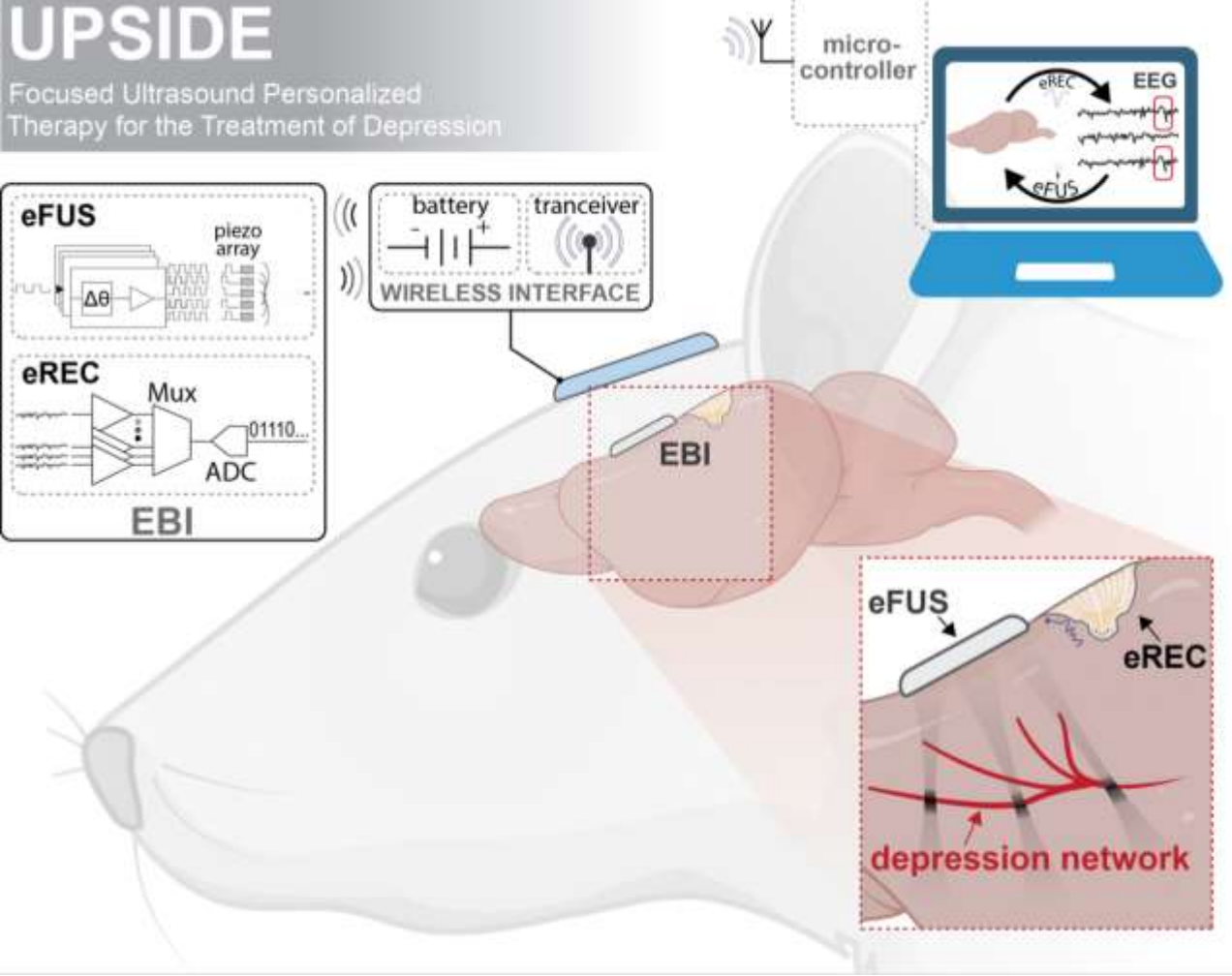

The vision of epidural focused ultrasound neuromodulation for Treatment-Resistant Depression

Tiago Costa, PhD
TU Delft
Faculty EEMCS – Microelectronics Department

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University Freiburg - Medical Centre
Department of Stereotactic and Functional Neurosurgery

This project has received funding the Europe European Union's Horizon Europe EIC-PATHFINDER progamme under grant agreement No. 101070931

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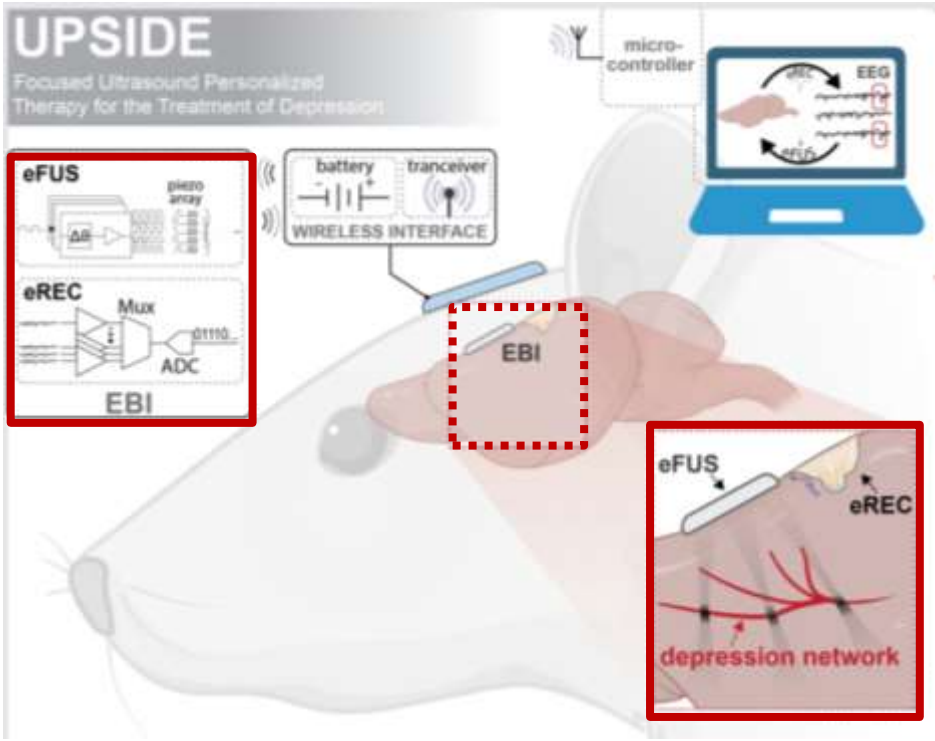
The project's vision…

….is to proposes an Epidural Brain Interface (EBI) featuring a **minimally invasive,** responsive **neural stimulation system** that utilizes **focused ultrasound** (eFUS) **multi-brain region** stimulation and high spatio-temporal resolution electrical recording (eREC) to **innovate the way we treat TRD**….



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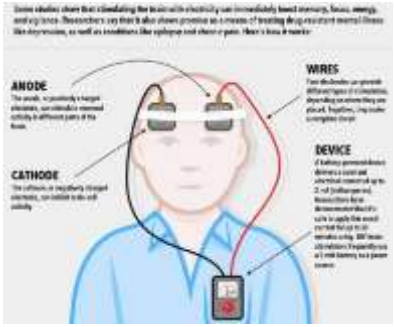
Neuromodulation in Psychiatric Disorders

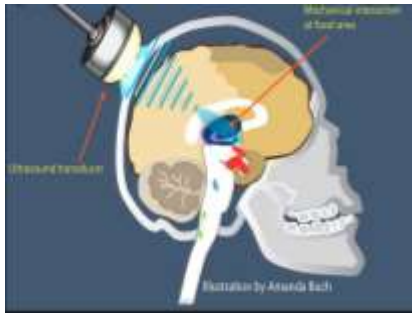
Transcranial Magnetic Stimulation (TMS)

Transcranial Direct Current Stimulation (tDCS)

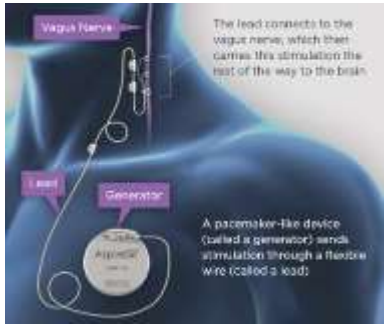


Electroconvulsive Therapy (ECT)

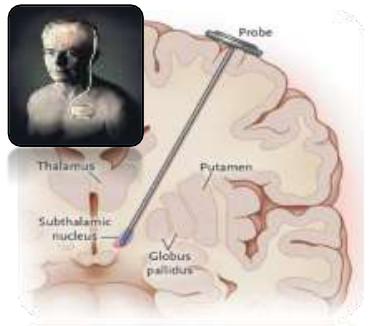
Transcranial Hi/Low intensity FUS (HI/LIFU)



Vagus Nerve Stimulation (VNS)



Deep Brain Stimulation (DBS)



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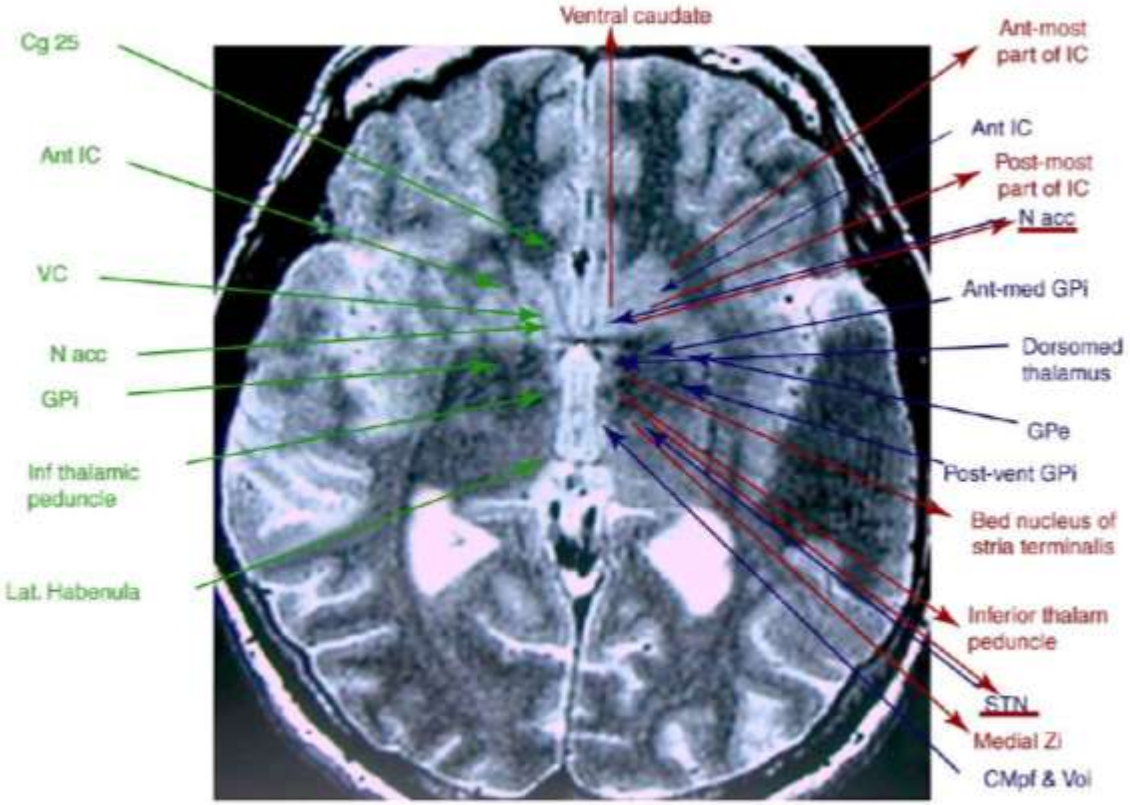
DBS in Psychiatric Disorders



Deep brain stimulation: from neurology to psychiatry?

Paul Krack[1,2], Marwan I. Hariz[3,4], Christelle Baunez[5], Jorge Guridi[6,7] and Jose A. Obeso[6,7]

Trends in Neurosciences, October 2010, Vol. 33, No. 10

„Which target to stimulate?“

…..or is that even the right question??

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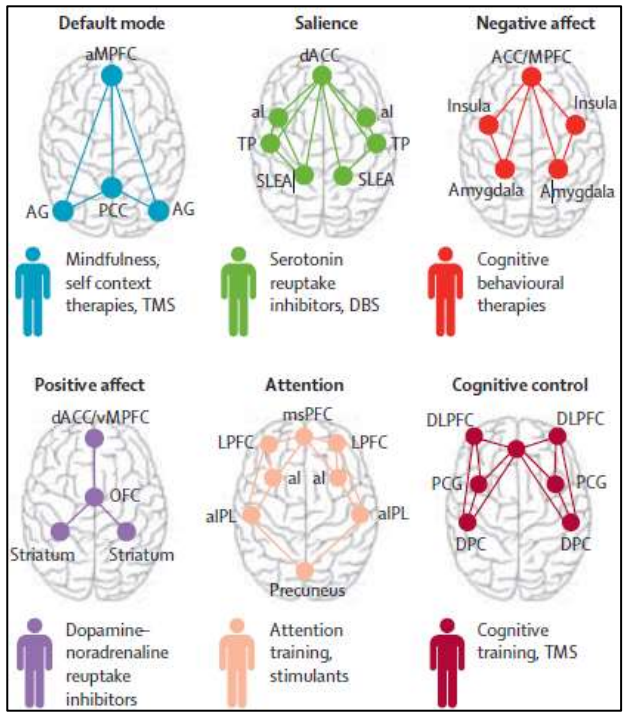
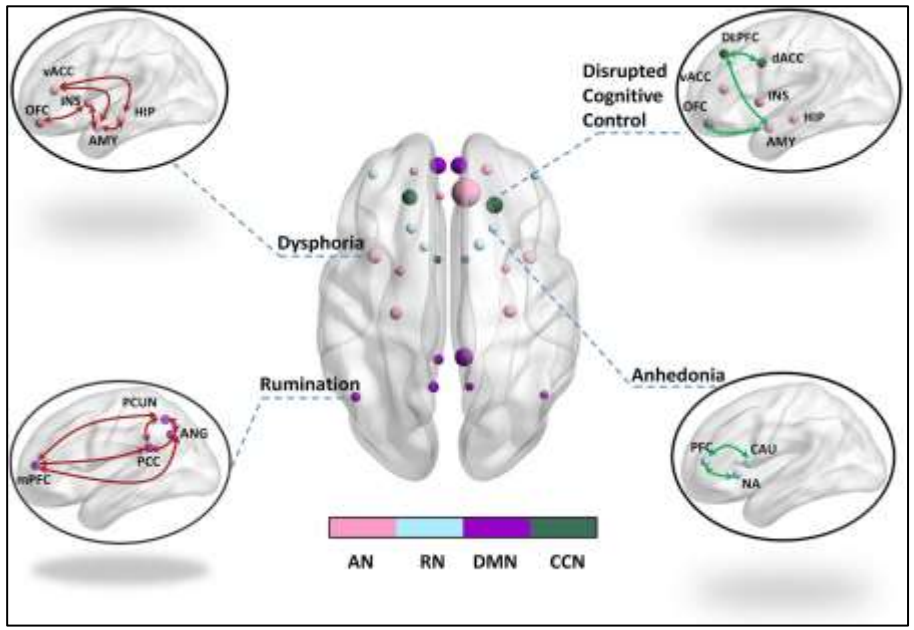
Networks associated with Depression



Precision psychiatry: a neural circuit taxonomy for depression and anxiety

Williams LM, Lancet Psychiatry 2016

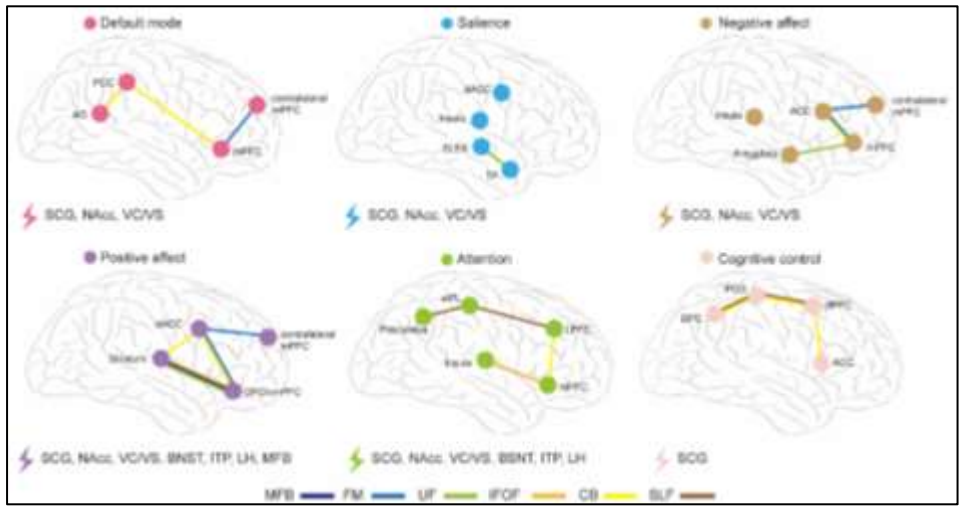


REVIEW ARTICLE

WILEY CNS Neuroscience & Therapeutics

A brain network model for depression: From symptom understanding to disease intervention

Li et al., CNS Neurosci Ther. 2018



White Matter Tracts Associated With Deep Brain Stimulation Targets in Major Depressive Disorder: A Systematic Review

Yu et al., Frontiers in Psychiatry 2022

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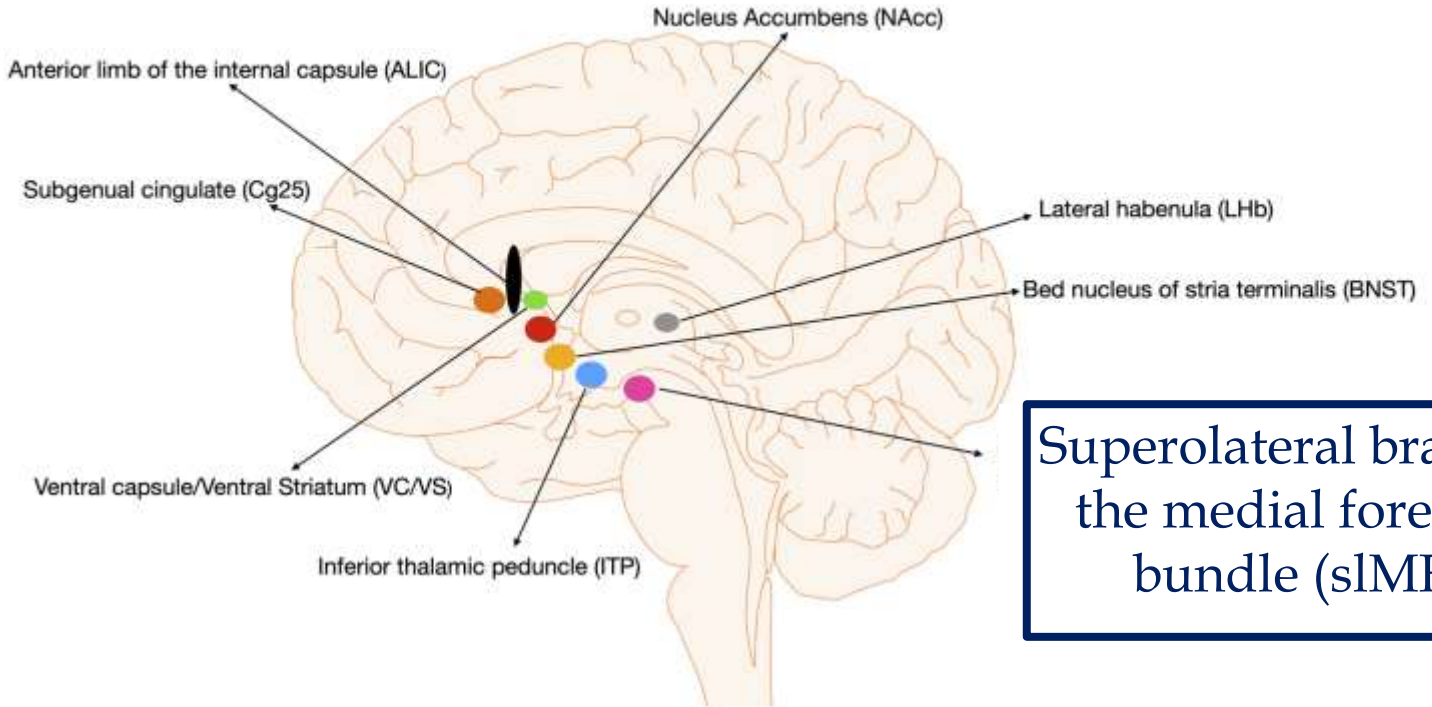
DBS and Depression



Superolateral branch of the medial forebrain bundle (slMFB)

REVIEW

Deep brain stimulation for psychiatric disorders: role of imaging in identifying/confirming DBS targets, predicting, and optimizing outcome and unravelling mechanisms of action

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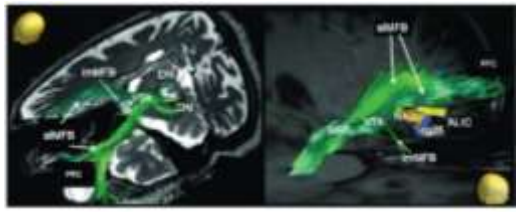
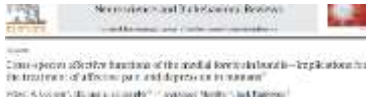
The Medial Forebrain Bundle (MFB)…

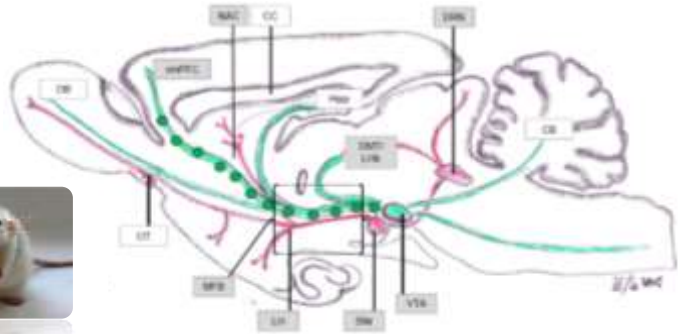
Why has the MFB become a clinical DBS target for TRD?
Why could it be one for eFUS?





- bidirectional projections between midbrain and forebrain
- multiple transmitter systems including DA, NA, GLU, GABA, etc
- feeds into multiple networks („Positive affect“/„Reward“/„Default mode“/„Cognitive and Control“
- the mesolimbic and mesocortical component of the bundle are associated with:

  motivation, exploration, drive-to-survive
  reward anticipation, reward orientated behavior
  „wanting“ vs „liking“



- *anhedonia* and *reduced motivation* are key clinical symptoms

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Clinical and preclinical MFB-DBS

Since 2013


Volker Coenen Thomas Schläpfer

Since 2015


Rapid Effects of Deep Brain Stimulation for Treatment-Resistant Major Depression

Thomas E. Schlaepfer, Bettina H. Bewernick, Sarah Kayser, Burkhard Mädler, and Volker A. Coenen

Fast onset and chronic improvement in the majority of patients
Schlaepfer et al, Biol.Psych. 2013

Deep brain stimulation to the medial forebrain bundle for depression- long-term outcomes and a novel data analysis strategy

Bettina H. Bewernick, MSc, PhD [a], Sarah Kayser, MD, MSc [a], Sabrina M. Gippert, MSc [a], Christina Switala, MSc [a], Volker A. Coenen, MD [b], Thomas E. Schlaepfer, MD [c,d,*]

Discontinuation of Superolateral Medial Forebrain Bundle Deep Brain Stimulation for Treatment-Resistant Depression Leads to Critical Relapse

On-going long-term follow-up, new cohorts and analysis
(Bewernick et al., Bra. Stim. 2017; Kilian et al., Biol. Psych. 2019)

Research paper

Deep brain stimulation of the medial forebrain bundle: Distinctive responses in resistant depression

A longitudinal study on deep brain stimulation of the medial forebrain bundle for treatment-resistant depression

Replication by other investigators
(Fenoy et al, Jour. Aff. Dis., 2016; Transl.Psych. 2018)

Electrical stimulation of the medial forebrain bundle in pre-clinical studies of psychiatric disorders

Máté D. Döbrössy [*], Luciano L. Furlanetti, Volker A. Coenen

Communication

New Insights into In Vivo Dopamine Physiology and Neurostimulation: A Fiber Photometry Study Highlighting the Impact of Medial Forebrain Bundle Deep Brain Stimulation on the Nucleus Accumbens

Lidia Miguel Telega [1,2,3,4] and Máté D. Döbrössy [1,2,*]

Neuromodulation in Psychiatric disorders: Experimental and Clinical evidence for reward and motivation network Deep Brain Stimulation: Focus on the medial forebrain bundle

Máté D. Döbrössy [1,2] | Chockalingam Ramanathan [1] | Danesh Ashouri Vajari [3] |

Medial forebrain bundle DBS differentially modulates dopamine release in the nucleus accumbens in a rodent model of depression

Danesh Ashouri Vajari [a,b], Chockalingam Ramanath
Volker A. Coenen [b,d,e,f], Máté D. Döbrössy [b,d,f,*]

Deep Brain Stimulation of the Medial Forebrain Bundle in a Rodent Model of Depression: Exploring Dopaminergic Mechanisms with Raclopride and Micro-PET

Stephanie Thiele [a,b] Arnd Sörensen [c] Jasmin Weis [a] Friederike Braun [c]
Philipp T. Meyer [c] Volker A. Coenen [a] Máté D. Döbrössy [a]

Slow Wave Sleep Deficits in the Flinders Sensitive Line Rodent Model of Depression: Effects of Medial Forebrain Bundle Deep-Brain Stimulation

Wilf Gardner, [a,b,c] Fanny Fochs, [b,c] Laura Durieux, [c] Patrice Bourgin, [a,c] Volker A. Coenen, [b,c] Máté Döbrössy [b,d,e,*] and

Electrophysiological and molecular effects of bilateral deep brain stimulation of the medial forebrain bundle in a rodent model of depression

F. Bühning [a,b], L. Miguel Telega [a,b,c], Y. Tong [a,b,c], J. Pereira [b,d], V.A. Coenen [a,b,c,f], M.D. Döbrössy [

The effects of bilateral, continuous, and chronic Deep Brain Stimulation of the medial forebrain bundle in a rodent model of depression

Stephanie Thiele [a,b], Luciano Furlanetti [c], Lisa-Marie Pfeiffer [a,b], Volker A. Coenen [a,c], Máté D. Döbrössy [a,c,*]

...n Union's Horizon Europe EIC-...101070931

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FUS induced bioeffects in the CNS

	Disorders / Mechanisms	Psychiatric Disorders	AD	PD	Essential Tremor	Epilepsy	Neuro Muscular Disorders	Neuro-pathic Pain	Intracerebral hemorrhage	Ischemic stroke	Cardio-vascular	Oncological
TISSUE DESTRUCTION	Thermal ablation	●		●	●	●	●	●			●	●
	Mechanical destruction	●				●					●	●
	Sonoporation	●		●								●
DRUG DELIVERY	Increased vascular permeability		●	●								●
	Local hyperthermia											●
	Drug delivery vehicles		●	●							●	●
	Vasodilation										●	●
	Vasocontriction											●
OTHER MECHANISMS	Chemotherapy sensitization											●
	Radiation sensitization											●
	Immunomodulation		●									●
	Clot lysis								●	●	●	
	Sonodynamic therapy											●
	Blood vessel occlusion/ coagulation										●	●
	Amplification of cancer biomarkers											●
	Stem cell homing		●	●								
	NEUROMODULATION	●		●	●	●	●	●				

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FUS induced neuromodulation

- UPSIDE is interested in **low intensity** stimulation that has **neuromodulatory** consequences
- typical parameters from the literature suggests that neuromodulation can be achieved at:

  200-500 kHz
  300-500 ms bursts of 0.5ms pulses
  1 kHz pulse repetition frequency (PRF)
  0.1 – 0.6 MPa pressure amplitude

- these parameters have shown to modulate Na^+, K^+, Ca^{2+} *transients*, *actions potentials*, and *synaptic transmission* via altering channel activity
- membrane deformation causing *capacitance changes*
- intramembrane *cavitation* model
- *mechanosensitive* ion channel modulation

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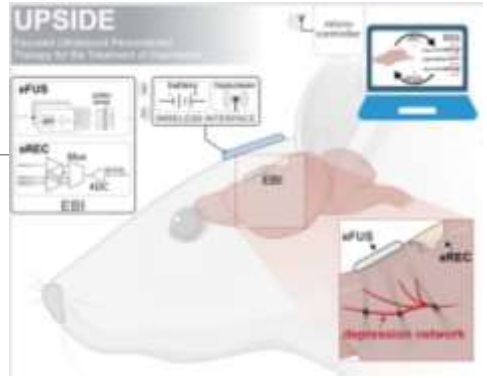
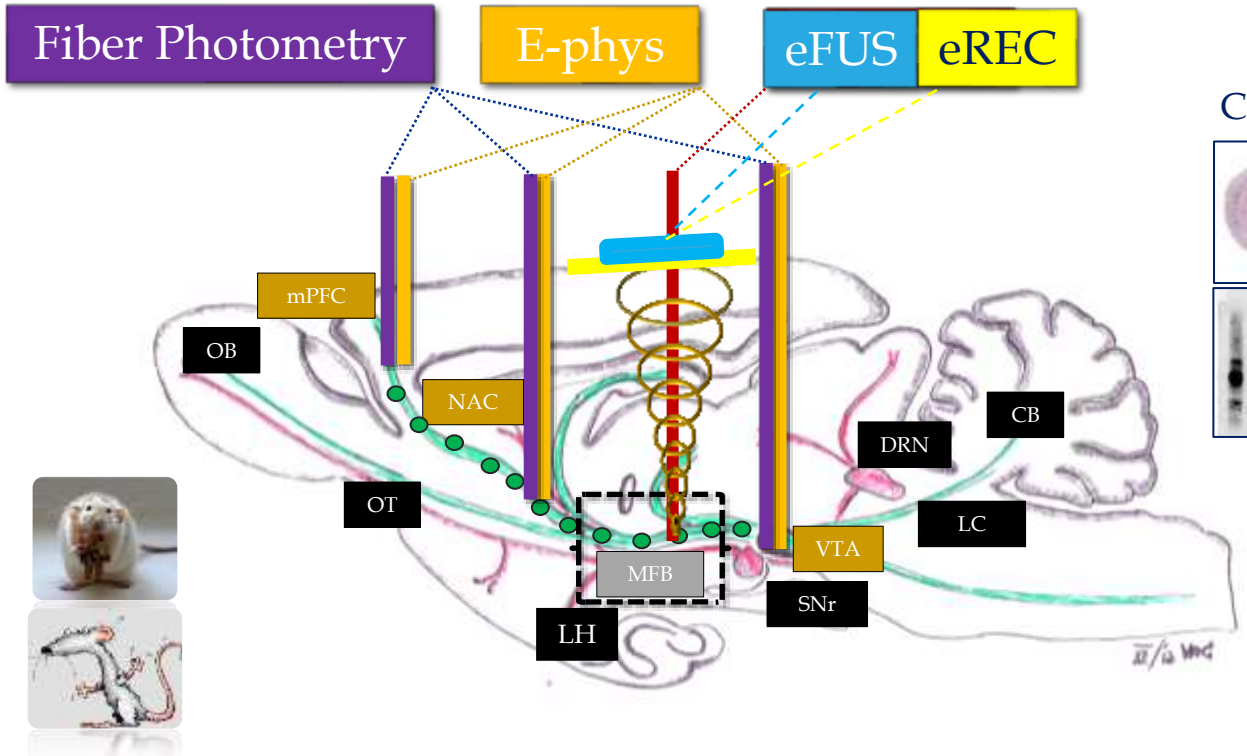
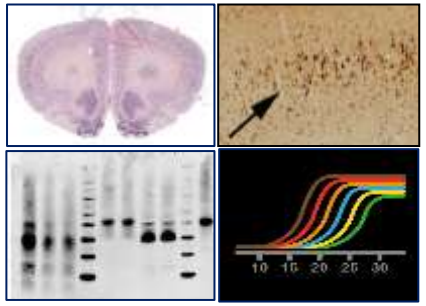
The experimental objectives…



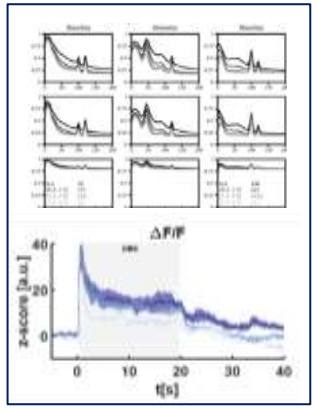
- … the *in vivo* acute and chronic investigation of the eFUS/eREC chip in a preclinical rodent model of depression …..



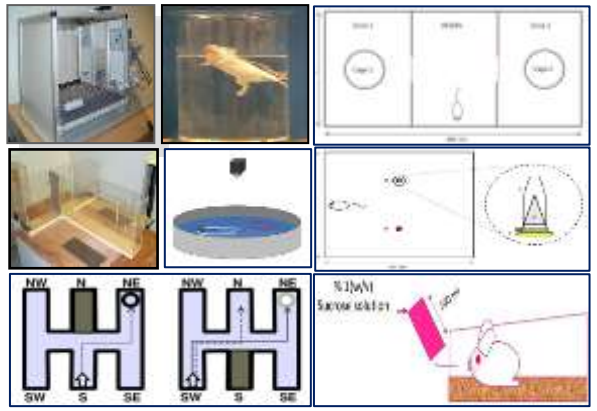
Cellular and molecular



Physiological



Behavioural



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Advantages of eFUS (in theory)….

1. Between being fully invasive and non-invasive
2. Permits acute and chronic stimulation
3. Steerability of beam:
   - possibility of adjustment on will
   - could be achieved with patient specific 3D brain atlas
4. Stimulation of multiple targets…simultaneously or sequentially
5. Would permit the integration of closed-loop control
6. …..

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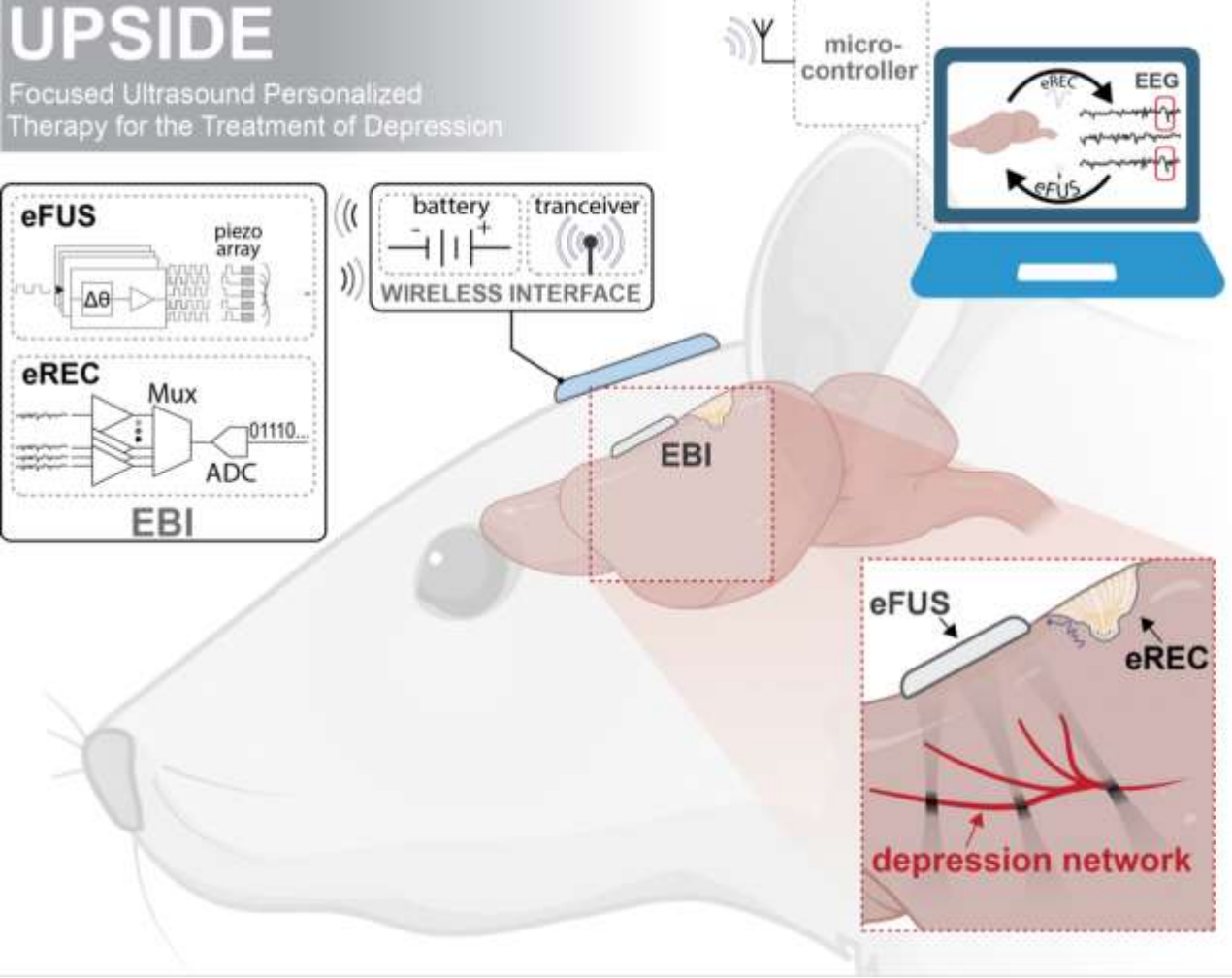

The vision of epidural focused ultrasound neuromodulation for Treatment-Resistant Depression

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