Disrupt, Potentiate, and Rewire: A Plausible Model for the Neurobiological Effects of Electroconvulsive Therapy?

Leif Oltedal
Professor, Department of Clinical Medicine, University of Bergen, Norway
Head of the Mohn Medical Imaging and Visualization Centre, Department of Radiology, Haukeland University Hospital, Bergen, Norway

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Disclaimer

AI tools (OpenAI ChatGPT, Claude Opus 4, Elicit, and AI Drive) were used to assist with literature searches, information organization, illustrations, and language editing.

I am not a psychiatrist by training, I am a neuroradiologist

All content, interpretation, and responsibility remain with the author.

Leif Oltedal

Ute Kessler

Olga Therese Ousdal

User panel

Neurostimulation and Brain imaging Research Group (NBiG)

GEMRIC

The Global ECT-MRI Research Collaboration

IMMIV

Global ECT-MRI Research Collaboration 2015-2025

After 10 years:
- **27 sites, 19 publications**
- **4 Bergen workshops, many conferences**
- **N ~ 1000**

GEMRIC
The Global ECT-MRI Research Collaboration

13 international participants from 10 sites

2015

35 participants from USA, Europe and Japan

2018

> 50 participants, 27 groups and 12 countries

2022

>50 participants, 27 groups, 17 GEMRIC sites, 10 countries

2025

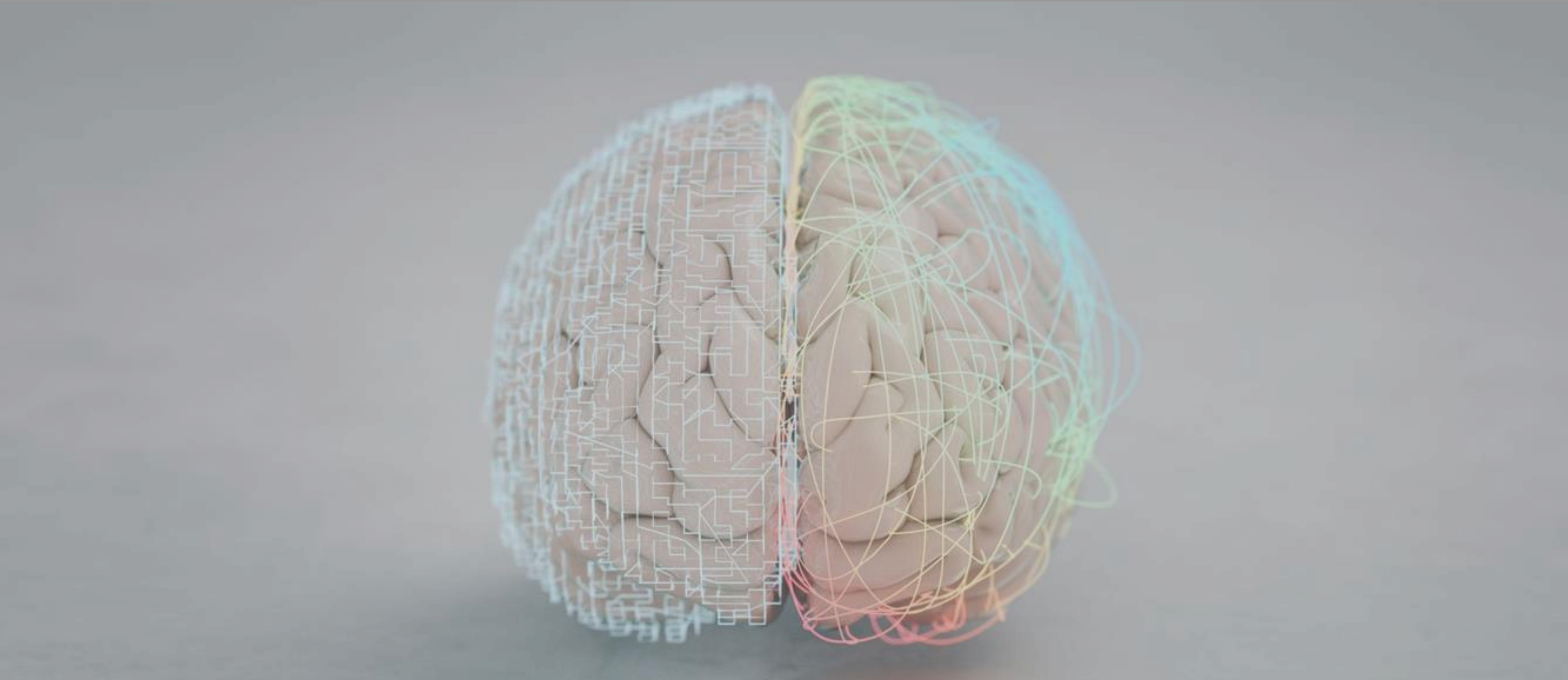
How does ECT work?

- While the procedure has been in use for more than eight decades, the mechanism of action remains unknown

Mean sentence:
Despite decades of research and its well-established clinical efficacy, the neurobiological mechanisms of action underlying the antidepressant effects of electroconvulsive therapy remain incompletely understood.

- While the precise neurobiological impact of ECT remains incompletely understood, but it is believed to operate through various mechanisms.

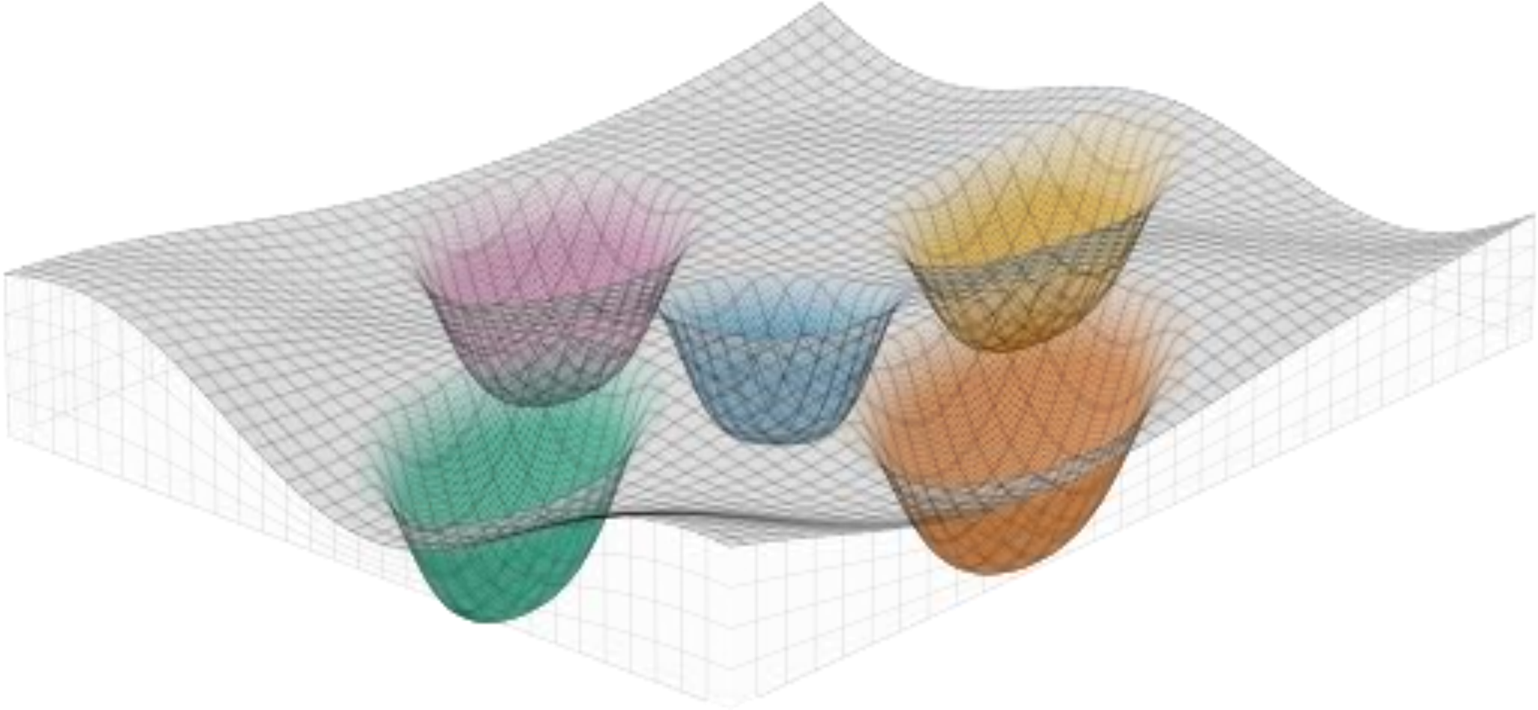
How does the brain work?



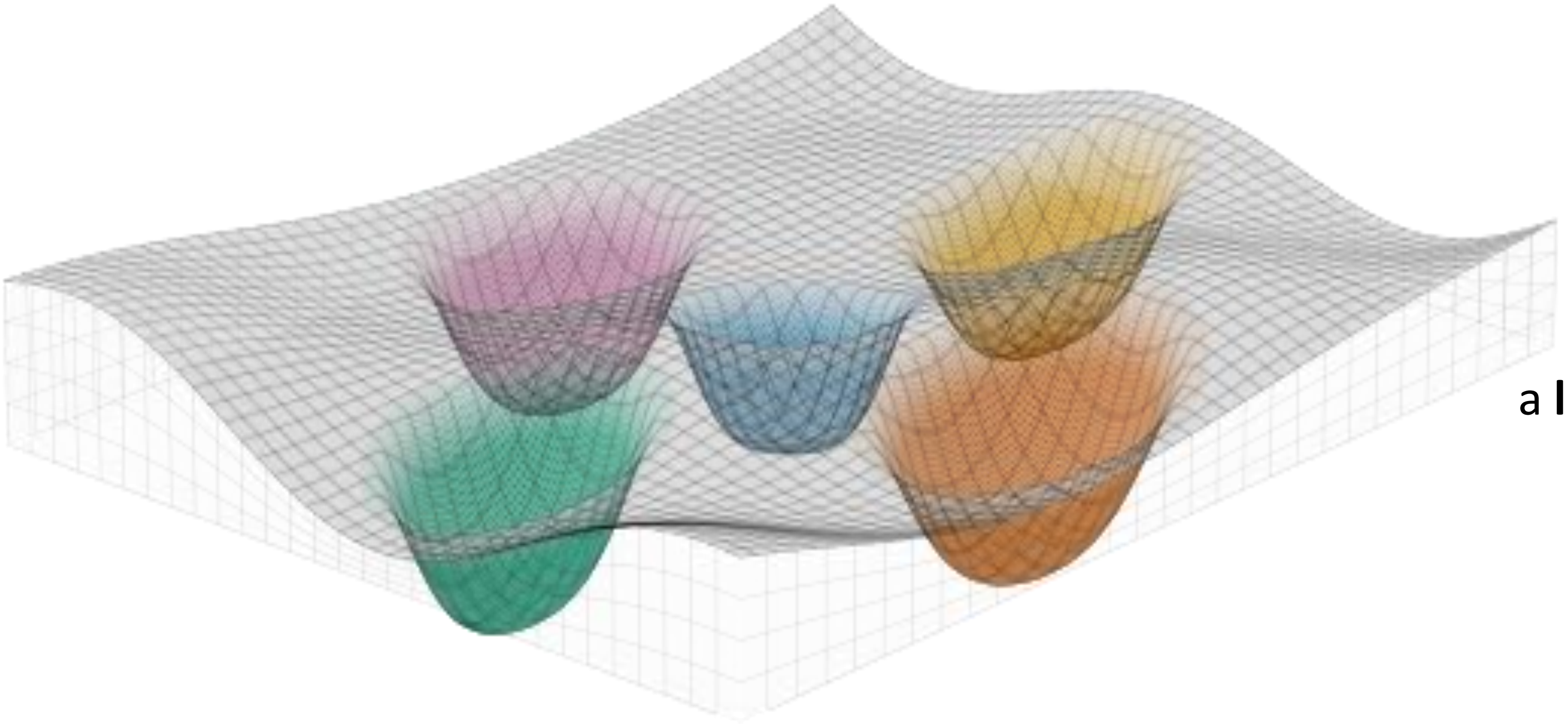
A brain network's view of brain function

«(...) our understanding of the principles and mechanisms underlying complex brain function and cognition remains incomplete. **Network neuroscience** proposes to tackle these enduring challenges.»

Bassett, D. S., & Sporns, O. (2017). Network neuroscience. ***Nat Neurosci***



A brain network's view of brain function



a **landscape of possible brain states**

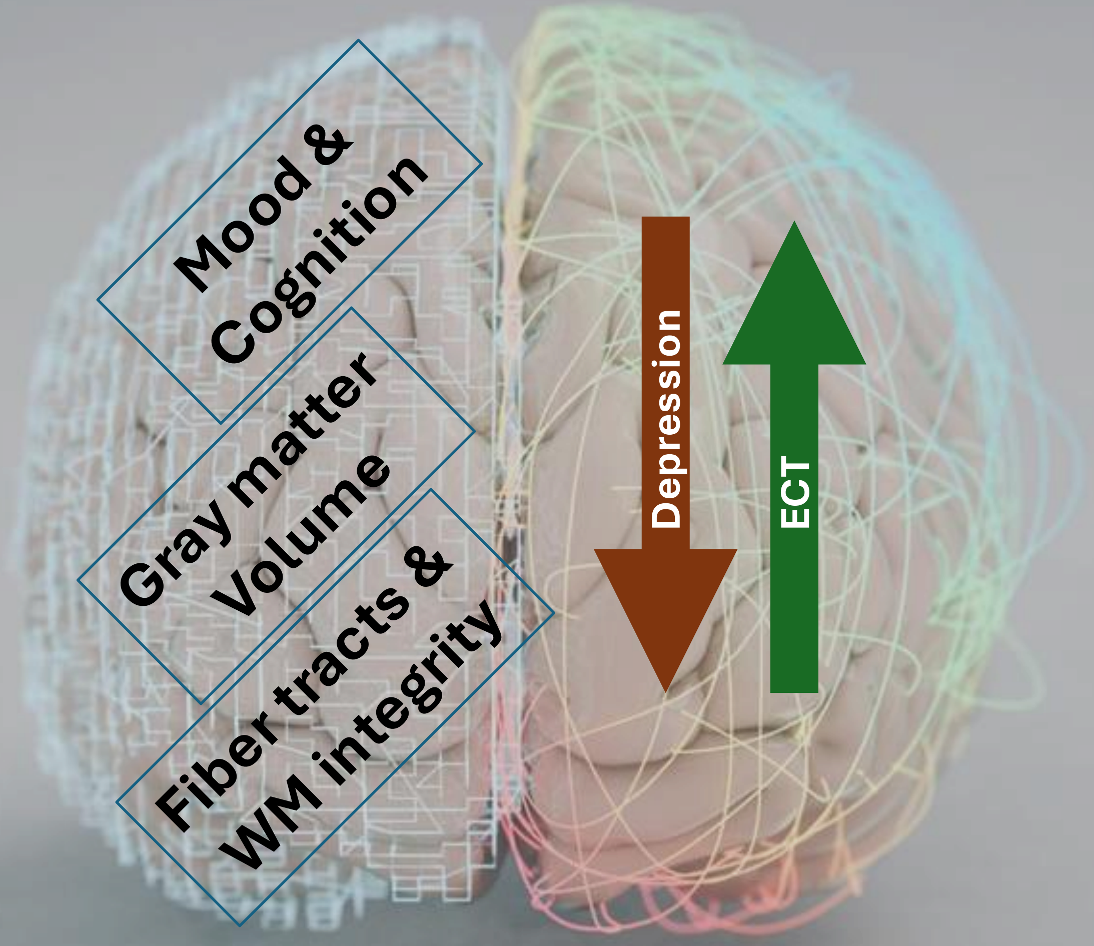
Each basin = a preferred network state
The depth of the basin = how stable or "attractive" that state is
The distance between basins = how easy or difficult it is to shift into another state
The overall landscape = the brain's global organization across many interacting networks

ECT Conceptual Model

Disrupt
maladaptive locked network activity

Potentiate
neuroplasticity

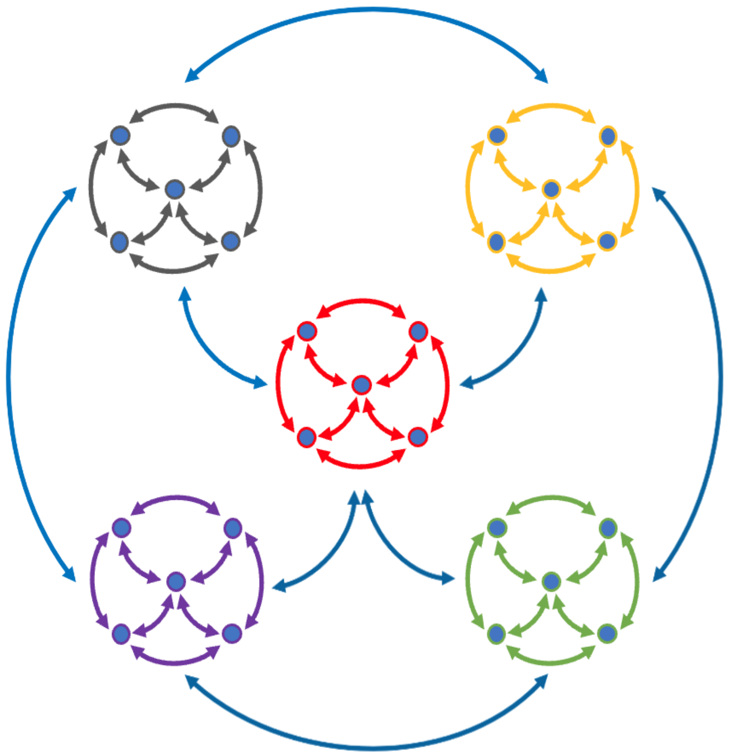
Rewire
neuronal connections and networks



A brain network's view of brain function

Depression as a neuronal network disorder - an imbalance in the brain's networks

A homeostatic brain state



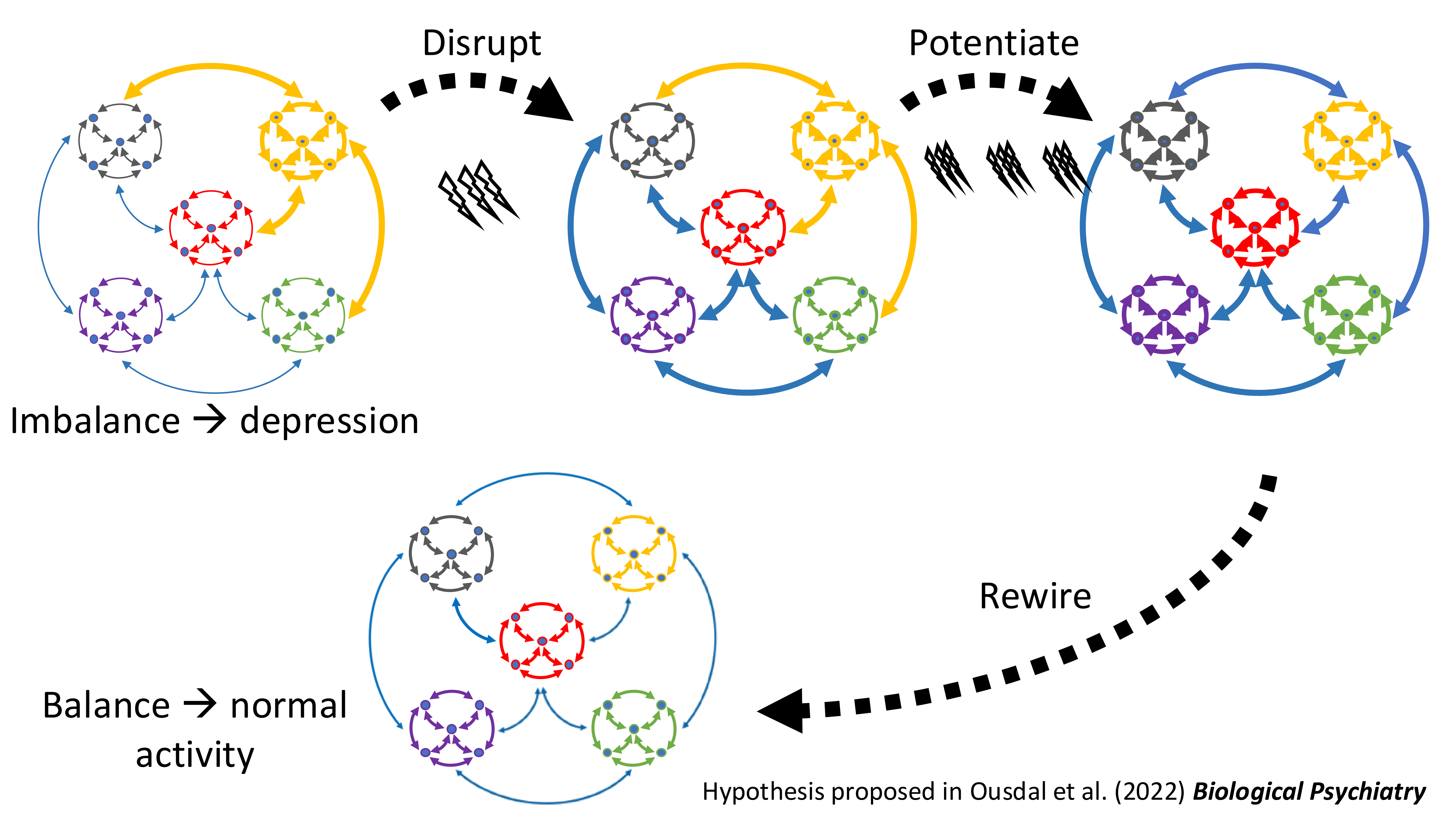
A

balanced dynamic equilibrium

«…highlight the central importance of homeostatic control of mood circuit connections and form the basis of a synaptogenic hypothesis of depression and treatment response.»

Duman, R. S., & Aghajanian, G. K. (2012). **Science**

Neuronal network disorder



Disrupt
Potentiate
Imbalance → depression
Rewire
Balance → normal activity
Hypothesis proposed in Ousdal et al. (2022) ***Biological Psychiatry***

Do we need yet another theory on how ECT works?

Existing theories

- Do not fully account for *disruptive effects*
- Do not explain the *temporal sequence* of changes
- Do not capture ECT's *broad mechanism of action*

A useful theory should also explain

- Why ECT works especially well in rigid or "locked" disorders
- Why ECT has such a broad therapeutic spectrum

Do we need yet another theory on how ECT works?

Hypothesis:

Severe depression may be one of many Locked Neuronal Network Disorders (NND)

Phase	Main Driver	Mechanism	Outcome
Disruption	Charge, pulse form, electrode placement, electric field	Seizure acutely disrupts pathological networks (locked neuronal depression networks)	Circuit destabilization
Potentiation	Brain's neurobiological response	Increased neuroplasticity, e.g. synaptic growth	Window of heightened plasticity
Rewiring	Patient's thoughts, emotions, experiences, and behavior	Strengthening of new connections and adaptive network activity during recovery	Network reorganization, a balanced flexible brain state, symptom relief

Advantages of the model

- Explains treatment efficacy, side effects, and relapse mechanisms
- Simple and intuitive for patients, clinicians, and researchers
- The model can be tested experimentally

Disrupt maladaptive locked network activity	**Potentiate** neuroplasticity	**Rewire** neuronal connections and networks

Hypothesis	Key Concept	References
Anticonvulsant D R	↑ seizure threshold, ↑ inhibitory tone in hyperactive (depressive) brain regions	(Sackeim 1999; Sackeim, Decina, … & Resor 1983)
Neurotransmitter D P R	alters brain chemistry of monoamines (5HT, DA, NE), GABA, glutamate	(Baldinger et al. 2014; Bergstrom & Kellar 1979)
Neuroendocrine D R	↑ hormones from the HPA axis (ACTH, cortisol), → endocrine homeostasis	(Fink & Ottosson 1980; Haskett 2014)
Neurotrophic P	↑ neuroplasticity, reversing stress-related atrophy and synaptic loss (hipp)	(Duman & Monteggia, 2006; Madsen et al. 2000; Segi-Nishida 2011)
Connectivity D R	disrupts and resets dysfunctional large-scale brain networks (e.g., DMN, Limbic)	(Farzan et al. 2014; Perrin et al. 2012)
Immuno-inflam. D R	transiently ↑ immune response → long-term anti-inflammatory shift	(van Buel et al. 2015) (Yrondi et al. 2018)

ECT Conceptual Model: Disrupt – Potentiate – Rewire

DPR – across time

Disrupt
maladaptive locked network activity

Potentiate
neuroplasticity

Rewire
neuronal connections and networks

ECT session level

ECT series level

ECT follow up level

TP1: Before
TP2: 2 hours after one session

TP3: After treatment series

TP4: 6mo follow up

ECT Conceptual Model: Disrupt – Potentiate – Rewire

DPR – candidate biomarkers across modalities

	Disrupt maladaptive locked network activity	**Potentiate** neuroplasticity	**Rewire** neuronal connections and networks
Clinical	confusion, postictal effects rapid symptom relief ↓ cognitive performance	↓/↑ cognitive performance increased behavioral plasticity? disrupted memory consolidation	cognitive performance improves symptom improvement memory function improves
Brain	disrupted blood brain barrier postictal suppression on EEG edema on MRI? ↓ fiber integrity/connectivity ↓/- neuronal integrity?	↑cortical excitability (TMS-EEG) ↑ hippocampal volume on MRI ↓/↑ fiber integrity ↓/↑ connectivity ↓/↑ neuronal integrity	normalized cortical excitation ↓ volume on MRI ↑ fiber integrity change FC in alpha and beta freq normal neuronal integrity
Immune, endocrine	↑ inflammation, cortisol	↑/↓ inflammation, cortisol	↓ inflammation, cortisol

ECT has a broad therapeutic spectrum

MDD is clinically heterogeneous

227 symptom combinations satisfy DSM-5 criteria for a major depressive episode

545 symptom combinations meet minimum ICD-11 criteria for a depressive episode

highly variable and multifactorial etiology

ECT

broad and non-specific mode of action
generalized effects on the brain and body

Does ECT work beyond affective disorders?

Study name — **Statistics for each study** — **Std diff in means and 95% CI**

Study name	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value
Anderson et al. (1987)	0.318	0.098	0.127	0.510	3.256	0.001
Fall et al. (2000)	0.515	0.137	0.246	0.785	3.751	0.000
Pintor et al. (2012)	0.657	0.116	0.429	0.884	5.650	0.000
Pridmore et al. (1995)	0.880	0.372	0.150	1.610	2.363	0.018
Usui et al. (2011)	1.004	0.137	0.735	1.273	7.323	0.000
Grover et al. (2018)	1.044	0.160	0.730	1.359	6.507	0.000
Douyon et al. (1989)	1.100	0.151	0.803	1.397	7.264	0.000
Ueda et al. (2010)	1.111	0.180	0.759	1.464	6.178	0.000
Calderón-Fajardo et al. (2015)	1.197	0.086	1.028	1.366	13.856	0.000
Birkett. (1991)	1.331	0.184	0.950	1.711	6.852	0.000
Williams et al. (2017)	1.342	0.178	0.993	1.691	7.541	0.000
Fall et al. (1995)	2.059	0.140	1.785	2.332	14.745	0.000
Nishioka et al. (2014)	3.647	0.437	2.790	4.504	8.339	0.000
	1.181	0.157	0.873	1.489	7.509	0.000

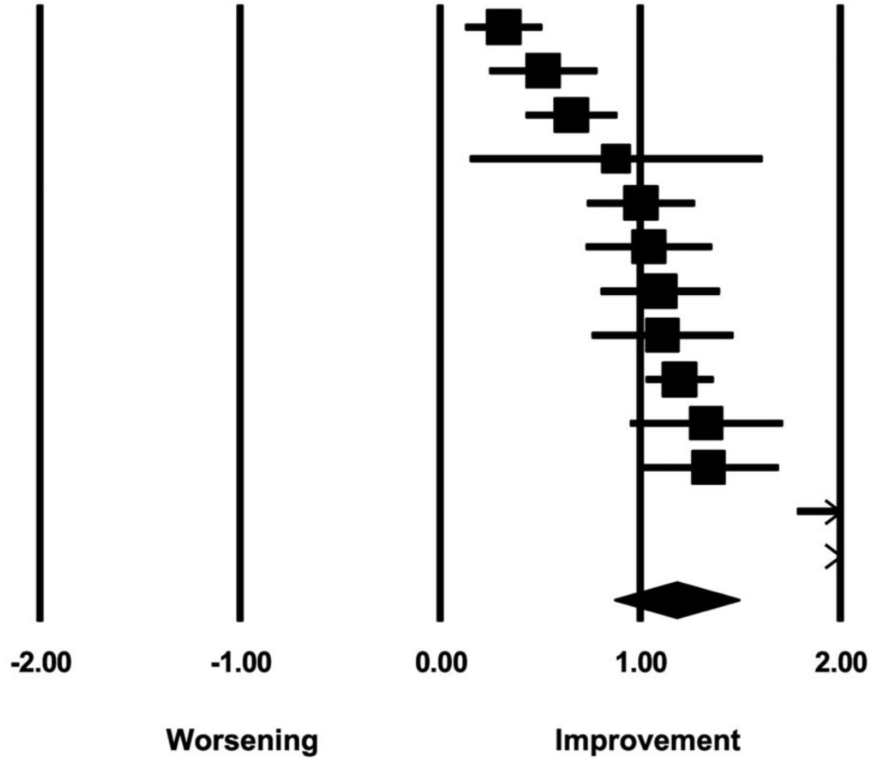
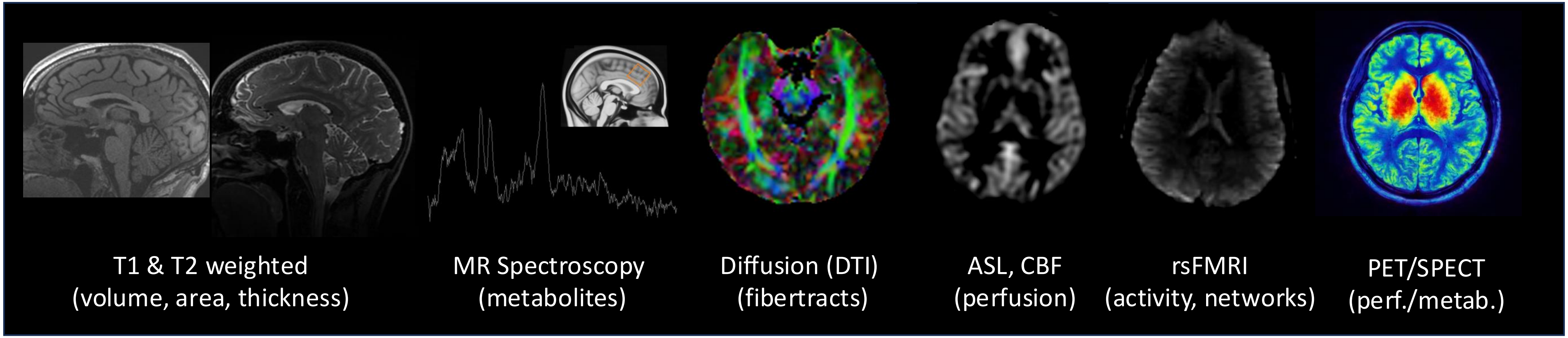


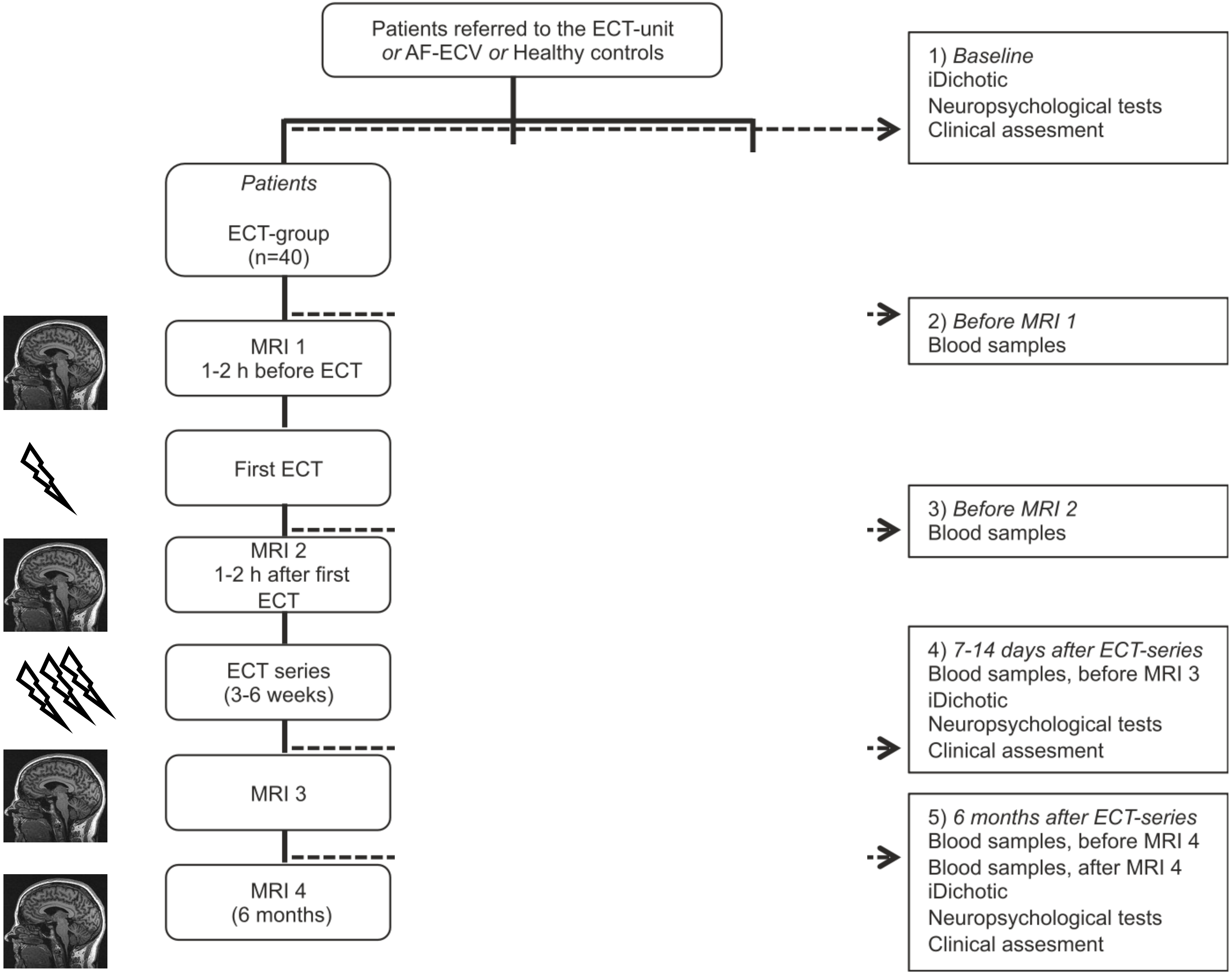
FIG. 1. Changes in motor function before and after electroconvulsive therapy. Squares are the effect size of single studies, and diamonds are pooled results. Std diff, standardized mean differences.

Takamiya, A et al. (2021). Electroconvulsive Therapy for Parkinson's Disease: A Systematic Review and Meta-Analysis. *Mov Disord.*



Neuroimaging, MRS, and dMRI of the brain after ECT

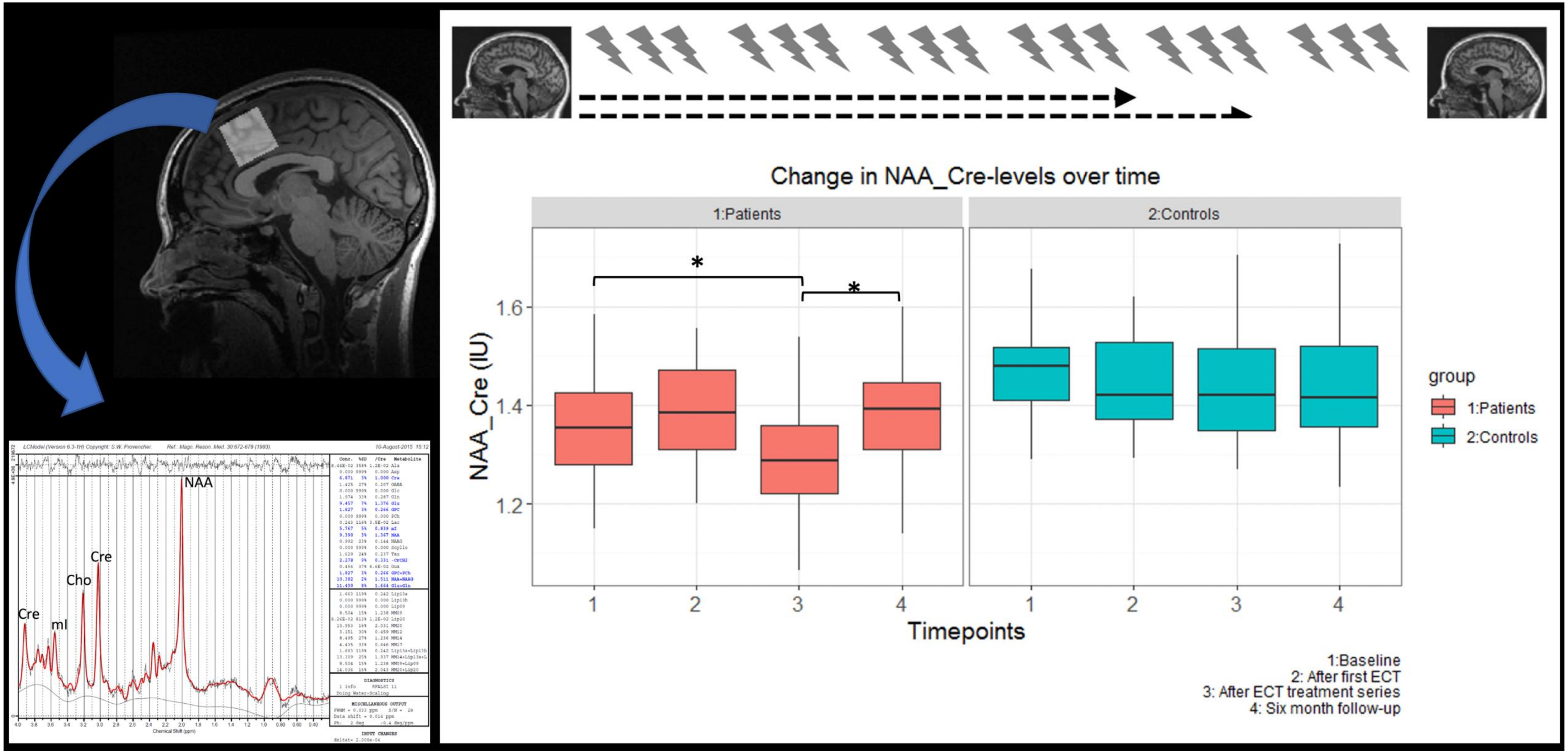
Is there support for the DPR model?


Patients referred to the ECT-unit
or AF-ECV or Healthy controls
Patients
ECT-group
(n=40)
MRI 1
1-2 h before ECT
First ECT
MRI 2
1-2 h after first ECT
ECT series
(3-6 weeks)
MRI 3
MRI 4
(6 months)
1) Baseline
iDichotic
Neuropsychological tests
Clinical assesment
2) Before MRI 1
Blood samples
3) Before MRI 2
Blood samples
4) 7-14 days after ECT-series
Blood samples, before MRI 3
iDichotic
Neuropsychological tests
Clinical assesment
5) 6 months after ECT-series
Blood samples, before MRI 4
Blood samples, after MRI 4
iDichotic
Neuropsychological tests
Clinical assesment

Disrupt
maladaptive locked network activity

Signs of disruption on MRS

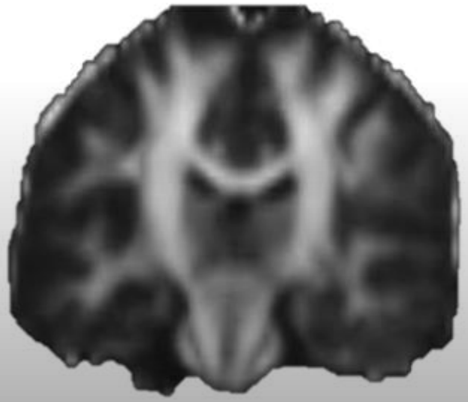
MRS before, during, and after ECT: NAA reduction following an ECT series



Erchinger et al. (2023) ***Frontiers in Psychiatry***

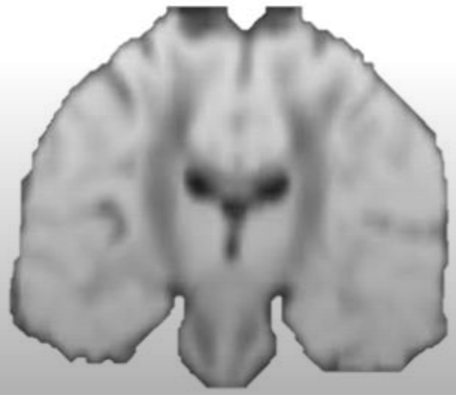
Restriction Spectrum Imaging (RSI)

Microstructure (subvoxel-level)



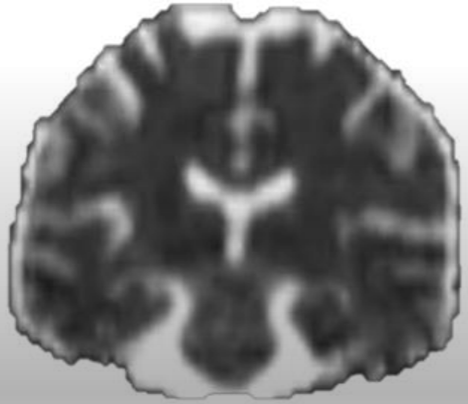
Intra-cellular/-axonal

(Restricted)



Extra-cellular

(Hindered)

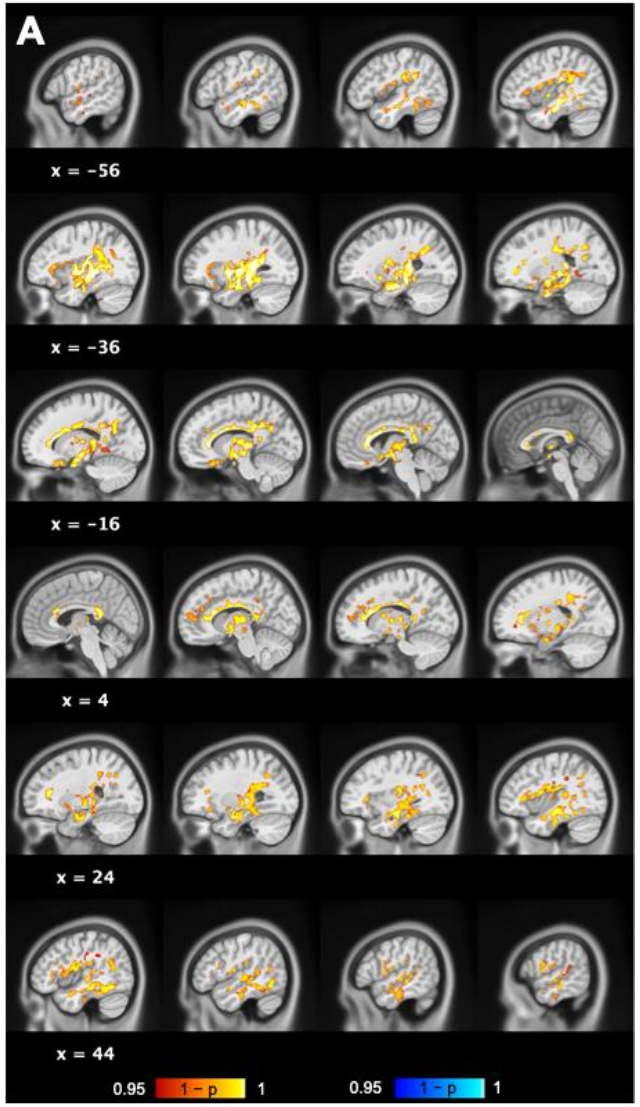


Free water

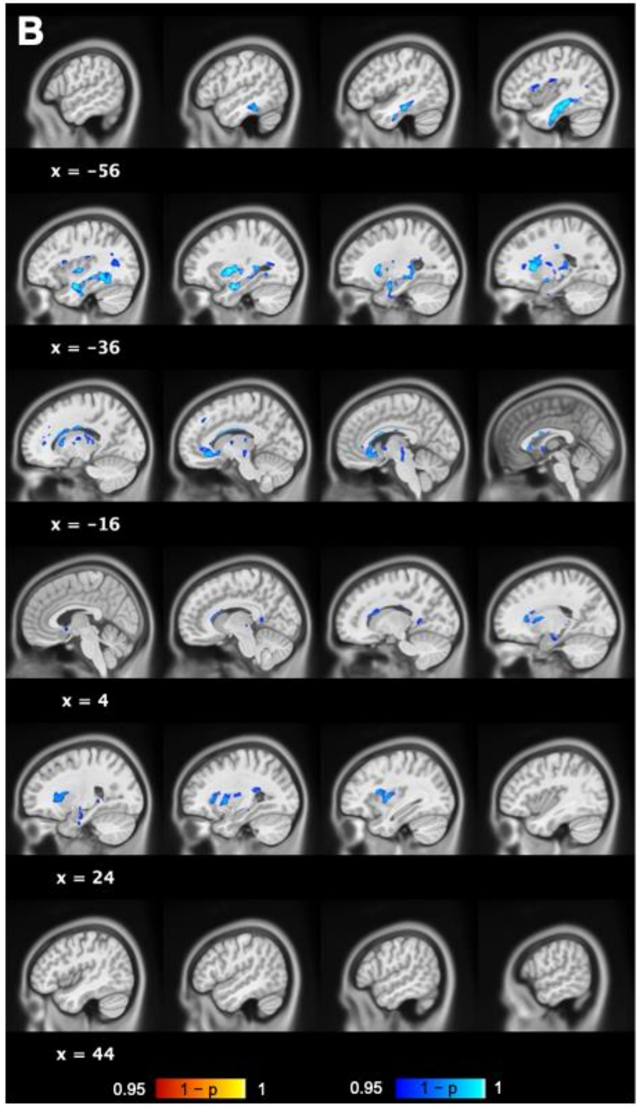
(Isotropic)

Disrupt
maladaptive locked network activity

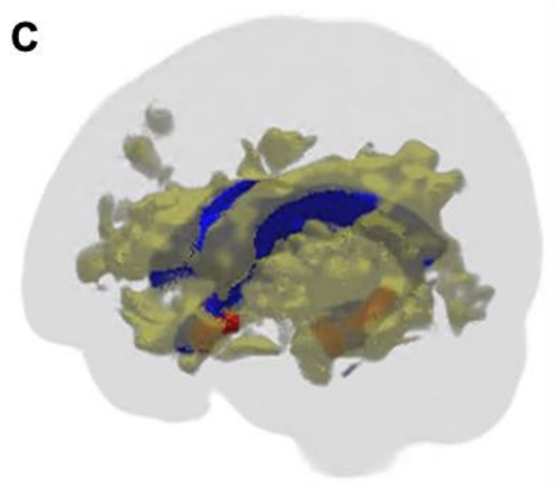
Signs of disruption on dMRI
RSI 2 hours after a single ECT seizure



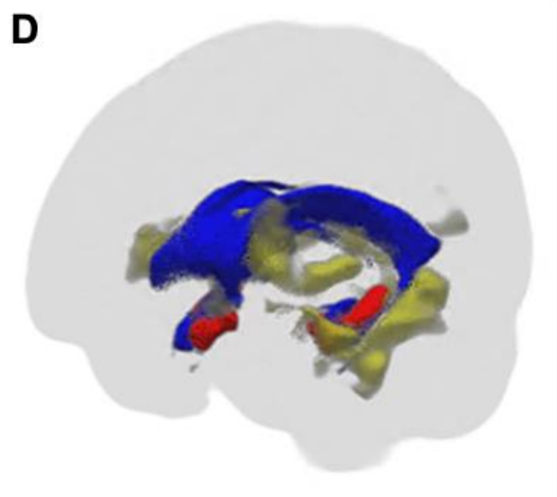
increased free water



decreased restricted diffusion



free water



restricted diffusion

Takamiya et al. (2025) ***Brain Stimulation***

Acute vasogenic edema (?) 2 hours after ECT

- increased free water/mean diffusivity
- decreased intracellular diffusion
- not observed in healthy control subjects
- not observed after anesthesia only
- resolved within 7–14 days, not detectable at 6 months

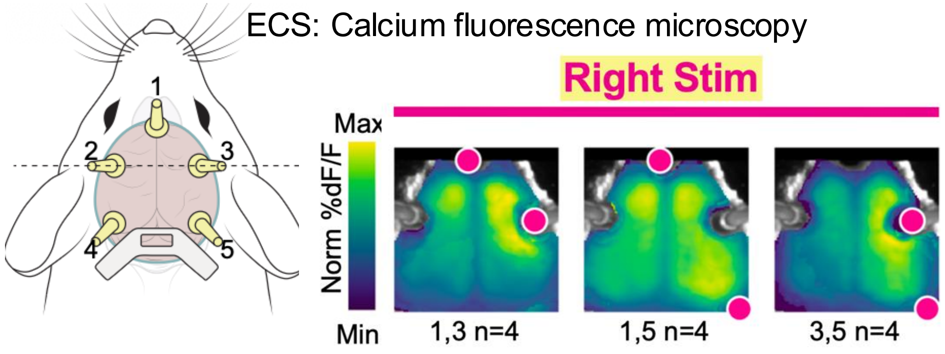
Takamiya et al. (2025) ***Brain Stimulation***

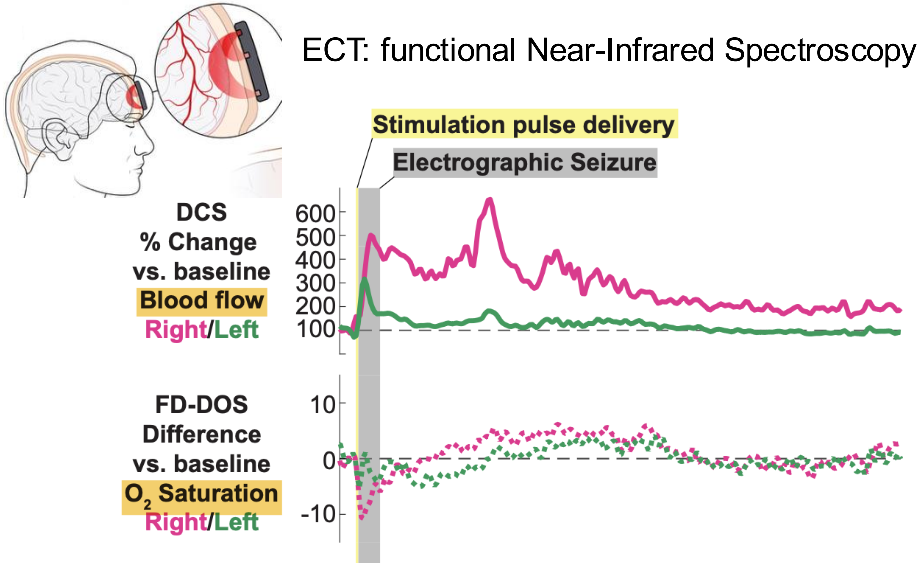
Disrupt
maladaptive locked network activity

Other (Neuroplastic) Mechanisms

- Cortical Spreading Depolarization (CSD)
  - slow wave of depolarization, after seizure
  - shaped by ECT stimulus

  → EF, Seizure, and CSD driving the neurobiological and clinical effects?
  - CSD known to occur after epileptic seizure, in migraine aura, stroke, TIA, SAH, TBI, ..
- Mechanism of CSD after ECT/ECS?
  - stimulating neuroplasticity, inhibitory surge, seizure termination mechanism?
  - disruptive on memory formation? (Paolino et al 1971 *Science*)



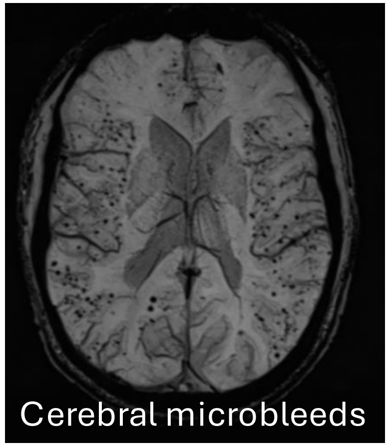


Rosenthal et al. (2025) *Nature Communications*

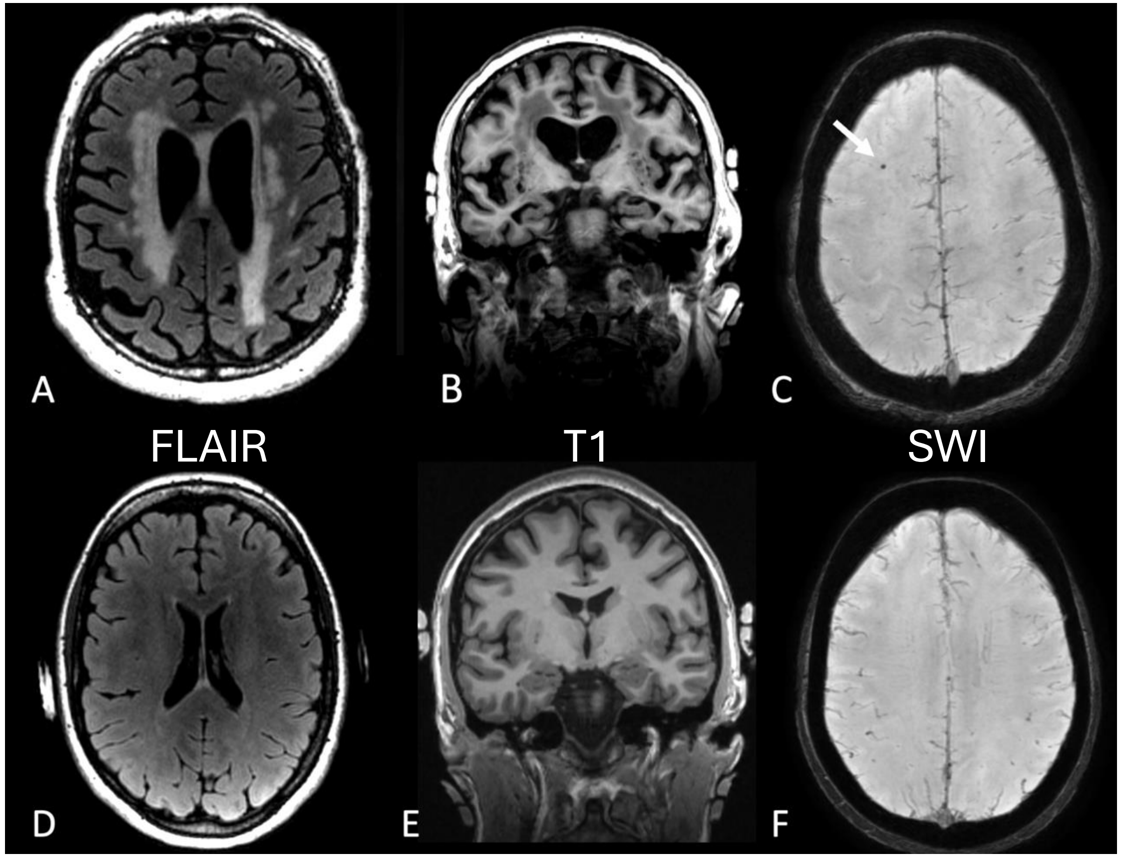
Disrupt

maladaptive locked network activity

≠ damage



Radiopedia.org



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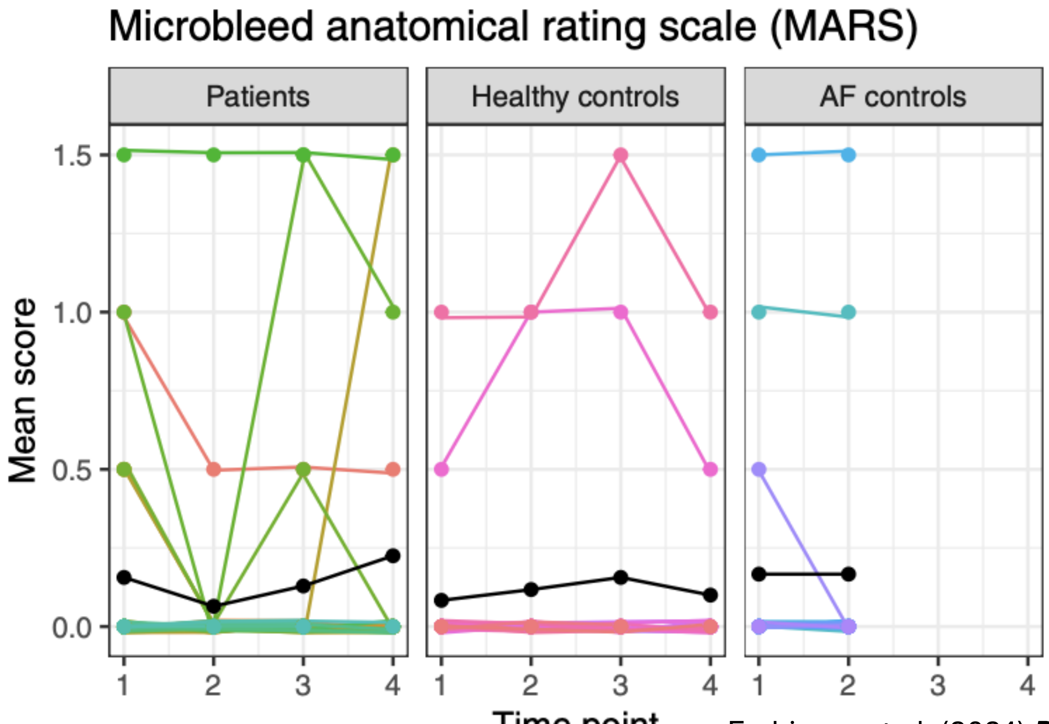
Archival Report

Biological Psychiatry: CNNI

Effects of Electroconvulsive Therapy on Brain Structure: A Neuroradiological Investigation Into White Matter Hyperintensities, Atrophy, and Microbleeds

Vera Jane Erchinger, Ole Johan Evjenth Sørhaug, Stein Magnus Aukland, Gunnar Moen, Peter Moritz Schuster, Lars Ersland, Renate Grüner, Ketil J. Oedegaard, Ute Kessler, Olga Therese Ousdal, and Leif Oltedal

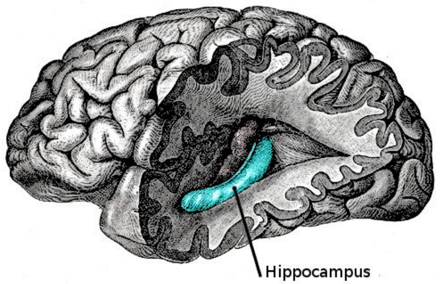
Change in radiological scores during treatment series

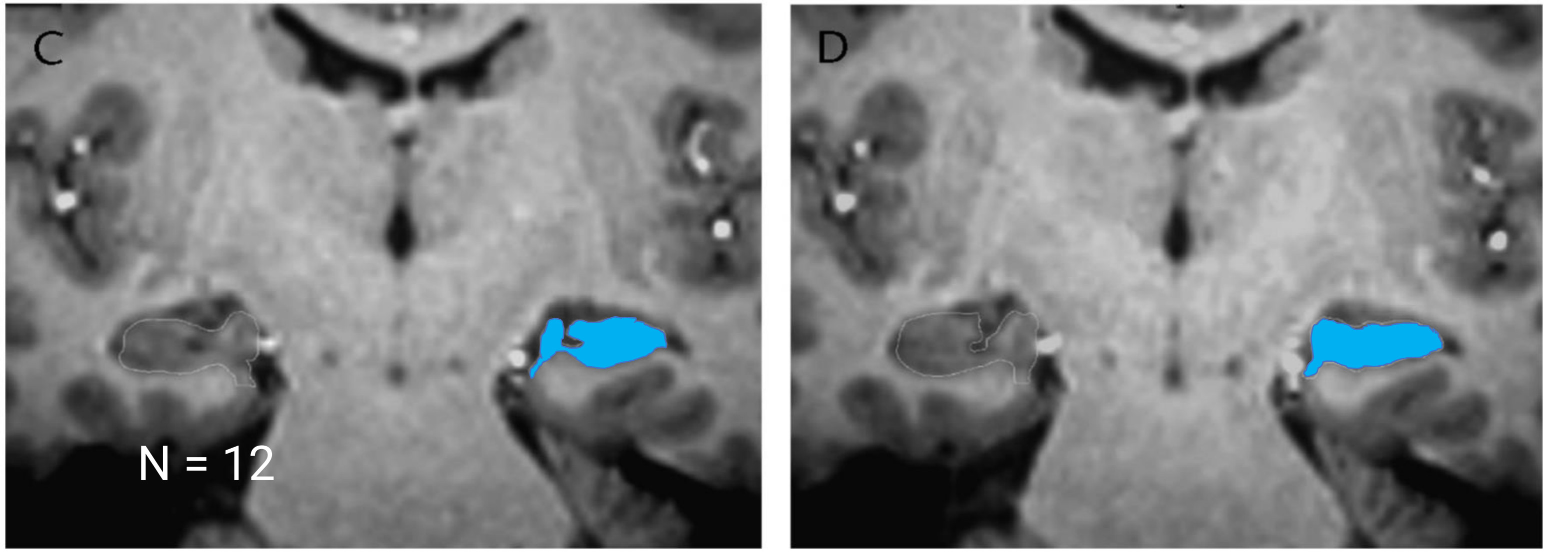


Erchinger et al. (2024) ***Biol Psychiatry CNNI***

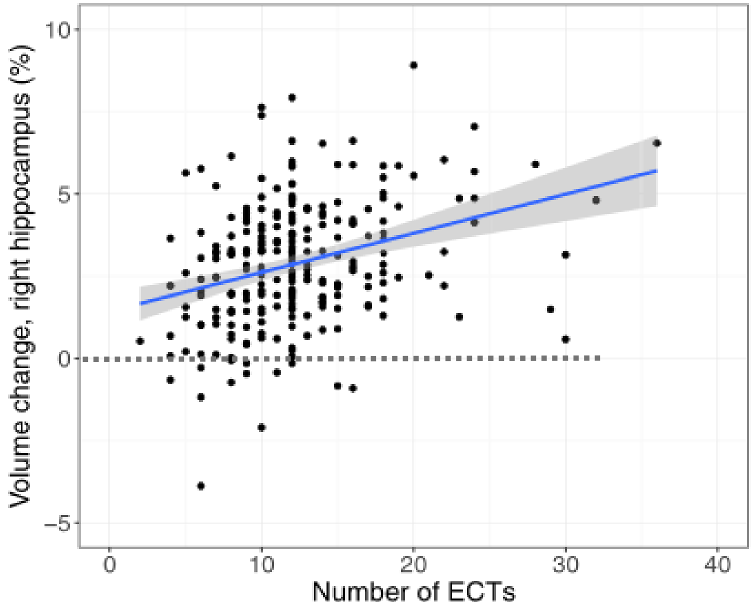
Potentiate

neuroplasticity





Adapted from Nordanskog P, et al. (2010). *J ECT*



Oltedal et al. (2018) *Biol Psychiatry*

Hippocampal volume increase post ECT

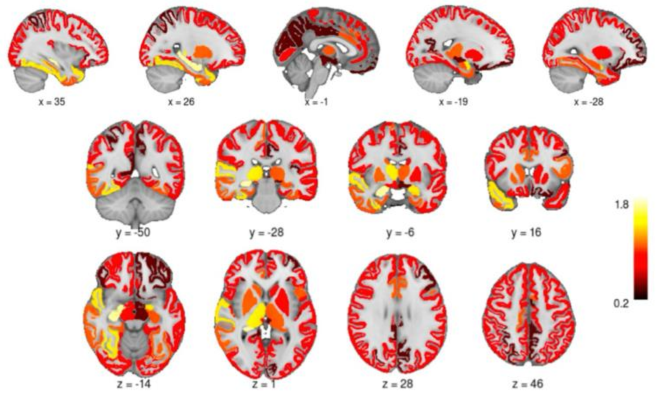
- 3-5% increase, return towards baseline at 3-12 months
- lateralized towards electrode placement (electrical field)
- most studies find no correlation to clinical improvement
- correlates with treatment number and is associated with cognitive side-effects

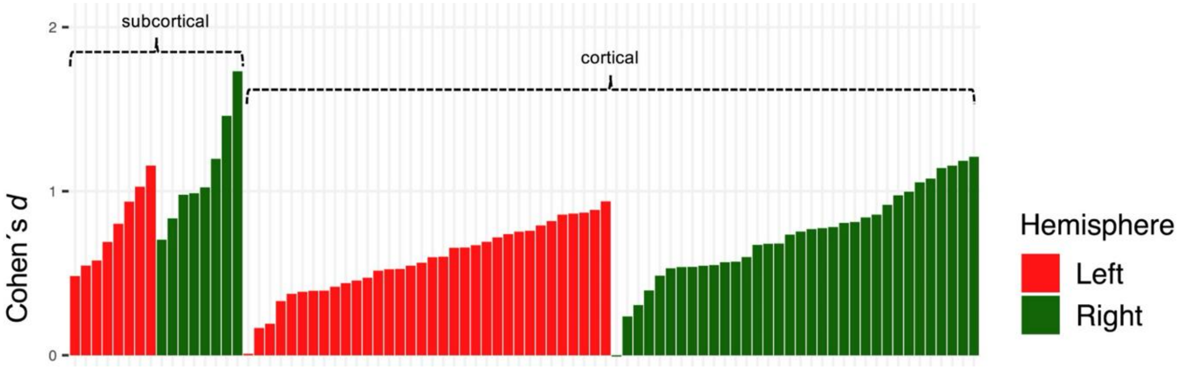
Argyelan et al. (2021) *Transl Psychiatry*
Ousdal et al. (2025) *Commun Med (Lond)*

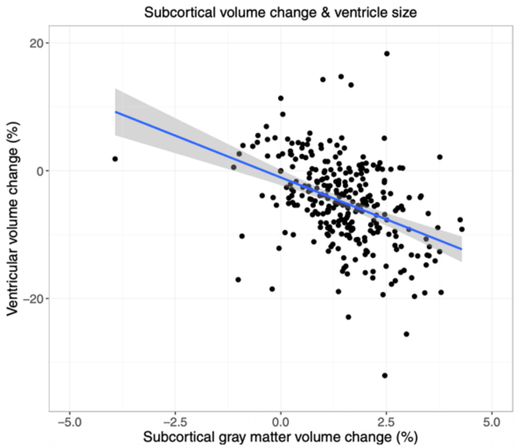
Potentiate

neuroplasticity

ECT: neuroimaging, broad effects



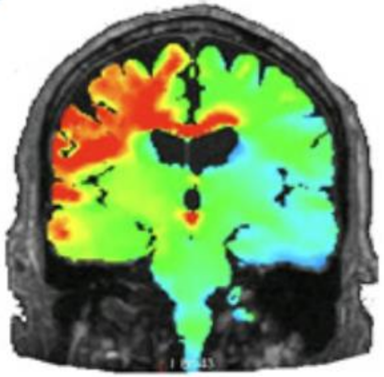




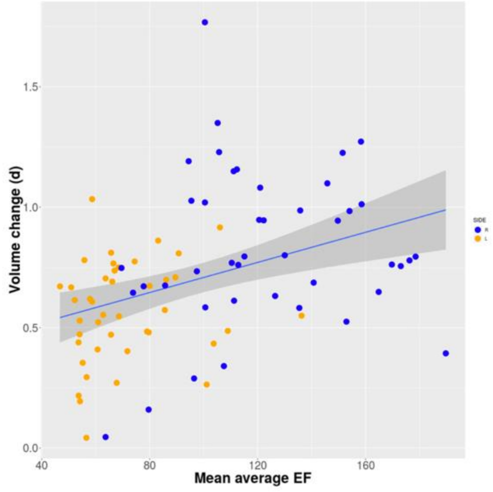
Ousdal et al. (2020) *Biol Psychiatry*

Volume increase post ECT is **broadly distributed**

- most pronounced in the **amygdala**
- on average ~ 1% increase
- lateralized towards electrode placement
- ventricles shrink
- correlated to **electrical field**
- detectable in hippocampus 2 h post first ECT



Brancati et al. (2021) *Brain Stimulation*



Argyelan et al. (2019) *eLife*

Potentiate

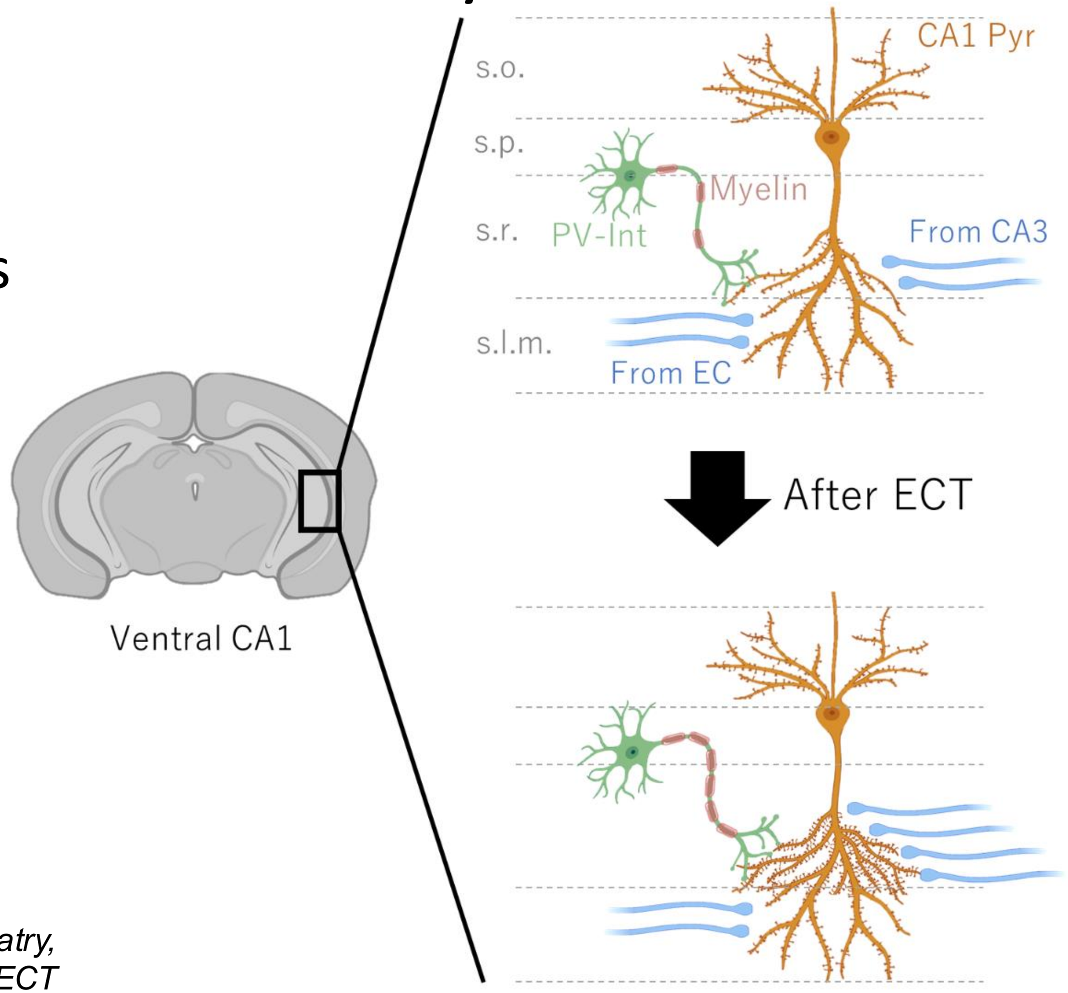
neuroplasticity

Synaptogenesis & Synaptic Plasticity

- Synapses
  - ↑ density of excitatory synapses
  - ↑ density and size of inhibitory synapses
  - ↑ myelination in interneurons

  - Mossy fiber sprouting
  - reversible loss of LTP
  - dendritic elongation, spine enlargement
  - presynaptic terminal size and density
  - ↑ synaptic proteins

Ousdal et al. (2022) *Biological Psychiatry,*
Bouckaert et al. (2014) *J ECT*
Deng et al. (2024) *Neuropsychopharmacology*



Abe et al. (2023) *Journal of Neurochemistry*

Rewire

neuronal connections and networks

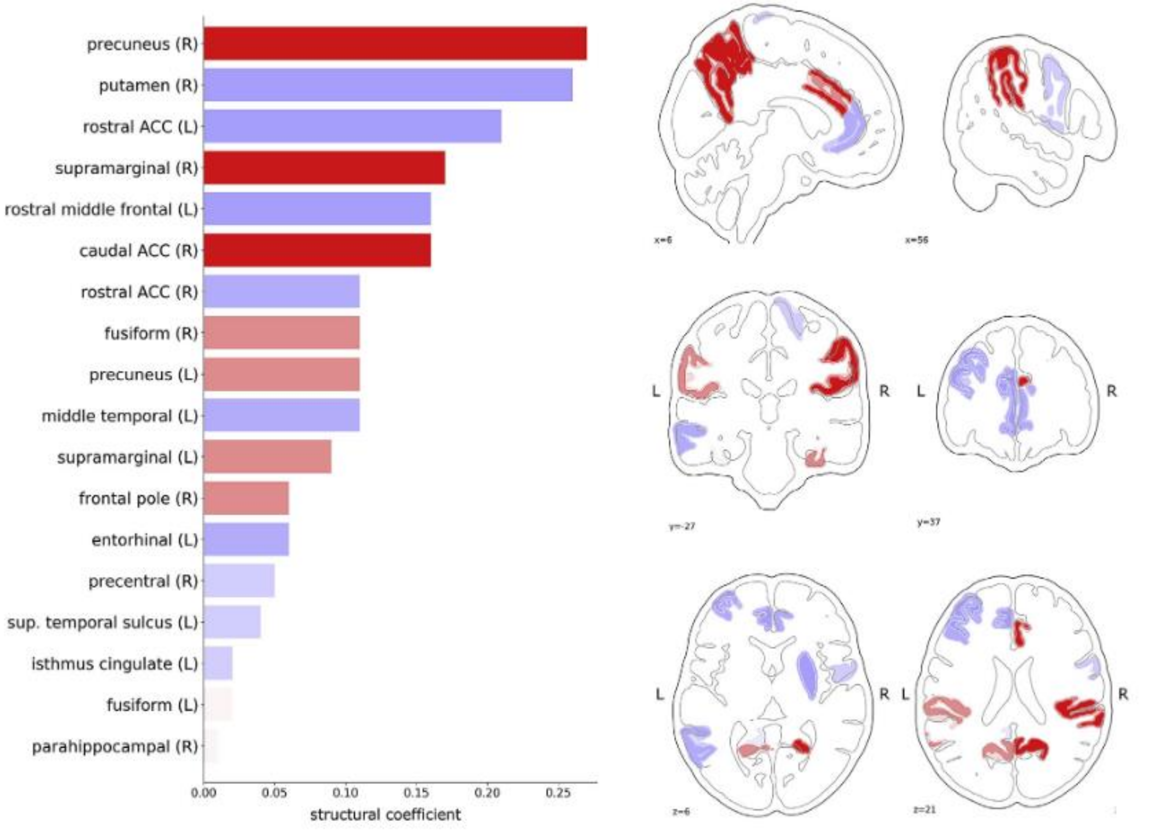
Patterns of volume change - **network effects**?

- machine learning analysis
- pattern of volume change
  - separates responders from non-responders with 75 % accuracy
  - separates RUL from BL electrode placement with 81 % accuracy

- in the figure:

  ↑increase in **red areas** → responders

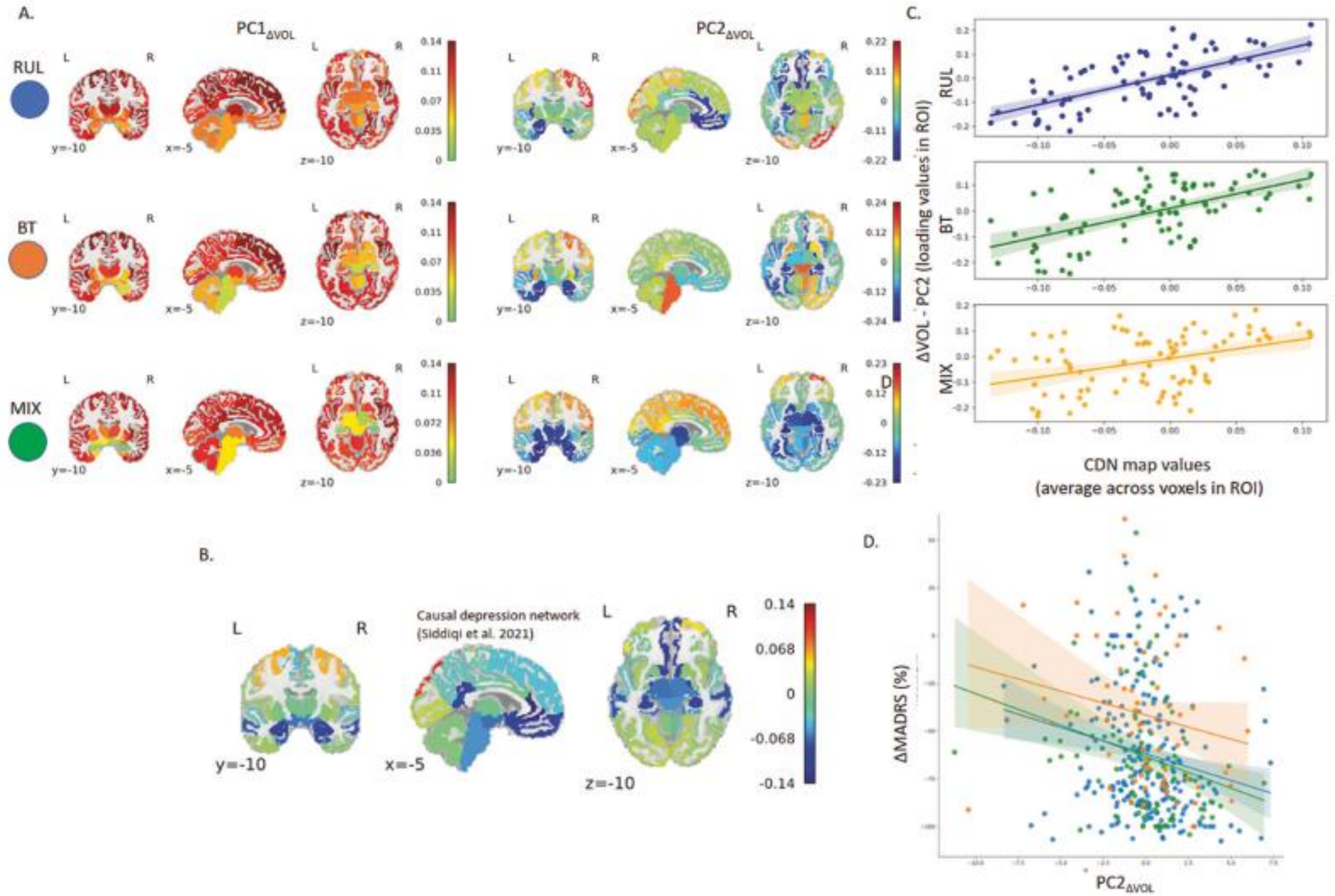
  ↑increase in **blue areas** → non-responders



Mulders et al. (2020) *Brain Stimulation*

Patterns of volume change - **network effects**?

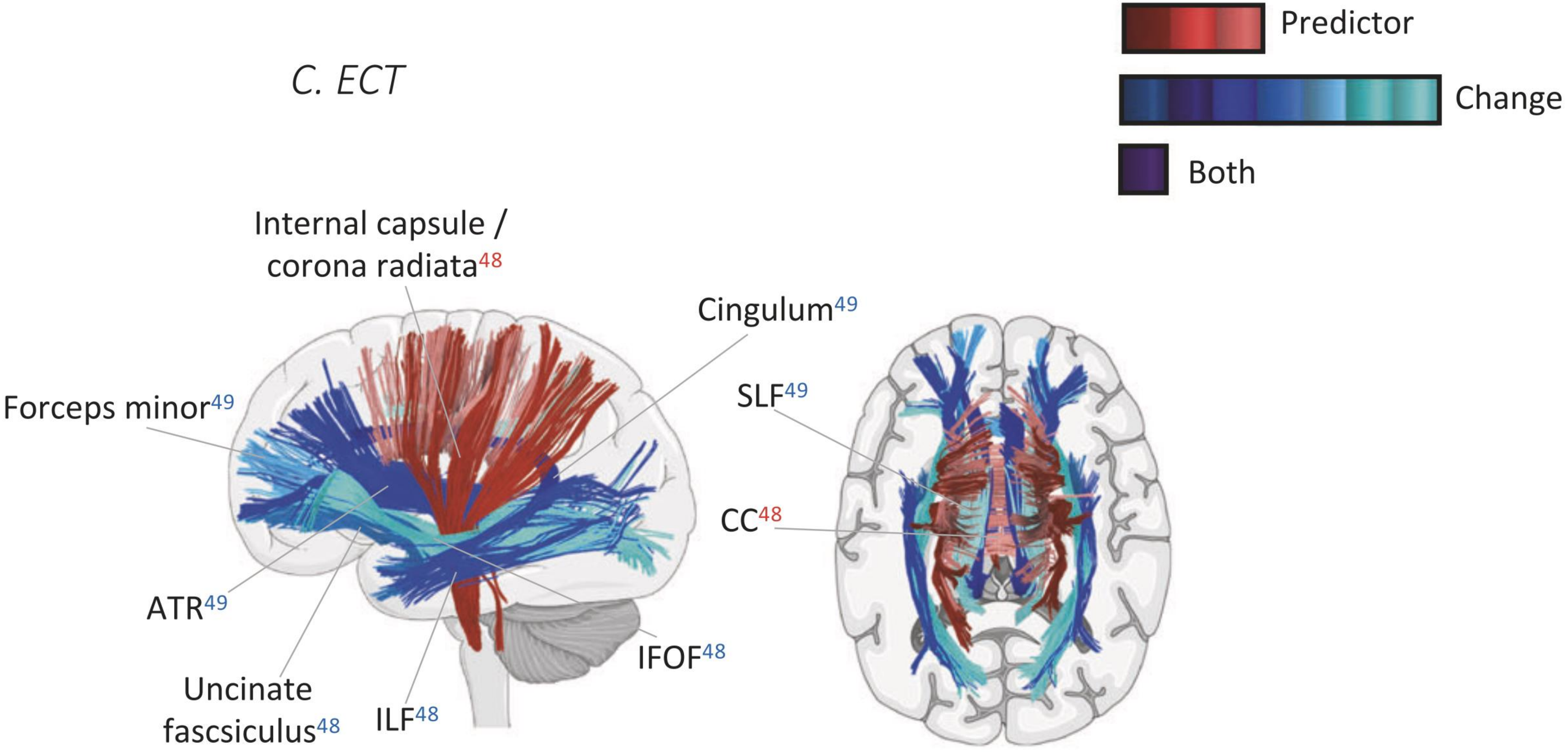
- principal component analysis
  - pattern of volume change in the second component resembles the ”causal depression network (CDN)”
  - caveat; CDN is based on rs-fMRI connectivity, lesion mapping method



Argyelan et al. (2023) *Mol Psychiatry*

Rewire
neuronal connections and networks

MRI structural connectivity and ECT



Tura and Goya-Maldonado (2023) *Translational Psychiatry*

GEMRIC ECT Neuroimaging: Key Results 2015–2025

Timeline of discoveries

2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025

2015: GEMRIC established; data sharing agreement

GEMRIC
The Global ECT-MRI Research Collaboration

- 2017 (**Oltedal**) GEMRIC consortium paper; pipeline; MRI protocols
- 2018 (**Oltedal**) Hippocampal + subcortical GMV ↑; session & placement effects
- 2019 (**Argyelan**) EF explains ΔVol topology; thresholds; RUL laterality
- 2024 (**Kiebs**) Cognition; heterogeneity
- 2019 (**Ousdal**) Broad GMV ↑, ventricle vol ↓
- 2024 (**Laroy**) Partial persistence in amygdala/hippocampus Δvol at 3-6 months
- 2019 (**Wade**) Symptom-dimensions with ECT
- 2024 (**Verdijk**) rs-fMRI LFPN ↑ ~ improvement
- 2020 (**Mulders**) Multivariate Δvol patterns predict response and electrode placement
- 2020 (**Ousdal**) Choice of statistical model matters
- 2021 (**Takamiya**) PMD: trait-like MPFC GMV deficit
- 2025 (**Ousdal**) Hippocampal body&tail Δvol (& EF) linked to side effect
- 2021 (**Opel**) BMI dampens Δvol
- 2021 (**Wade**) Symptom dimensions improve prediction
- 2022 (**van de Mortel**) GMV↑ without robust rs-fMRI change
- 2023 (**Argyelan**) CDN-like pattern predicts outcome; ↑ overall EF amplitude ~ ↓ outcome
- 2023 (**Blanken**) No sex difference in ECT outcome
- 2023 (**Bruin**) Multimodal models; DMPFC, precuneus, thalamus among most informative
- 2023 (**Ten Doesschate**) Directed network rebalancing; posterior DNM - insula

Journal	IF	N	Year(s)
Molecular Psychiatry	10.1	1	2023
Biological Psychiatry	9.0	3	2020, 2019, 2018
Brain Stimulation	8.4	5	2024 ×2, 2023, 2022, 2020
eLife	8.0	1	2019
Communications Medicine	6.3	1	2025
Psychological Medicine	5.5	1	2023
Journal of Affective Disorders	4.9	1	2023
Schizophrenia Bulletin	4.8	1	2021
Human Brain Mapping	4.6	1	2021
NeuroImage: Clinical	4.1	1	2017
Journal of Psychiatric Research	3.2	1	2024
Journal of Psychiatry & Neuroscience	3.3	1	2021
The Journal of ECT	1.8	1	2019

Structure (GMV)

- Widespread GMV ↑, ventricles ↓
- Session- and placement-dependent
- Mostly transient; some persistence

Function (rs-fMRI)

- DMN normalization
- Within LFPN ↑ relates to improvement
- Few global changes with HC controls

EF/Dosing/Side effects

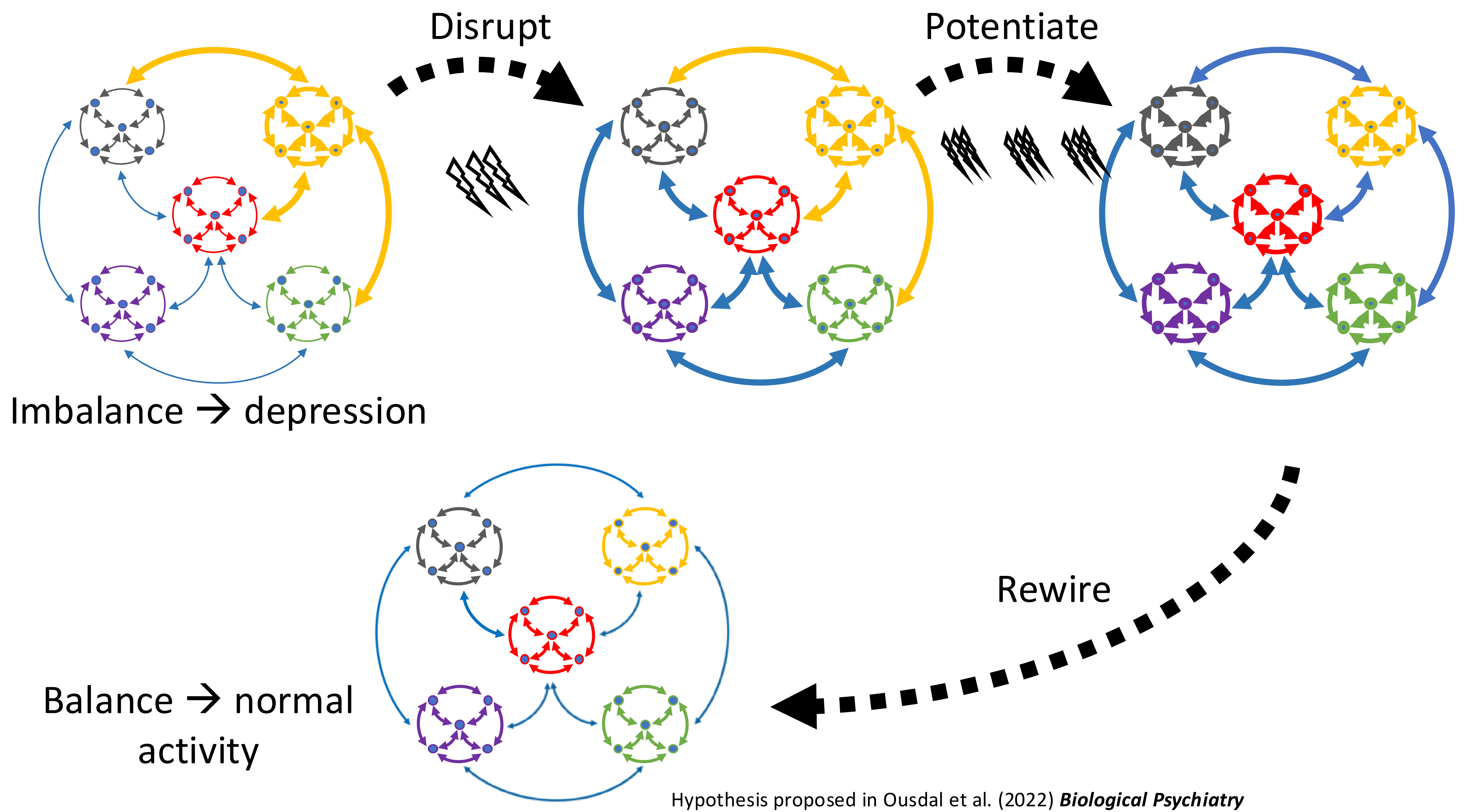
- EF maps ΔVol topology, ceiling behavior
- High overall EF ≠ better outcome
- Hippocampal ΔVol linked to side effect

Moderators

- Psychotic MD ↓ baseline volume
- BMI dampens subcortical Δvol
- Sex ≈ equal outcomes, age favors remission

Modeling

- Multivariate Δvol patterns predict effect
- CDN-like change signature helpful
- Symptom-dimension models perform best

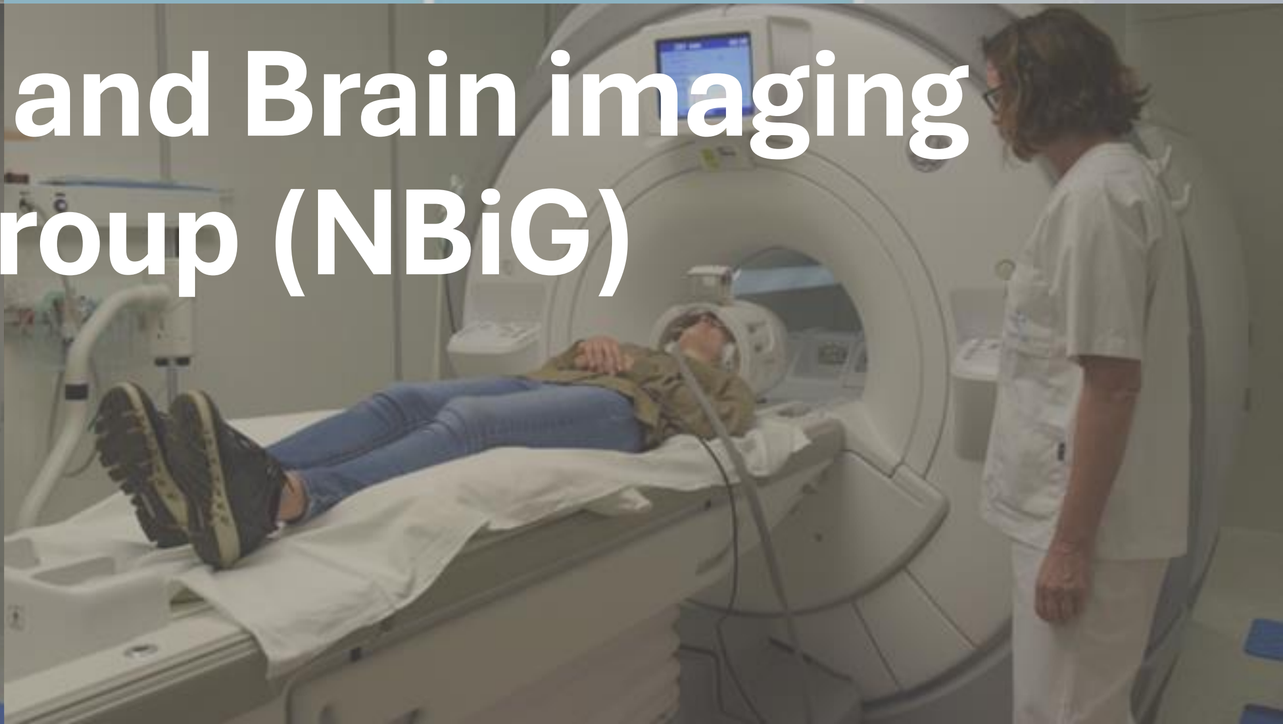


Disrupt
Potentiate
Imbalance → depression
Rewire
Balance → normal activity
Hypothesis proposed in Ousdal et al. (2022) ***Biological Psychiatry***

mmiv.no/ectinfo

ectinfo.nl

Neurostimulation and Brain imaging Research Group (NBiG)



Project Group and Collaborators

GEMRIC
The Global ECT-MRI Research Collaboration

Leif Oltedal (Coordinator, Bergen, Norway)
Hauke Bartsch / Anders M Dale (San Diego, USA)
Bogdan Draganski (Lausanne, Switzerland)
Miklos Argyelan (New York, USA)
Katherine Narr / Randall Espinosa (Los Angeles, USA)
Christopher Abbott (New Mexico, USA)
Amit Anand (Cleveland, USA)
Philip van Eijndhoven / Indira Tendolkar (Nijmegen, the Netherlands)
Annemieke Dols / Max L Stek (Amsterdam, The Netherlands)
Louise Emsell (Leuven, Belgium)
Pia Nordanskog (2)/ Paul Hamilton (Linköping, Sweden)
Anders Jørgensen / Martin Balslev Jørgensen (Copenhagen, Denmark)
Ronny Redlich (Münster, Germany)
Carles Soriano Mas (Barcelona, Spain)
Akihiro Takamiya (Tokyo, Japan)
Guido van Wingen (Amsterdam, the Netherlands)
Joan Camprodon (Boston, USA)
Maximilian Kiebs/Rene Hurlemeann (Bonn, Germany)
Alexander Sartorius/Traute Demirakca (Mannheim, Germany)
Linda van Diermen (Antwerp, Belgium)
Jeroen van Warde (Arnhem, the Netherlands)
Antoine Yrondi (Toulouse, France)
Joan Prudic (New York, USA)
Noora Tuovinen (Innsbruck, Austria)
Hannah Maier (Hannover, Germany)
Tobias Bracht (Bern, Switzerland)
Urvakhsh Mehta (Bangalore, India)
Sarah Lisanby (Bethesda, USA)

Neurostimulation and Brain Imaging Research Group (Bergen)

Leif Oltedal, Professor, MD, PhD
Ute Kessler, Professor, MD, PhD, Head of ECT unit
Olga Therese Ousdal, Associate Professor, MD, PhD
Turid Helen Felli Lunde, Research Coordinator
Jan Haavik, Professor, MD, PhD
Lars Ersland, PhD
Renate Grüner, Professor, PhD
Ketil J Ødegaard, Professor, MD, PhD
Vera Erchinger, PhD
Andrea Stautland, PhD student
Kjersti Sellevåg, PhD student
Ieva Leskauskaite, MD
Eivind Haga Ronold, PhD
Hauke Bartsch, Associate Professor, PhD

Local collaborators

Mohn Medical Imaging and Visualization Centre
Bergen fMRI group
K.G. Jebsen Centre for Research on Neuropsychiatric Disorders
Mood and Cognitive Function Group
Regional Quality Registry of ECT Treatment in Helse Bergen and Helse Stavanger

UNIVERSITAS BERGENSIS

BMH SENTERET · HELSE BERGEN Haukeland Universitetssykehus · UC San Diego SCHOOL OF MEDICINE · MMIV · BERGEN fMRI GROUP