ECT – What do we know about possible mechanisms of action and effects on the brain

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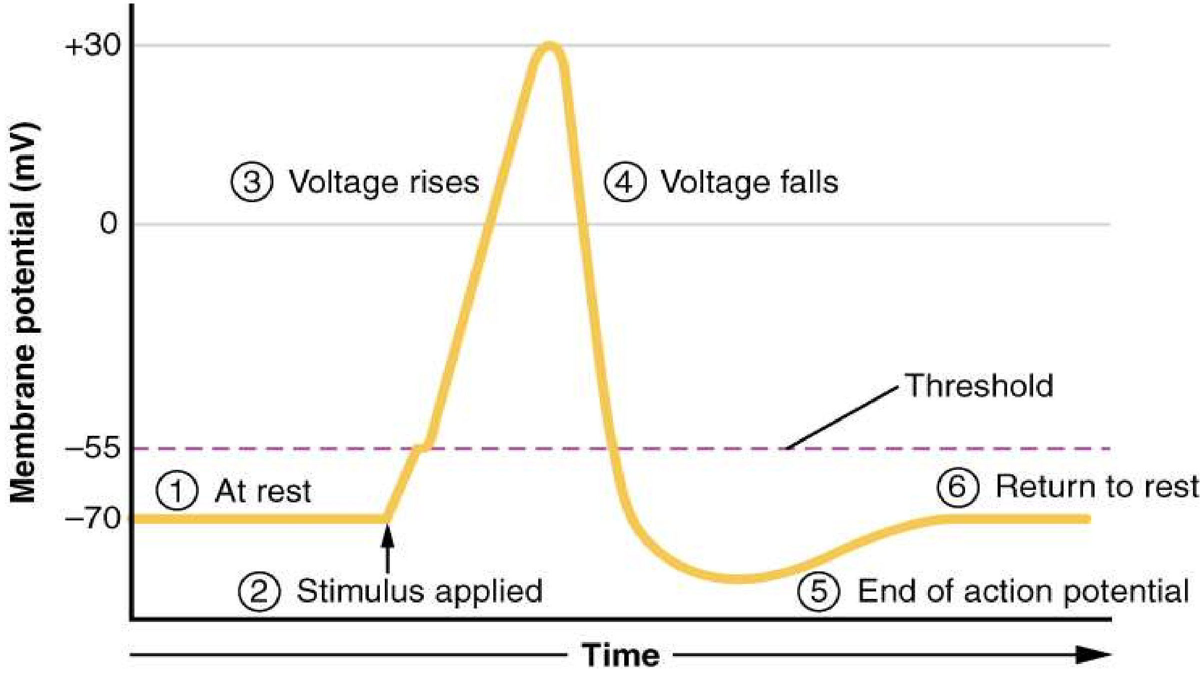
How does ECT work?

- Knowledge on mechanisms of action
  - Contributes to development of more advanced forms of treatment
  - «Personalized predictions»
- Animal models
  - ECS (electroconvulsive stimulation/shock)
  - Histological investigations etc.
- Studies on humans
  - Neuroradiologi
  - Biochemical analysis of blood, CSF

Neurophysiology



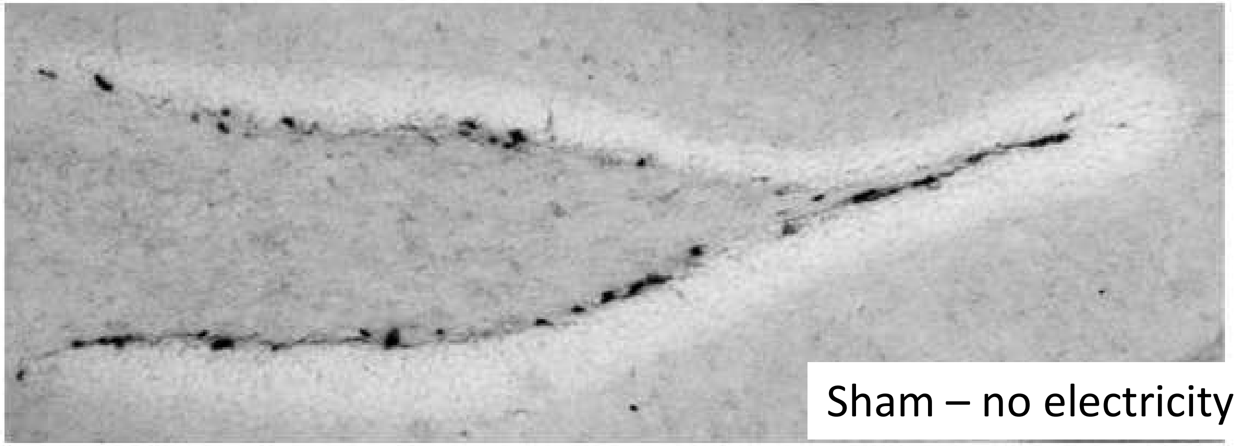
- Synchrone depolarisation of large groups of neurons
- Self-limiting epilepsy-like seizures
- Generalised (also including subcortical regions, the limbic system and the brain stem)

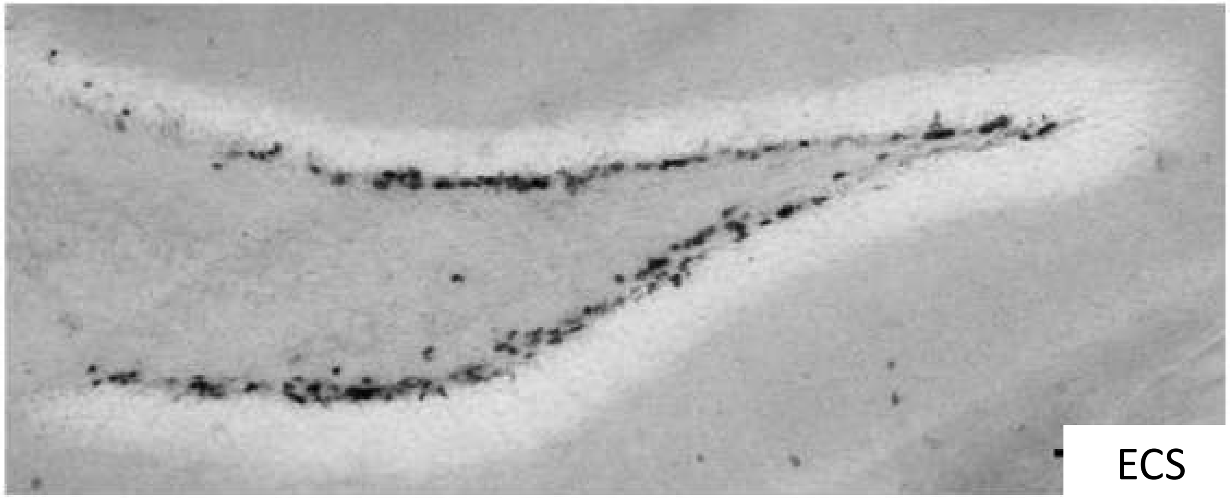
Biological effects / Neurobiological domains

- Neuroplasticity
- «Neural connectivity»
- Neurotransmitters
- Endocrine mechanisms
- Autoimmune mechanisms

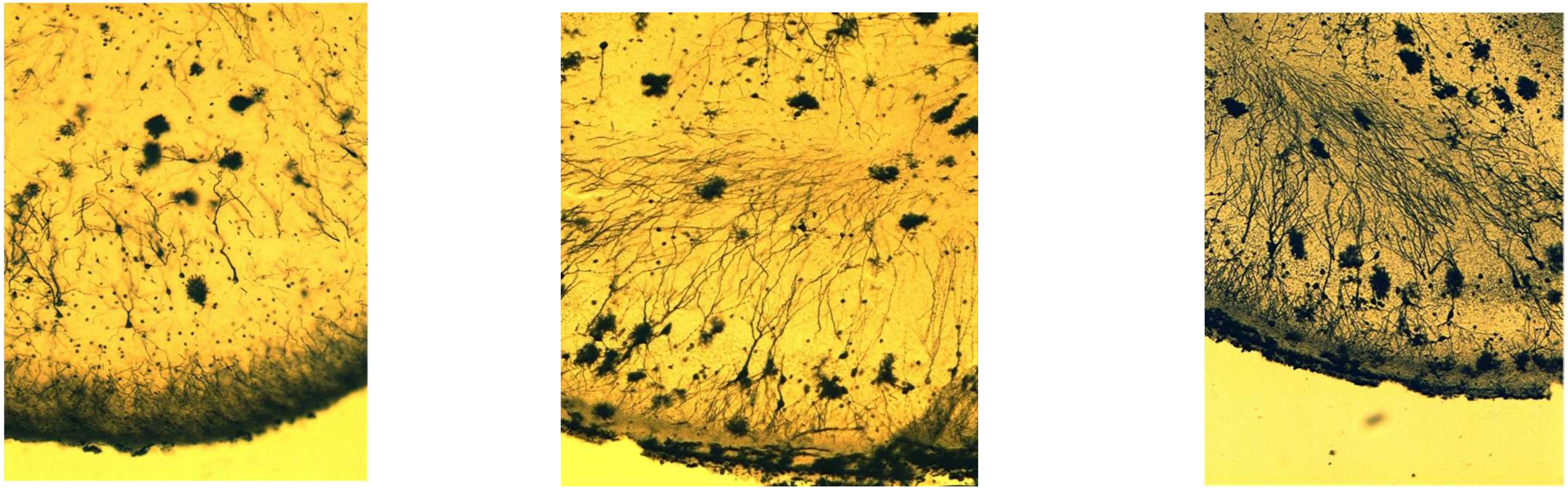
Neuroplasticity

- The brain’s ability to reorganise itself
- Generation of new synapses and neurons
- Gyrus dentatus in hippocampus
- Reduced neurogenesis in depression
- Cortisol





Rotheneichner et al., 2014 Hippocampal Neurogenesis and Antidepressive Therapy: Shocking Relations



Sham (no electricity)	10 mC	40 mC

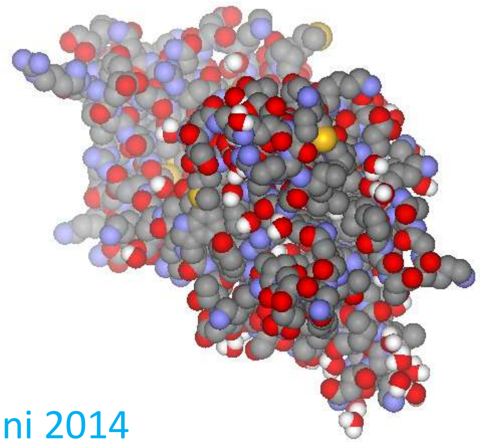
Smitha, J ECT, 2014 Images in ECT, ECS Dose-Dependently Increase Dendritic Arborization in the Rat Hippocampus

BDNF

brain derived neurotrophic factor

- stimulates
  - Generation of new neurons
  - Axonal growth
  - Synaptic and dendritic plasticity
- Regulation of neuron activity
- Effect on memory and mood
- ↓ in depression
- ↑ following ECS/ECT both in the brain and in blood plasma

Huang, Reichardt, 2001



Brunoni 2014

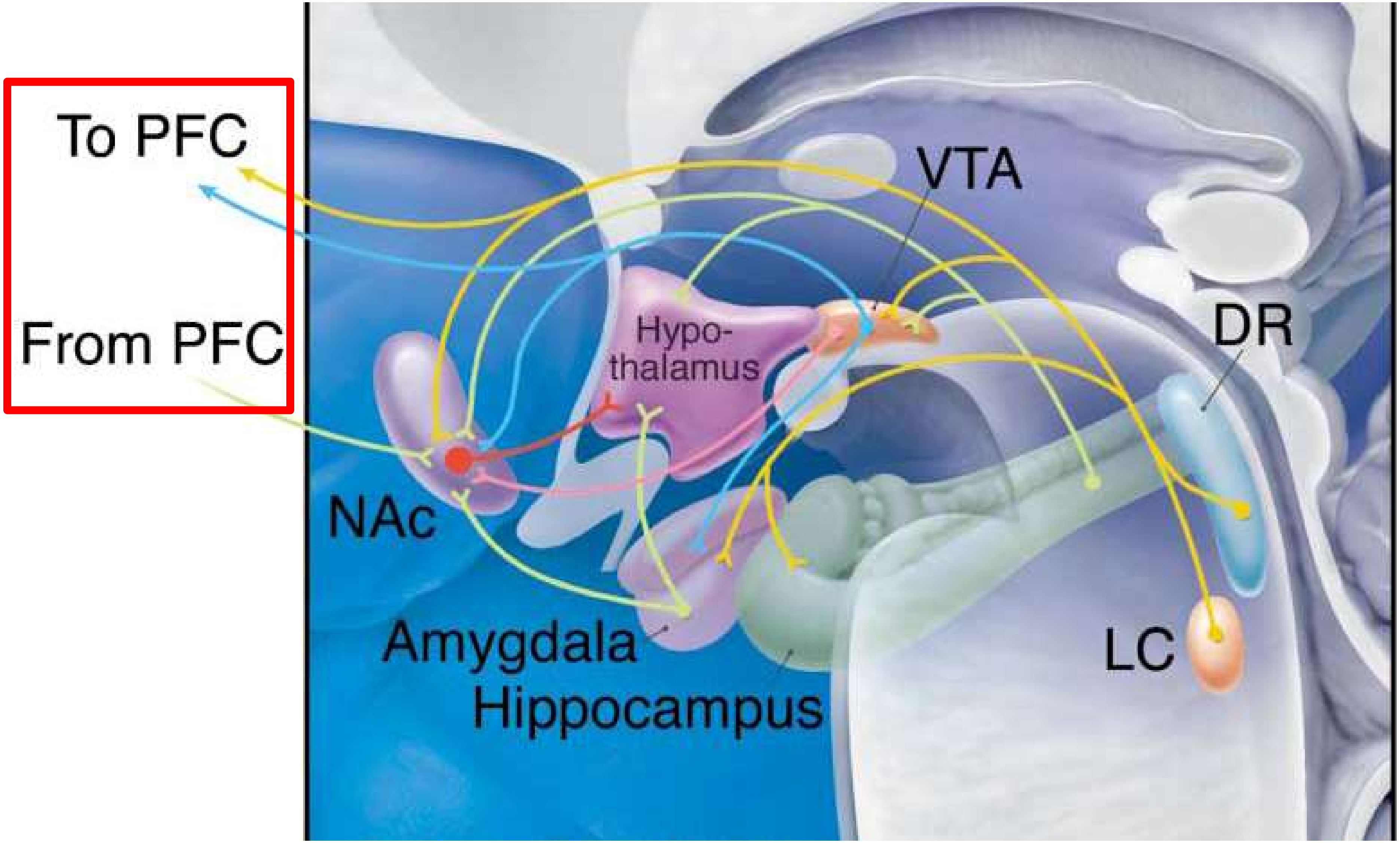
van Buel et al. Transl Psychiatry. 2015 Jul 28;5

Neuroplasticity

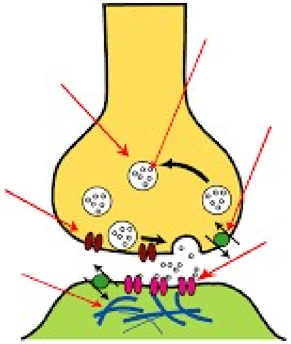
- Robust results from animal studies
- ECS increases dendritic arborisation and cell proliferation in hippocampus
- Dose dependent, lasting effect
- Functional nerve cells that form new synapses

(Chen et al. 2009, Smitha 2014)

- Neuroanatomy/neuroplasticity
- **«Neural connectivity»**
- Neurotransmitters
- Endocrine mechanisms
- Autoimmune mechanisms


To PFC
From PFC
VTA
Hypo-
thalamus
DR
NAc
Amygdala
Hippocampus
LC

- Neuroanatomy/neuroplasticity
- Neural connectivity
- **Neurotransmitters**
- Endocrine mechanisms
- Autoimmune mechanisms



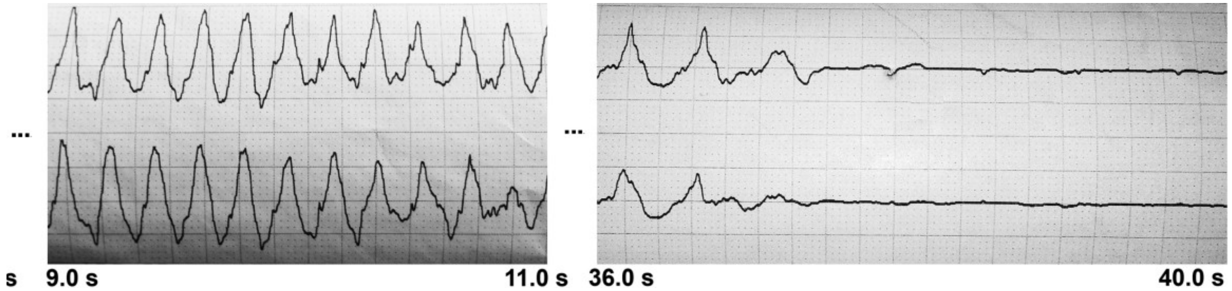
Neurotransmitters

- ECS affects the release of neurotransmitters
  (Glue et al., Psychopharmacology 1990
- Focus on serotonergic and dopaminergic transmission
  - Receptor binding, number of receptors, sensitive
  - Upregulation of postsynaptic 5-HT1A and downregulation of 5-HT2A receptors (Baldinger et al. J ECT 2014)
- Association to antidepressive response??
- Noradrenaline

↓ α2-adrenoreceptor (increased noradrenergic transmission)
(Lillethorup et al. Eur Neuropsychopharmacol. 2015)

- Glutamate

Anticonvulsant hypothesis



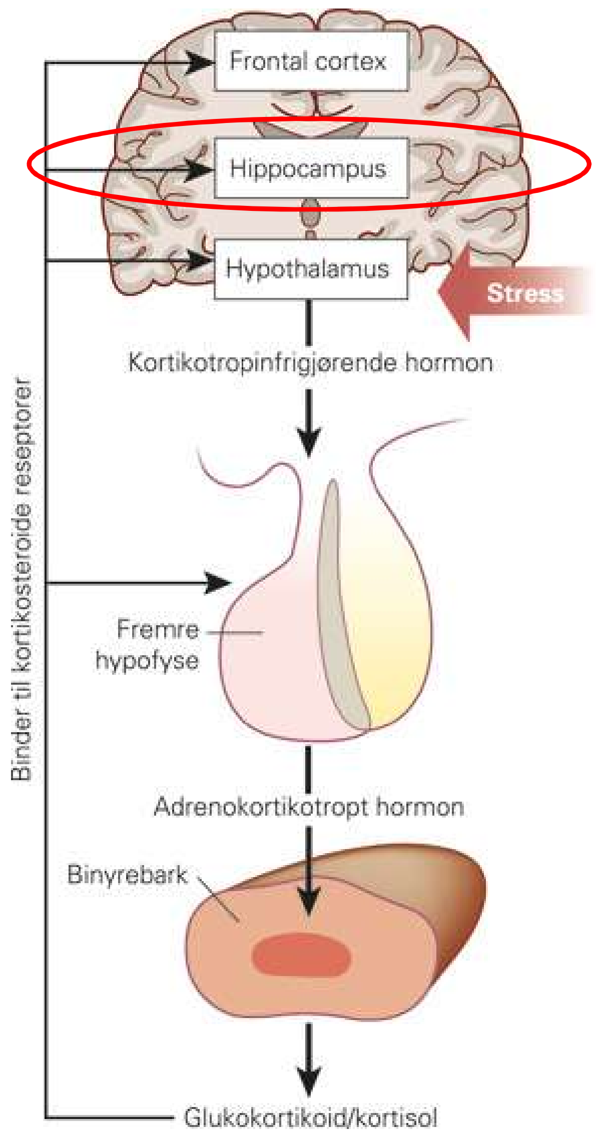
- seizure termination
- postictal suppression and ↑ seizure threshold
- Correlates with antidepressive effect

  Sackeim J ECT 1999;15(1):5-26
- GABA (γ-aminobutyric acid): important inhibitory transmitter
- ↑ release of GABA and ↑ GABAergic transmission

  Sanacora 2003

- Neuroanatomy/neuroplasticity
- «Neural connectivity»
- Neurotransmitters
- **Endocrine mechanisms**
- Autoimmune mechanisms

HPA-axis
(Hypothalamic–pituitary–adrenal axis)



Tidsskr Nor Legeforen 2010; 130: 932-5

Dysregulation of HPA-axis in depression:

- Cortisol hypersecretion
- Glucocorticoid resistance:
  - No dexamethasone suppression
  - No anti-inflammatory effect even in elevated level of glucocorticoids
- Reduced neuroplasticity

Endocrine mechanisms in ECT

- Single ECT treatment:

  stress reaction with increase in cortisol
- ECT series:

  normalises dysfunction in the HPA-axis

(Yrondi et al. Brain Stimul. 2018;11(1):29-51. ECT, depression, the immune system and inflammation: A systematic review)

- Neuroanatomy/neuroplasticity
- «Neural connectivity»
- Neurotransmitters
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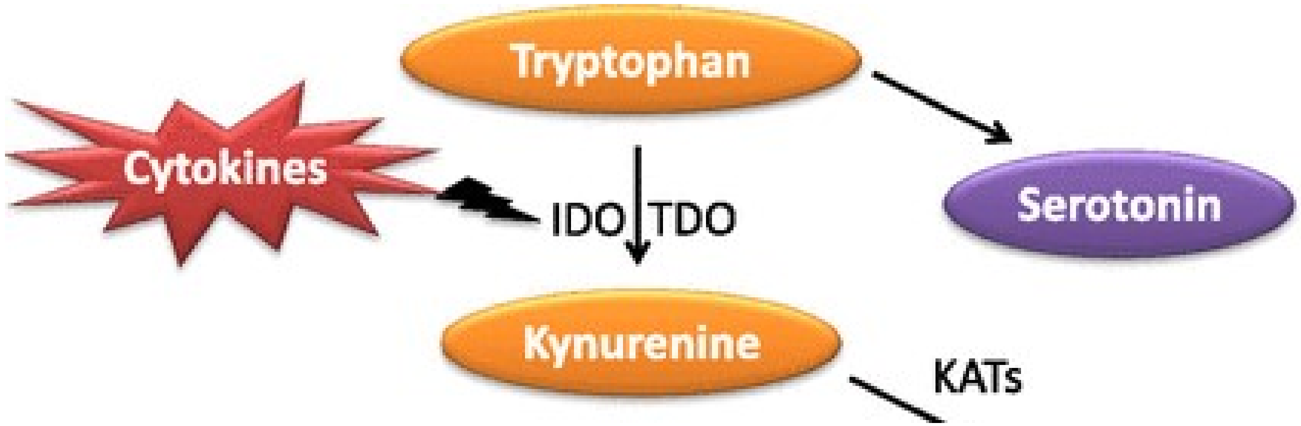
- **Autoimmune mechanisms**

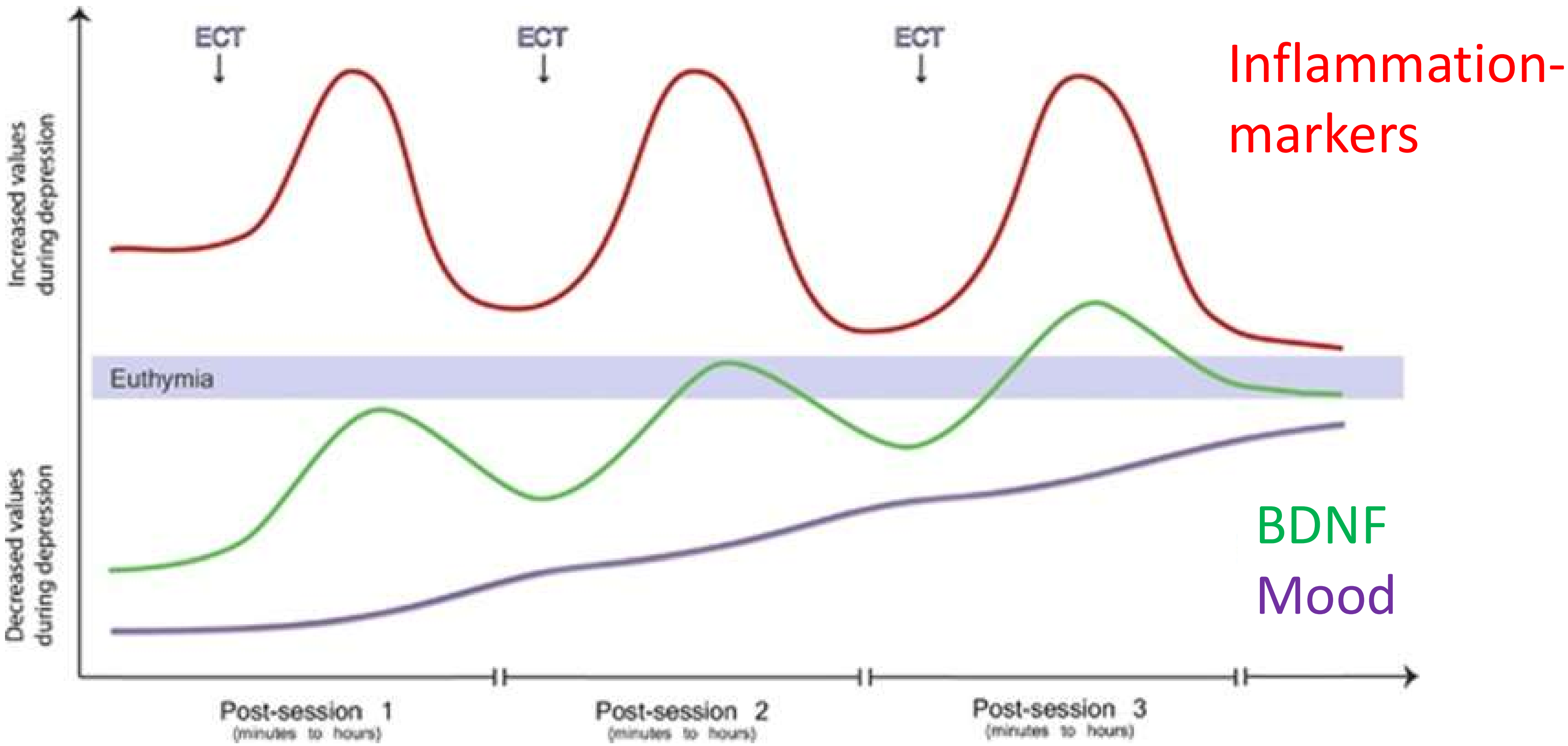
Depression as inflammation

- Pro-inflammatory markers ↑ in depression
  - ↑ TNFα, IL-6, IL-1β, CRP
- Cytokines stimulate the HPA axis
- Cytokines aktivate IDO which transforms tryptophan into neurotoxic substances rather than into serotonin

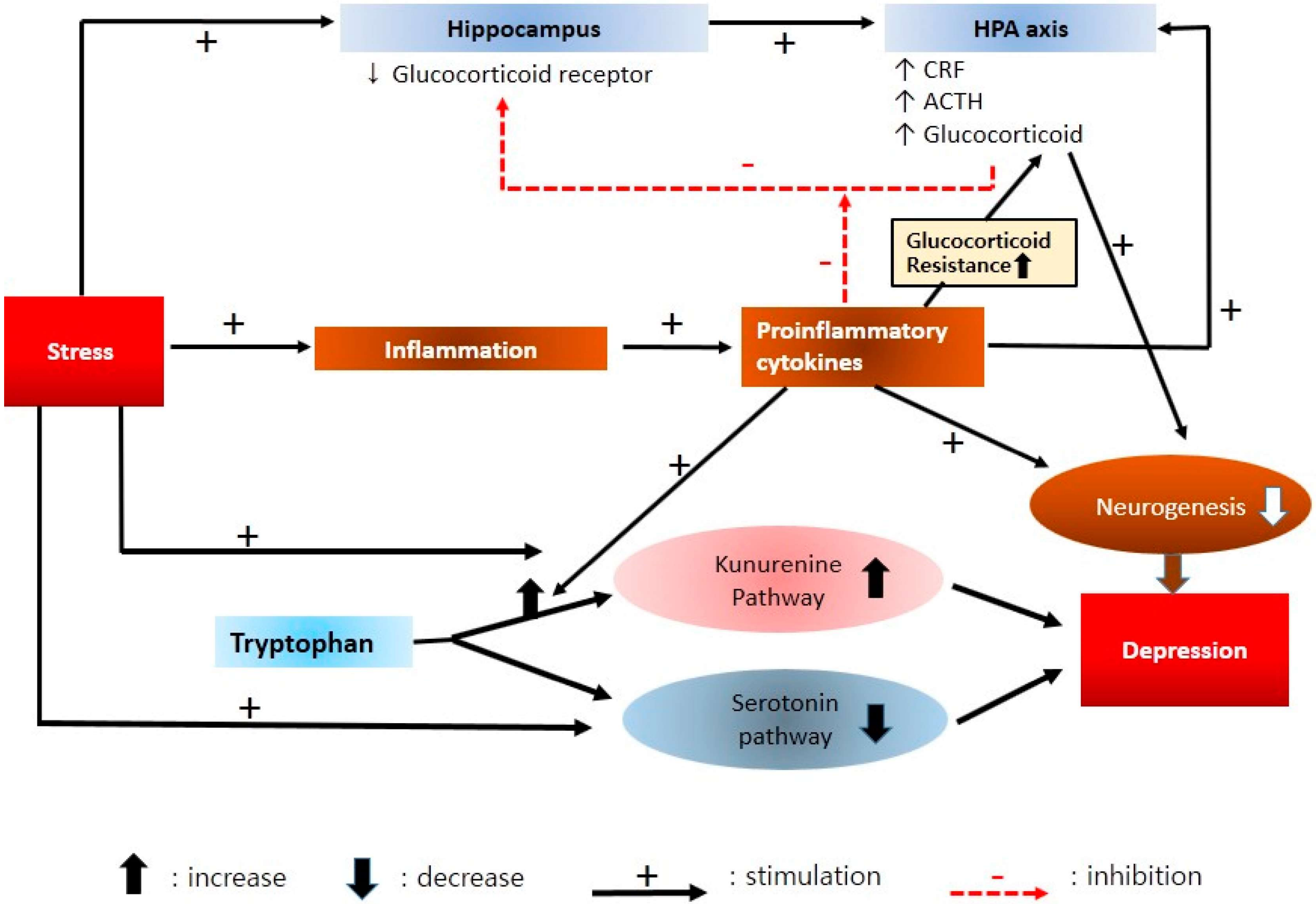


- single ECT: acute, transient immune activation
- repetitive ECT : ↓immune activation ?

Guloksuz et al. 2014, Järventausta et al. 2016



van Buel et al. Transl Psychiatry. 2015 Jul 28;5
Immune and neurotrophin stimulation by electroconvulsive therapy: is some inflammation needed after all?



Jeon, Int. J. Mol. Sci. **2016**, 17, 381;

GEMRIC - The Global ECT-MRI Research Collaboration

- Founded in June 2015
- Principal idea: mega-analyses of combined study → new discoveries
- First phase: up to 550 subjects (patients / controls)
- Clinical and neuroimaging data before and after ECT
- In future: aim at increasing the sample size to 2000 subjects
- Want to join? Leif.Oltedal@uib.no

GEMRIC

The Global ECT-MRI Research Collaboration

The Global ECT-MRI Research Collaboration

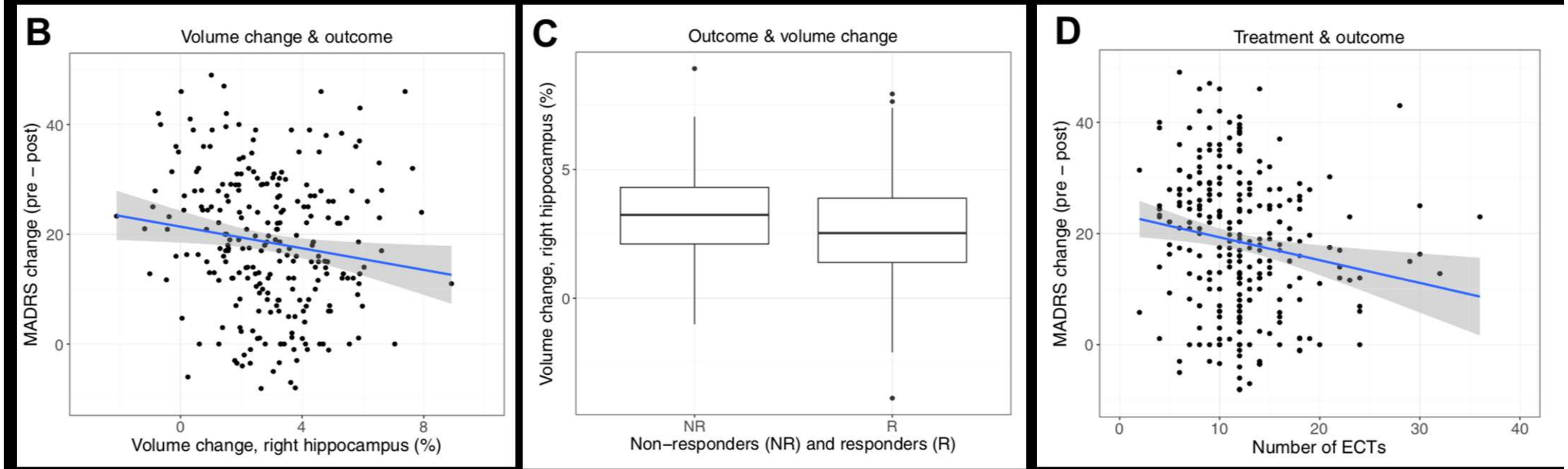
Data and processing pipelines are shared to a common server at University of Bergen

All analyses and data processing are done on the server

Pipelines are set up as Docker containers – which means standardization, independence of operating systems and reproducible results

no	Proposer	Site	Title	Status
1	Leif Oltedal	University of Bergen	ECT-induced structural brain changes; a collaboration using data from multiple centers. (nov 2014)	2 Papers published, 1 in revision
2	Annemieke Dols	GGZinGeest/VUmc, Amsterdam	Does a neuroimaging marker predict the outcome of electroconvulsive therapy in severe depression? A replication study applying multivariate pattern analysis	Analysis ongoing
3	Philip van Eijndhoven	Doners Institute, Nijmegen	Prediction of response to ECT by support vector classification	In GEMRIC review
4	Miklos Argyelan	The Zucker Hillside Hospital, NY, USA	Electrical field modelling of ECT therapy to predict response and side effects	In submission
5	Amit Anand	Cleveland Clinic, USA	ECT Effects on the Brain's Structural Functional Connectome	Starting
6	Benjamin Wade	UCLA, USA	Factor analysis of ECT-related change in clinical response scales and relationships with brain features	1 Paper submitted, 1 in preparation
7	Benjamin Wade	UCLA, USA	Boosting the generalizability of clinical outcome prediction following ECT using instance- weighted domain adaptation and unsupervised clustering	Analysis ongoing
8	Freek ten Doesschate	Rijnstate/AMC, Amsterdam	Dynamic causal modelling in depression and its treatment with ECT	Starting
9	Miklos Argyelan	The Zucker Hillside Hospital, NY, USA	The relationship between the changes in resting state dynamics and the local electrical field induced by ECT therapy	Starting
10	Carles Soriano-Mas	IDIBELL, Barcelona	Modulation of voxel-wise multiband amplitude of low frequency fluctuations after ECT	Starting
11	Olga Therese Ousdal	University of Bergen	Effects of ECT on amygdala and hippocampus subfield volumes	Data processed
12	Nils Opel	Department of Psychiatry, Münster	Influence of pre-treatment BMI on clinical and brain structural changes during ECT	Starting
13	Bogdan Draganski	University of Lausanne, Switzerland	Interaction between ECT-induced grey matter volume changes and antidepressant medication	Starting
14	Carles Soriano-Mas	IDIBELL, Barcelona	Structural covariance of the hippocampus and hippocampal volume changes after ECT	Analysis ongoing
15	Akihiro Takamiya	Keio University, Tokyo	Aberrant brain structure and ECT response in psychotic depression.	Starting
16	Christopher Abbott	University of New Mexico	Depression biotypes in an ECT sample	Withdrawn

Current status and results



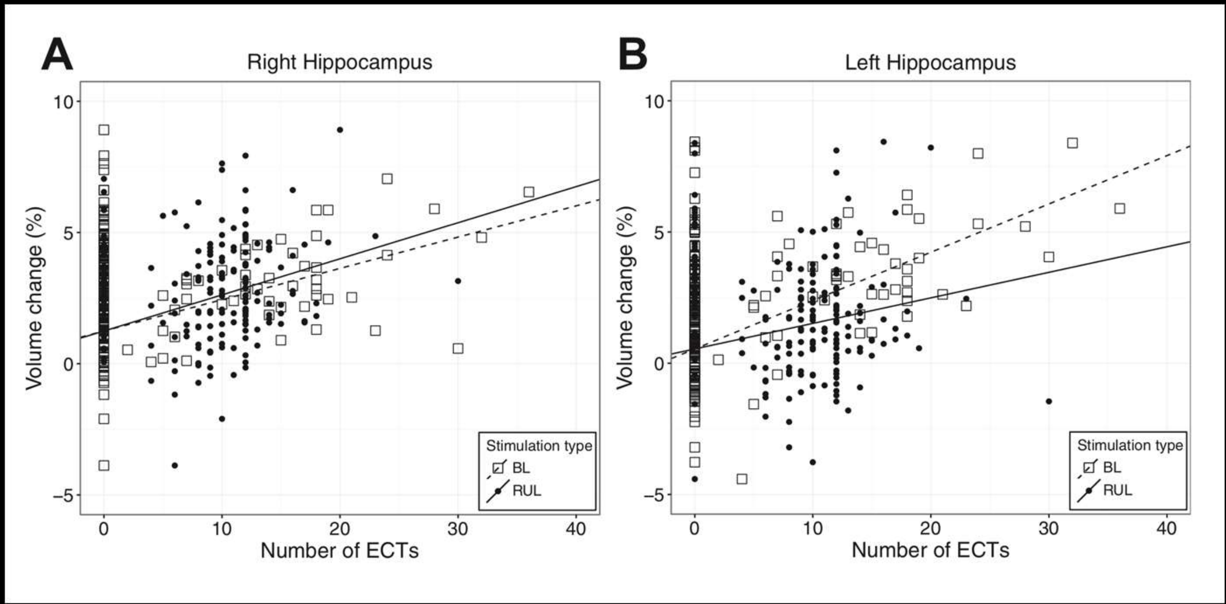
<u>Conclusions</u>

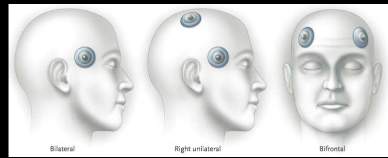
Volume change depends on number of ECTs

Clinical outcome is not related to volume change of the hippocampus

Oltedal et al. (2018) *Biological Psychiatry*

Current status and results





Lisanby SH (2007). N Engl J Med 357: 1939-1945.

<u>Conclusions</u>

Volume change depends on electrode placement

→ Importance of electrical field?

Oltedal et al. (2018) *Biological Psychiatry*

Current, ongoing and future…

Prediction
R/NR from preECT rsFMRI
R/NR from structural pre and change
Psychotic symptom & structure

Brain structure (sMRI)
Hippocampus ~ clinical outcome
Changes throughout the brain
Subfields (Amygdala & Hippocampus)
Gray matter change and medication
BMI and structural effects
Covariance of structural changes
Effect of psychotic symptoms

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Resting state (rsfMRI)
Effective connectivity
E-field and low fALFF
Changes in fALFF in various bands

E-field
E-field & volume change
E-field & clinical outcome
Development of a simulator or ECT

Blood biomarkers
Tryptophan pathway
DNA / RNA

GEMRIC-Members

Name	Site
Leif Oltedal/Ute Kessler/Ketil Ødegaard/Jan Haavik	Bergen, Norway
Hauke Bartsch/Anders M Dale	San Diego, CA, USA
Katherine Narr/ Randall Espinosa	Los Angeles, CA, USA
Christopher Abbott	Albuquerque, NM, USA
Louise Emsell/Mathieu Vandenbulcke	Leuven, Belgium
Pia Nordanskog/Paul Hamilton	Linköping, Sweeden
Indira Tendolkar/Philip van Eijndhoven	Nijmegen, Netherlands
Martin Balslev Jørgensen	Copenhagen, Denmark
Annemieke Dols/Mardien Oudega/Max L. Stek	Amsterdam,Netherlands
Guido van Wingen	Amsterdam,Netherlands
Ronny Redlich	Munster, Germany
Carles Soriano Mas/Marta Cano	Barcelona, Spain
Joan Camprodon	Boston, USA
Maximilian Kiebs/Rene Hurlemann	Bonn, Germany
Alexander Sartorius/Traute Demirakca	Mannheim, Germany
Linda van Diermen	Antwerpen, Belgium
Jeroen van Waarde	Arnhem, Netherlands
Akihiro Takamiya	Tokyo, Japan
Amit Anand	Cleveland, USA
Bogdan Draganski	Lausanne, Switzerland
Miklos Argyelan	NY, USA