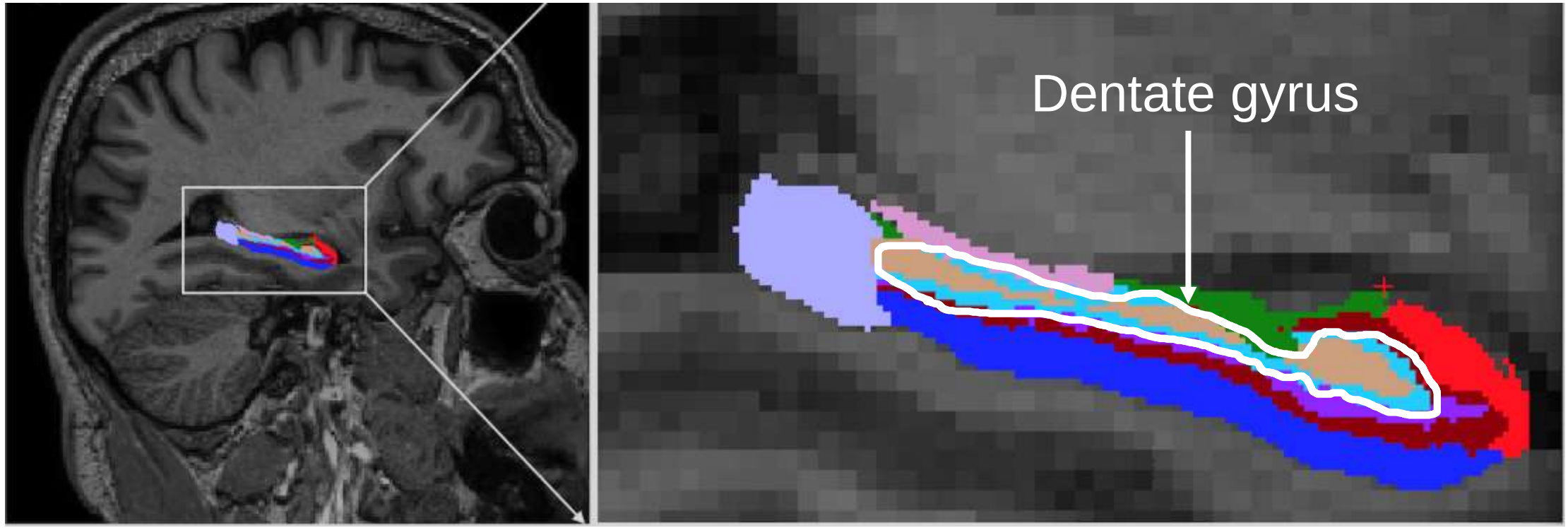
- Brain Derived Neurotrophic factor (BDNF) and VGEF
  - Important for memory
  - Metanalyses: BDNF is low in depression
  - Up to 10% decrease in hippocampal volume on MRI
- After ECT
  - Increases in BDNF, VGEF
  - An increase in hippocampal volume on MRI
- After ECS (in rats)
  - A 2.6-fold increase of neurogenesis in dentate gyrus



Madsen et al 2000
Videbech & Ravnkilde 2005
Bolwig & Madsen 2007, Taylor 2008
Bouckaert F et al. 2014
Olesen MV et al. Hippocampus 2015 & 2017
Eliwa et al. 2017
Chen et al. 2019, 2020
Gbyl & Videbech 2018, Gbyl et al. 2019
Luan et al. 2020
Malberg & Madsen 2021

Neurotrophic hypothesis (II)

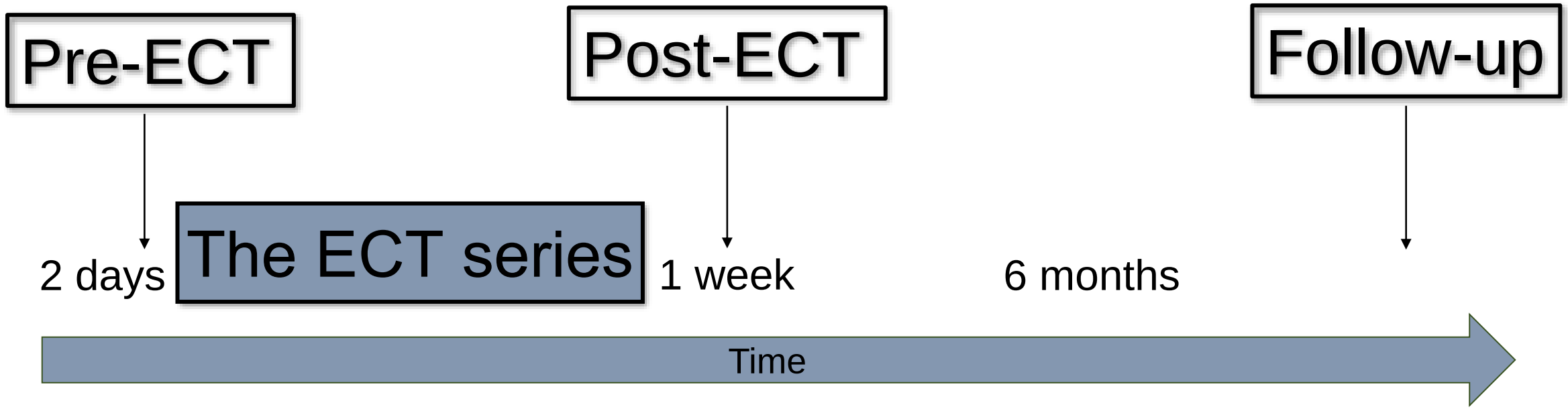
- The clinical effect of ECT is linked to increased neurogenesis
- Neurogenesis is present in human brain throughout life



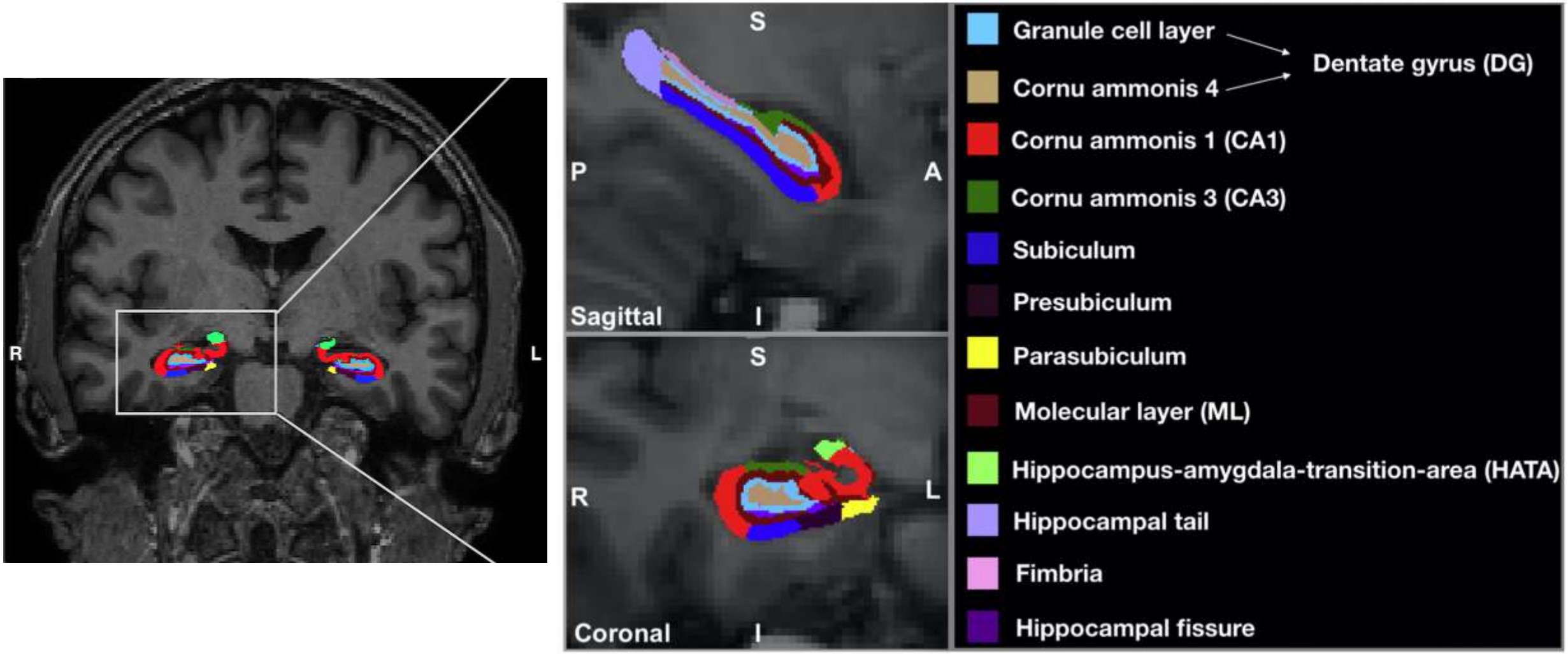
Eriksson PS et al., Nat Med 1998
Fuchs E & Flügge G, Neural Plast 2014

Research questions

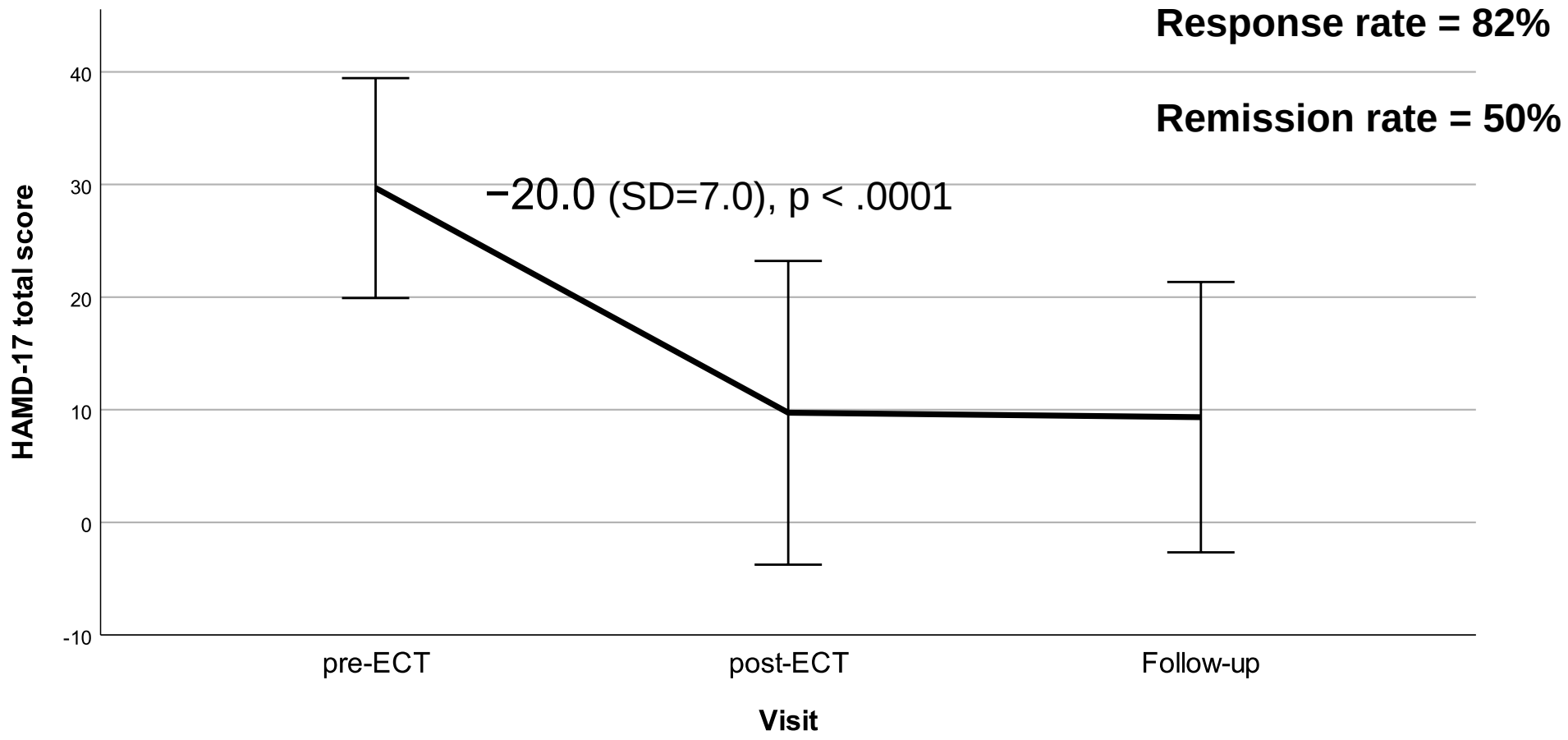
- Hippocampal volume is increased by ECT, but only temporarily, why?
- Only in the dentate gyrus?
- The effect on the cortex?
- Long-term effects?
- Relationship with the clinical effect?
- Can baseline structural MRI predict response?



- Gbyl K, Rostrup E, Raghava JM, Carlsen JF, Schmidt LS, Lindberg U, Ashraf A, Jørgensen MB, Larsson HBW, Rosenberg R, Videbech P. Cortical thickness following electroconvulsive therapy in patients with depression: a longitudinal MRI study. Acta Psychiatr Scand. 2019 Sep;140(3):205-216.
- Gbyl K, Støttrup MM, Mitta Raghava J, Xue Jie S, Videbech P. Hippocampal volume and memory impairment after electroconvulsive therapy in patients with depression. Acta Psychiatr Scand. 2021 Mar;143(3):238-252.
- Gbyl K, Rostrup E, Raghava JM, Andersen C, Rosenberg R, Larsson HBW, Videbech P. Volume of hippocampal subregions and clinical improvement following electroconvulsive therapy in patients with depression. Prog Neuropsychopharmacol Biol Psychiatry. 2021 Jan 10;104:110048.

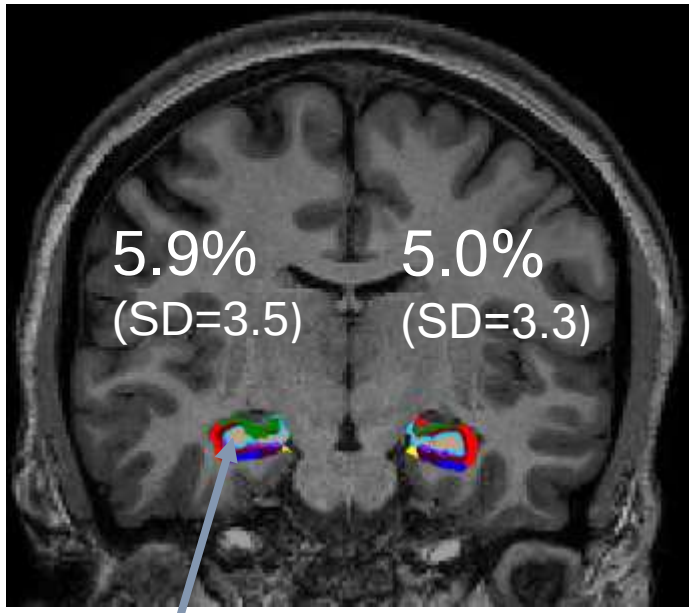

R
L
S
P
A
Sagittal
I
S
R
L
Coronal
I
Granule cell layer
Cornu ammonis 4
Dentate gyrus (DG)
Cornu ammonis 1 (CA1)
Cornu ammonis 3 (CA3)
Subiculum
Presubiculum
Parasubiculum
Molecular layer (ML)
Hippocampus-amygdala-transition-area (HATA)
Hippocampal tail
Fimbria
Hippocampal fissure

Clinical effect of ECT

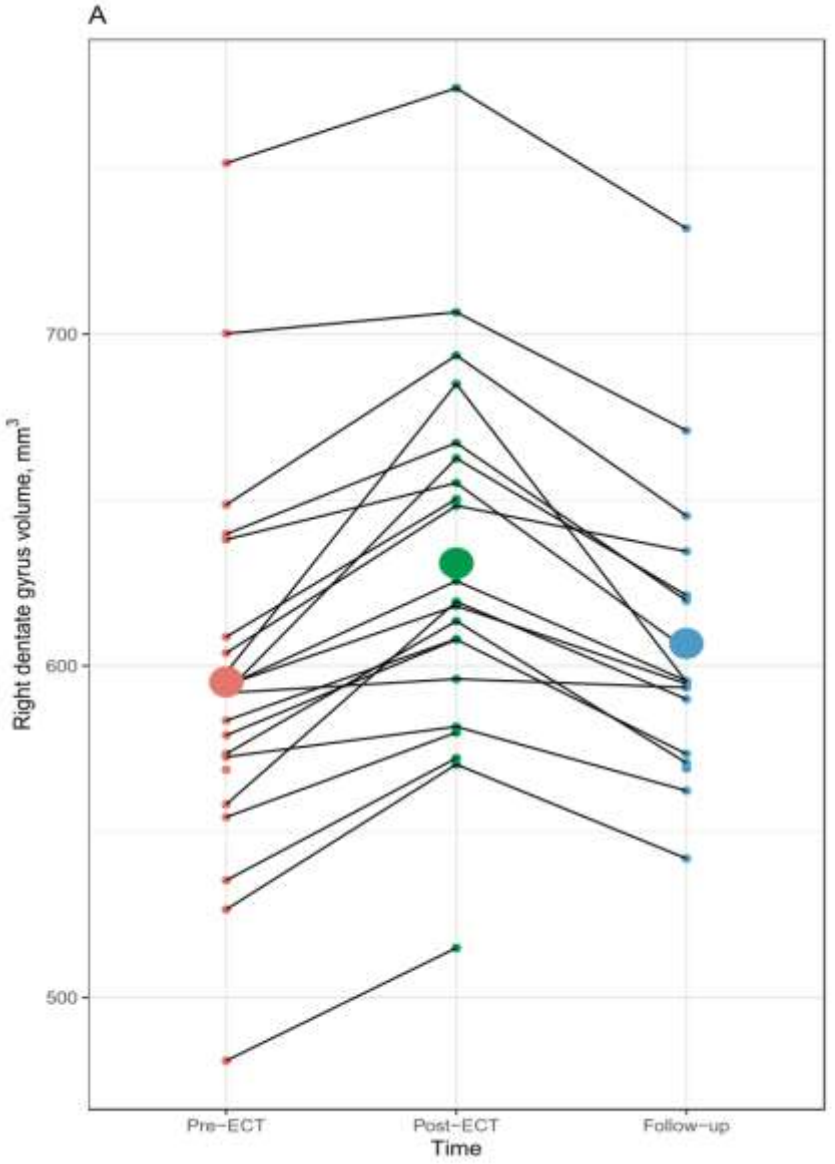


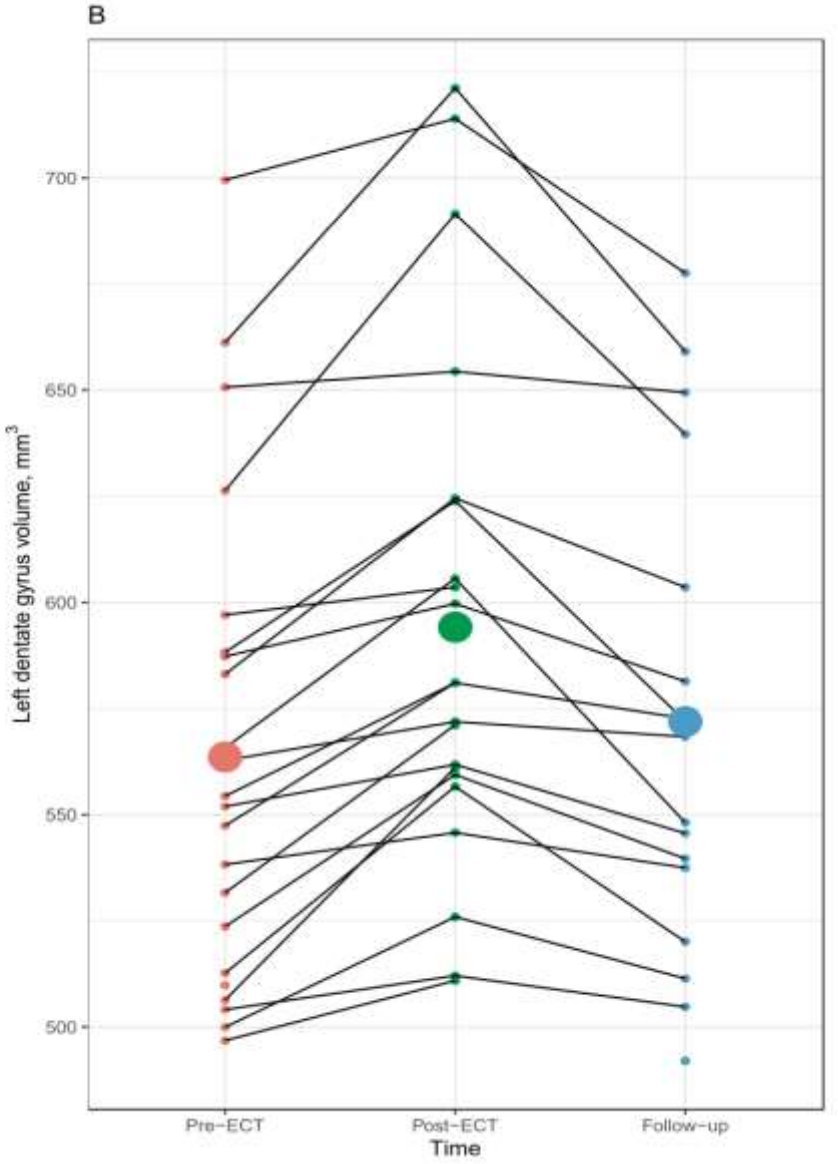
Error Bars: +/- 2 SD

Change in dentate gyrus volume

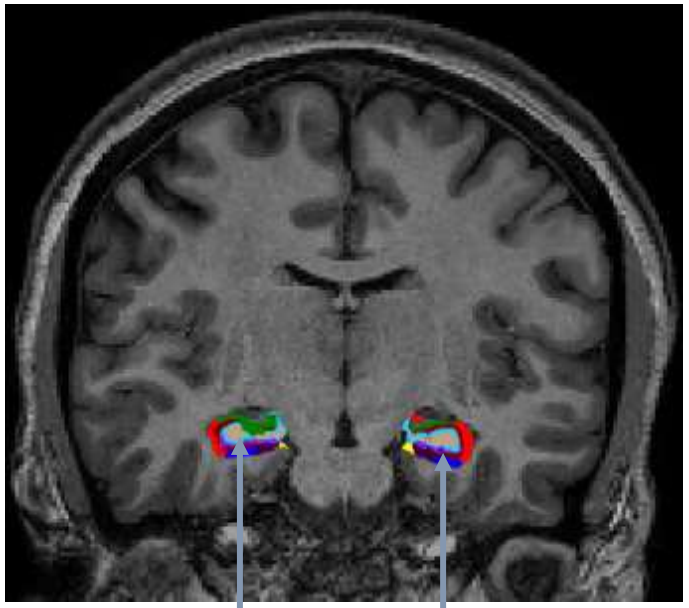


Right dentate gyrus

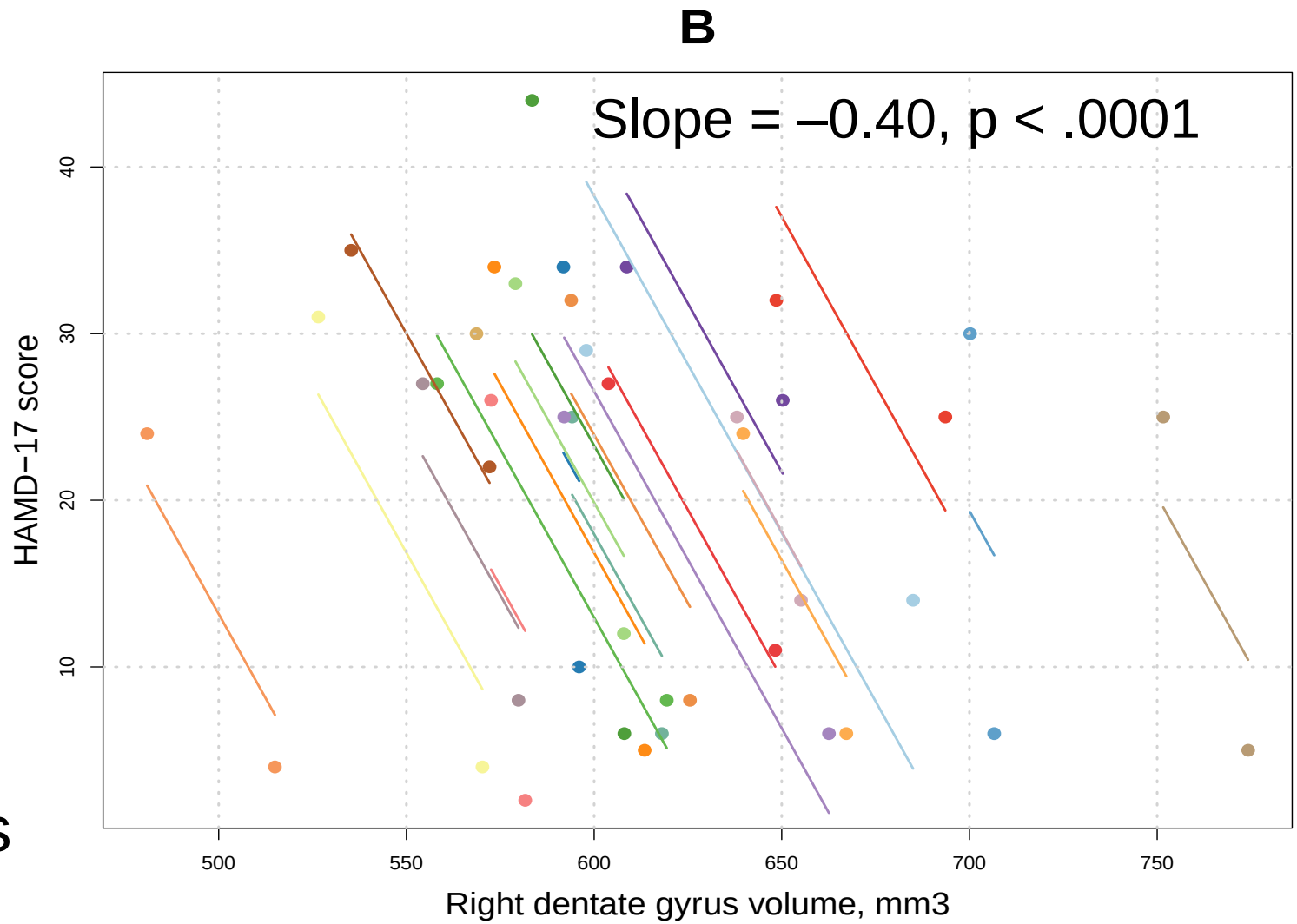




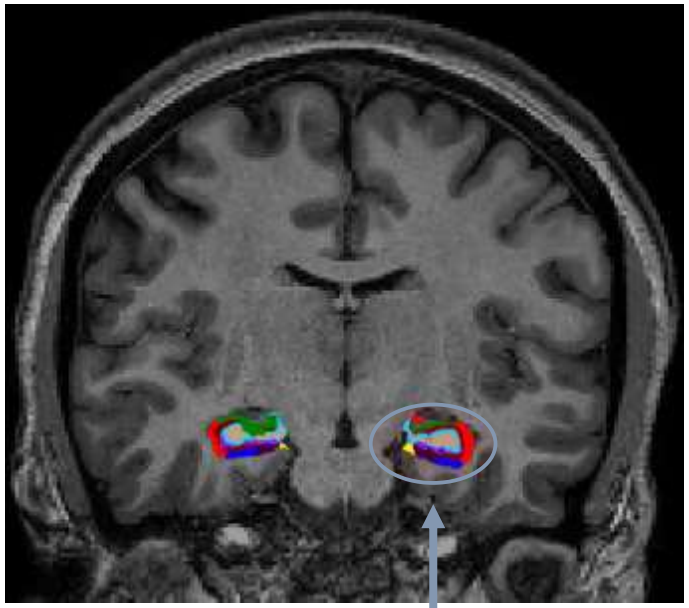
Volume increase correlates with clinical improvement



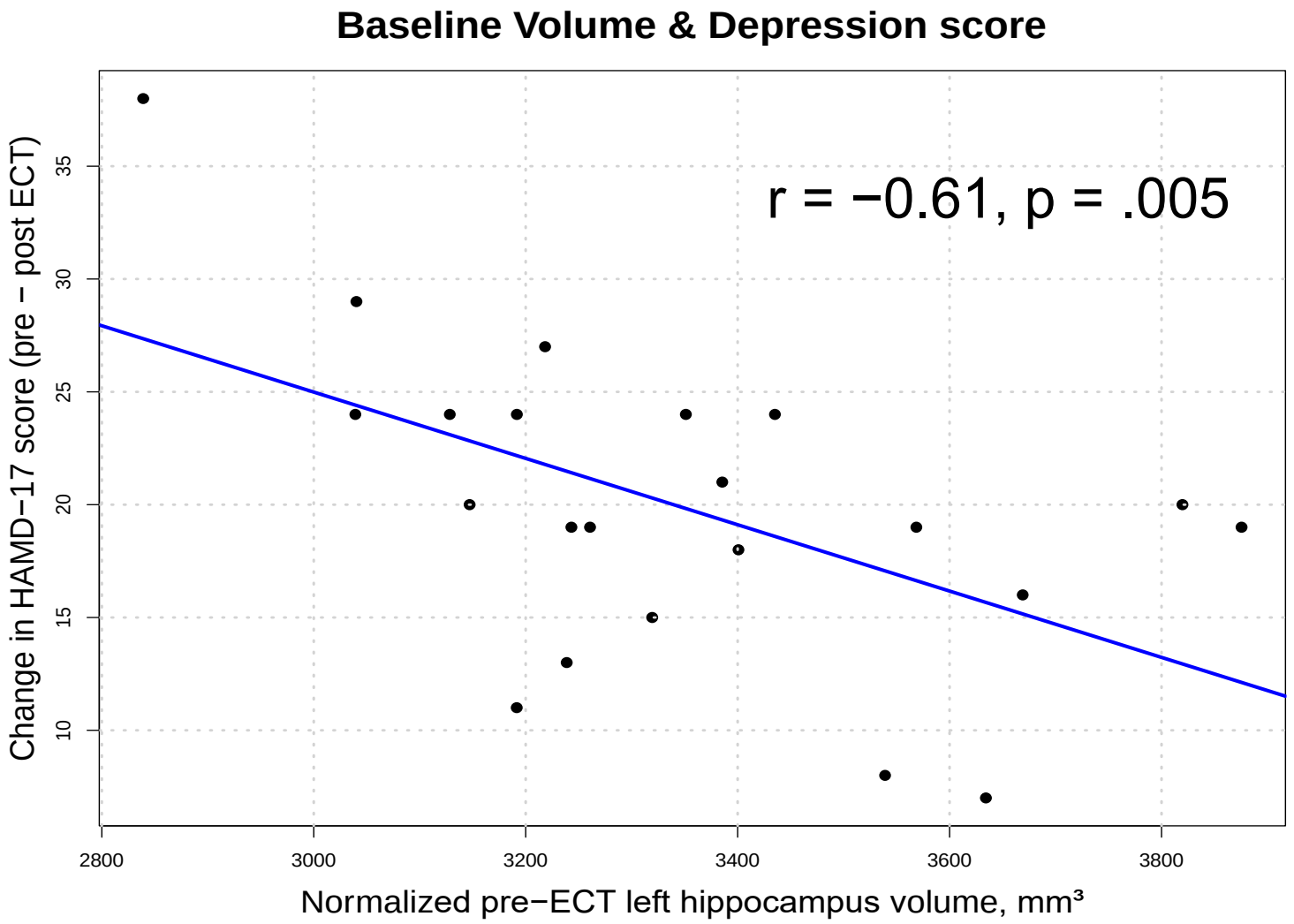
Right & left dentate gyrus



Baseline volume predicts clinical outcome



Left hippocampus

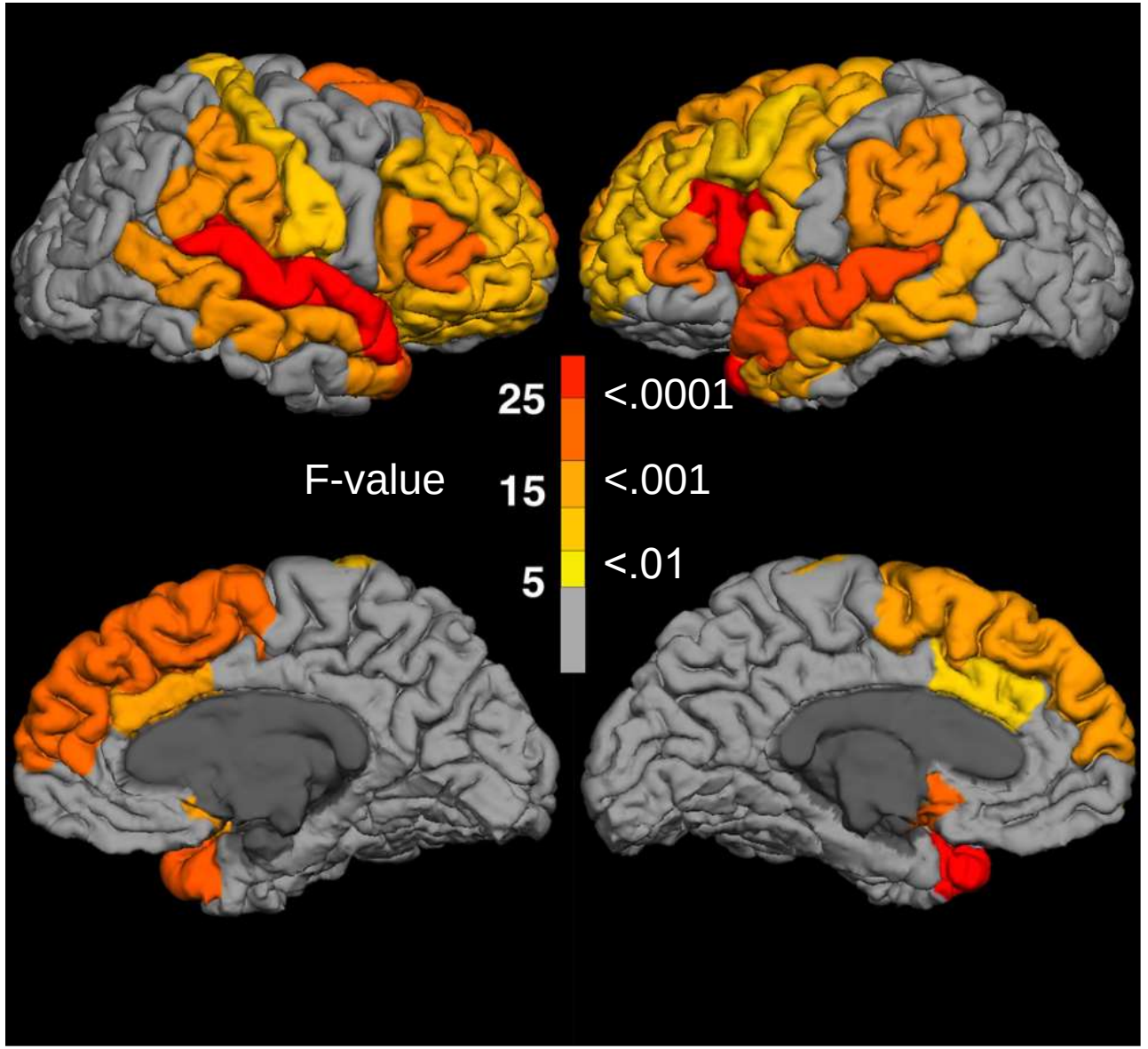


Verbal Memory impairment
Screen for Cognitive Impairment in Psychiatry (SCIP)

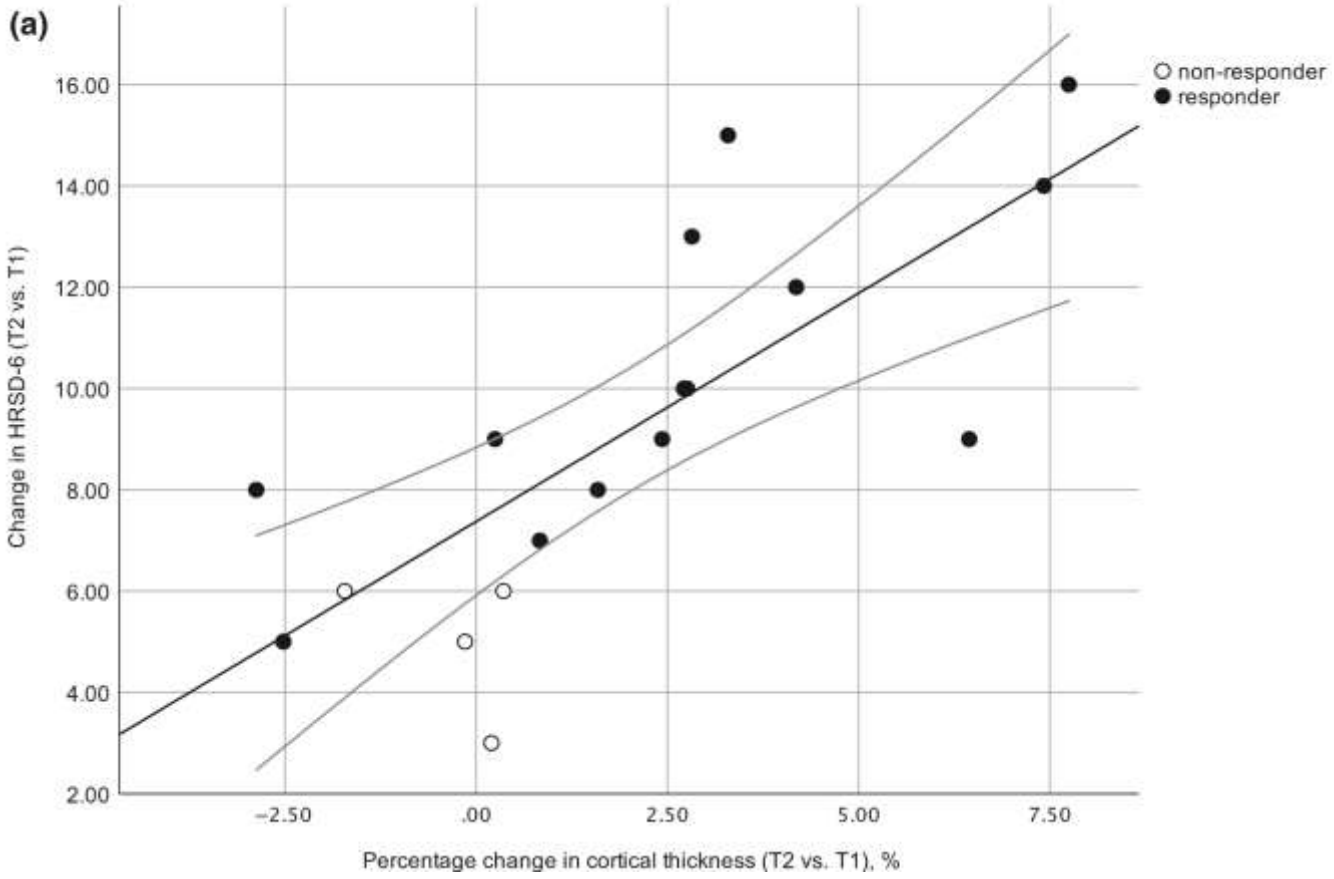
- Repeated measurements statistics (FDR-corrected)
- Correlation between DG volume and reduction in
  - Right DG, $r = -0.85$, df = 18, $p = 0.0000002$
  - Reft DG, $r = -0.58$, df = 18, $p = 0.008$

Change in cortical thickness

- 26 cortical regions
- Frontal & temporal lobe
- Symmetrically distributed
- Increase = 2.3% (SD=0.9)



Right orbitofrontal cortex – Psychomotor retardation



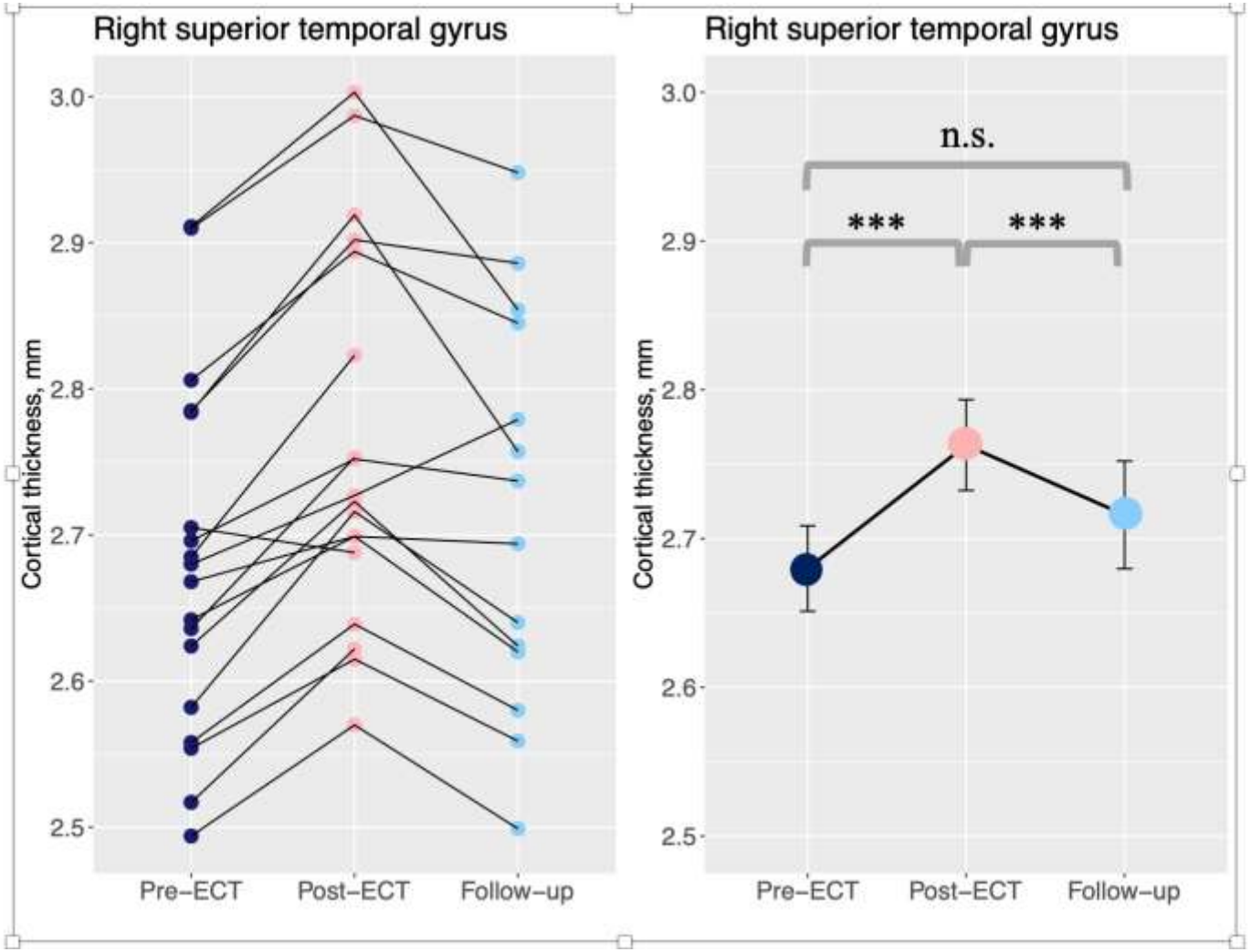
52.9% of the variance of the change in HRSD-6 could be explained by change in OFC thickness

Regression analysis:
A 1% increase in thickness was associated with 0.9 point reduction on HRSD-6 controlling for age (beta = 0.9; 95% CI = 0.5 to 1.3; t = 4.4; P = 0.0005)

Gbyl et al. 2019
Videbech et al. 2002

Change in cortical thickness

Right
superior temporal gyrus



Gbyl et al. 2019

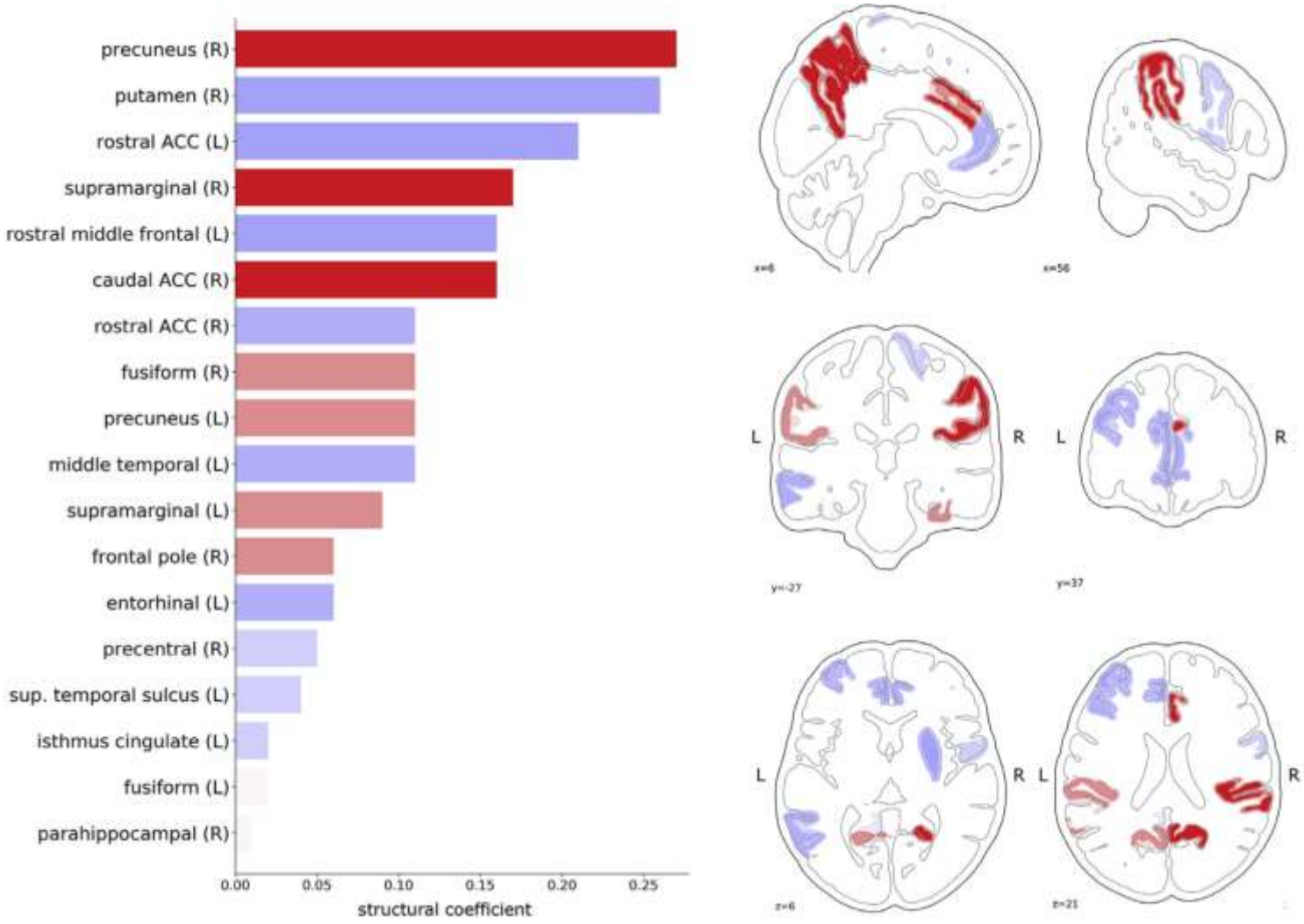
Main findings (Gbyl et al. 2019, 2021, 2021)

1. ECT increase the volume of the DG and most other hippocampal subregions
2. ECT increase the thickness of many cortical (mainly fronto-temporal) areas
3. The increase is correlated with clinical improvement
   - DG change is correlated to poorer verbal memory
4. Smaller baseline hippocampal subregions predicted better outcome
5. Trend for thinner cortical thickness predicting better response
   - No association with cognitive side-effects
6. The increases in volume were temporary

Potential mechanisms

- Edema of the tissue? Not according to studies using
  - DWI & DTI studies
  - DWI & FLAIR (our sample)
  - No edema in relaxometry studies
- Could it be:
  - Neurogenesis – probably not
  - Dendritic branching?
  - Synaptogenesis?
  - Gliogenesis?
  - Angiogenesis?

Madsen TM et al., Biol Psychiatry 2000
Madsen TM et al., Neuropsychopharmacol 2007
Olesen MV et al. Hippocampus 2015
Chen F et al. European Neuropsychopharmacol 2009
Nuninga JO et al., Brain Stimul 2020
Szabo K at al., Neurol Res 2007
Kunigiri G at al., Indian J Psychiat 2007
Nuninga JO et al., Mol Psychiatr 2020



Discriminative map associated with treatment response to electroconvulsive therapy and corresponding structural coefficients.

Multivariate analyses of 192 cases
Red: Increased in responders
Blue: Increased in non-responders

A pattern of structural changes in cortical midline, striatal and lateral PF areas discriminates responders from non-responders (75% accuracy, $p < 0.001$)

Mulders et al 2020

Conclusions

1. ECT increases the GM in most hippocampal subfields and primarily fronto-temporal cortex. These increases are temporary
2. Their mechanisms are elusive; neuroplasticity may be one of them
3. Their relationship with clinical improvement is complex
4. The predictive value of baseline hippocampal volumes requires further research
5. There is no evidence that ECT causes persistent brain damage