



Tampere University Hospital

New Research on ECT and development of neuromodulation for treatment of depression

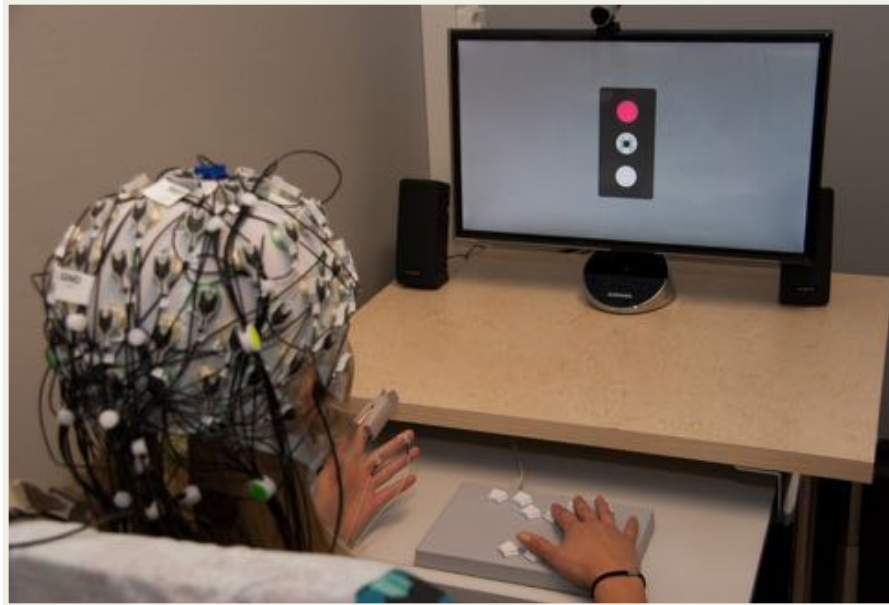
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<http://www.uta.fi/med/tutkimus/kayttaytymisneurologia/index.html>



Behavioral Neurology Research Unit

- **Aims**
 - ***At better understanding***
 - of brain networks, mechanisms, dynamics behind cognition, emotion and behavior
 - the effect of brain disorders, brain damage and neuromodulation on mental functions
 - ***To develop better methods***
 - For detecting alterations in cognition, emotion and behavior
 - ***To identify biomarkers***
 - For adjusting or optimizing neuromodulation parameters

<http://www.uta.fi/med/tutkimus/kayttaytymisneurologia/index.html>

The effect of neuromodulation on cognitive and affective brain functions

Electroconvulsive therapy (ECT)

- Depression

Vagus Nerve stimulation(VNS)

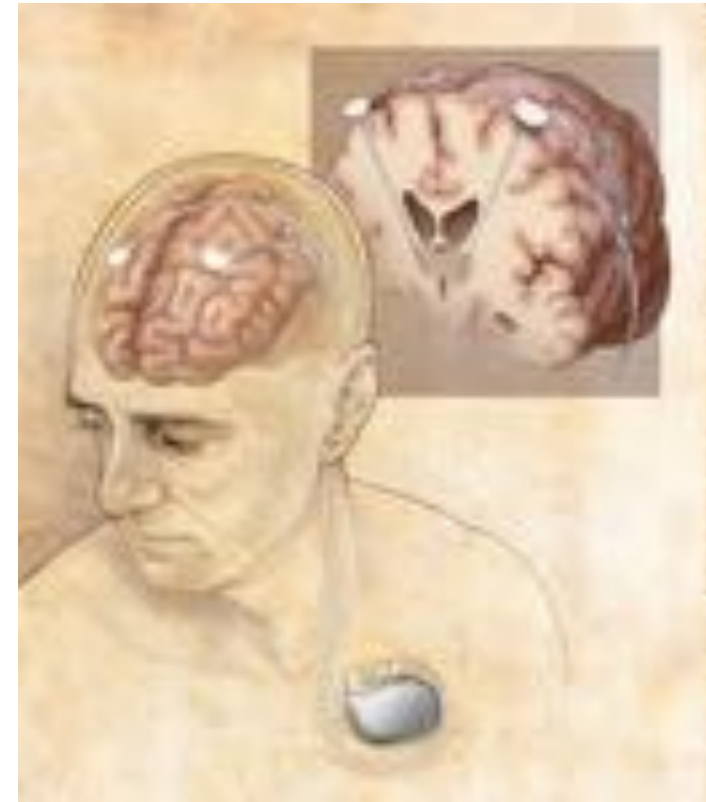
- Epilepsy

Transcranial Direct Current Stimulation (TDCS)

- Depression
- Neurological Rehabilitation?
- Enhancing Cognition?

Deep Brain Stimulation (DBS)

- Epilepsy, depression, OCD



Behavioral Neurology Research Unit - Methods

Brain Physiology

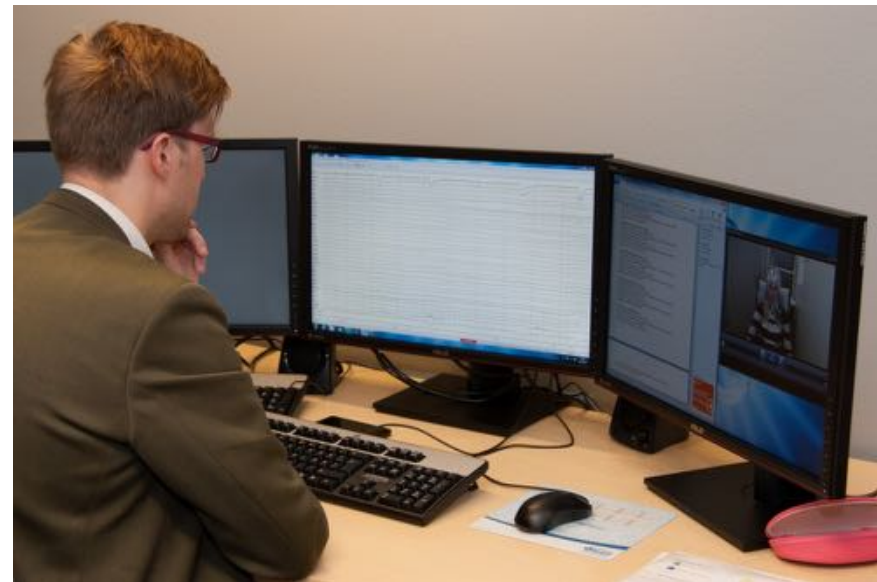
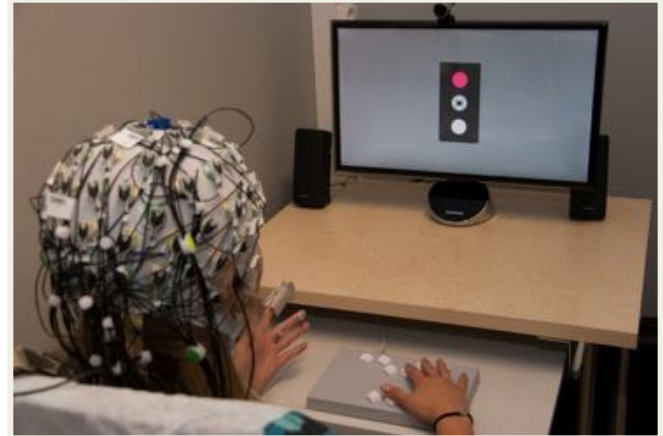
- 64 channel active electrode EEG

Autonomic nervous system

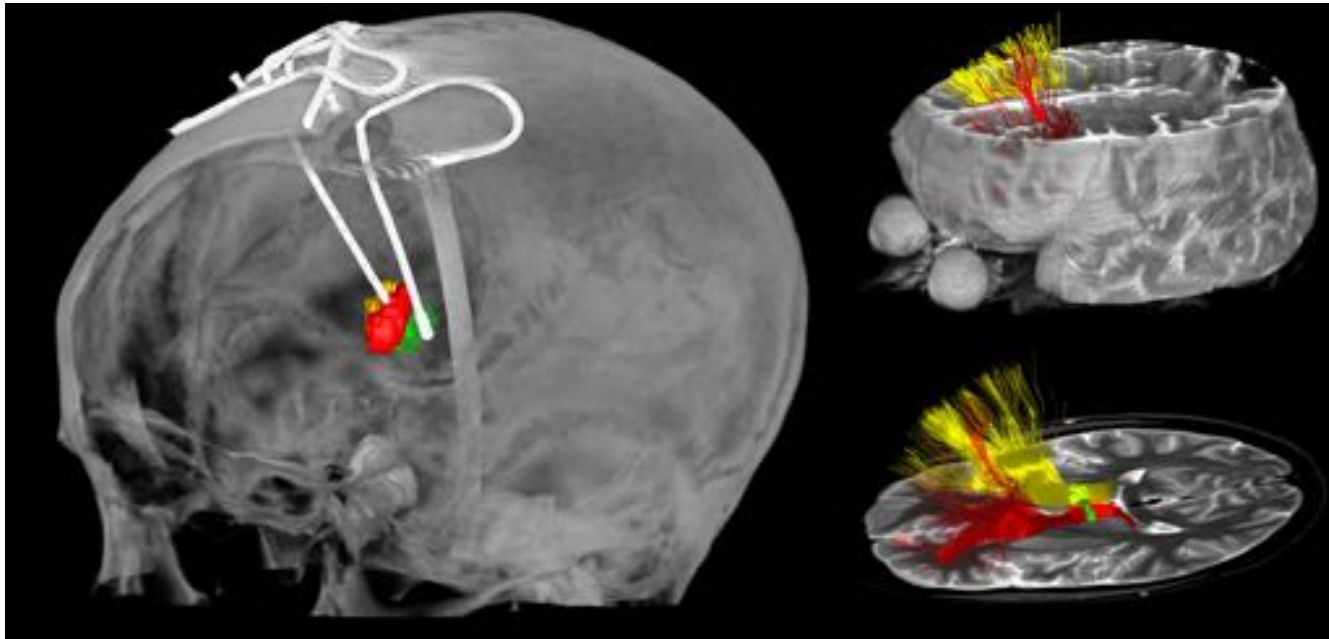
- Skin conductivity measurement
- Pulse, ECG

Behavior

- Performance, reaction times, accuracy
 - *Computer based test of attention and executive functions*
- Standardized questionnaires

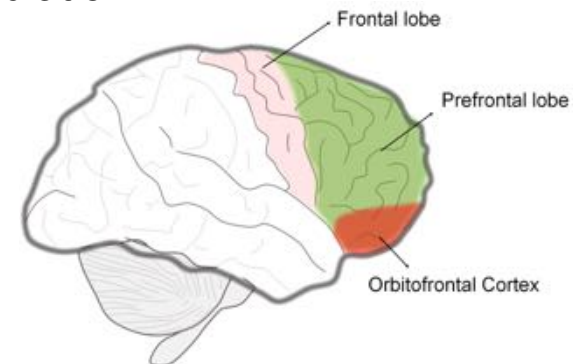


Lesion method



Reversible "lesion"/dysfunction in deep brain structures – key nodes of associative and limbic circuitry with deep brain stimulation

Focal brain lesion due to brain injury





Tampere University Hospital



Behavioral
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Research Unit

ECT for Major Depressive Disorder (MDD) and executive functions

Jari Peräkylä, Kaija Järventausta,
Piia Haapaniemi, Kaisa Hartikainen

Attentional resources

Attention is a prerequisite for other cognitive functions such as memory

Two different aspects of attention

- Bottom-up: reaction to external impulse
 - stimulus driven
- Top-down: conscious control of attention
 - goal driven (frontal lobes)
- Processing capacity is limited
 - We need neural mechanisms to direct our attention to things of importance
 - *"competition" for attentional resources*
 - *Emotional stimuli capture these resources*

Executive Functions

A very broad term including:

- Regulation of attentional resources
- Control of cognitive and emotional processes



Executive functions are crucial for daily life

- Guide behavior towards a goal especially when facing novel non-routine situations
- Orchestrates use of other cognitive capabilities: attention, memory, etc.

Key functions

- Formation of goals
- Planning actions to achieve the goals and
- Monitoring the execution of those actions

Executive functions and self-regulation



Working Memory

Ability to keep information active, easily retrievable and shield it from distraction



Inhibition

Deliberately inhibit dominant, automatic, habitual or prepotent responses



Shifting, i.e. Cognitive flexibility

Ability to shift between multiple Tasks, goals and mental sets back and forth

Self-regulation: Goal-directed behavior, personal strivings

Self-control: Overriding unwanted, prepotent impulses or urges

Emotional self-regulation

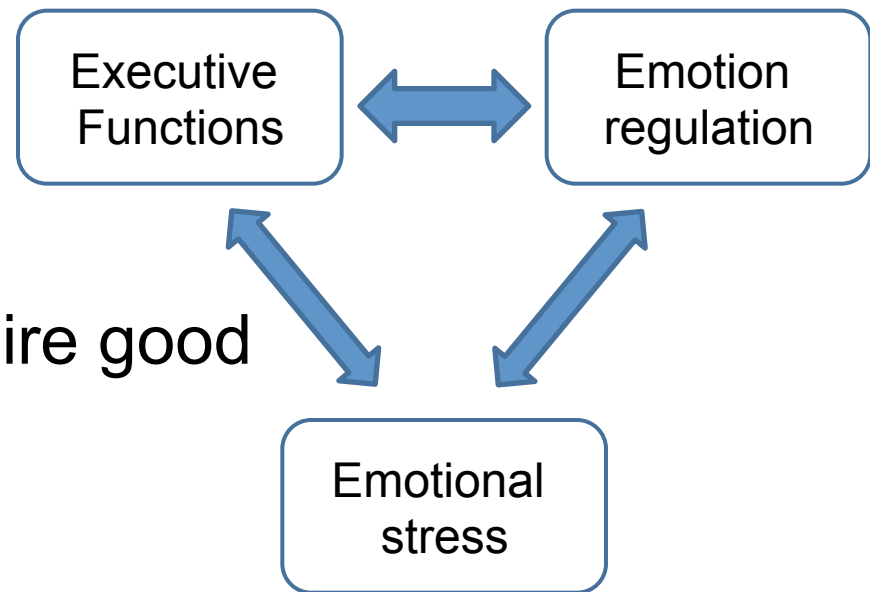
Positive strategies

- Re-appraisal
- Problem solving
- Acceptance

Positive strategies require good Executive Functions!

Negative strategies

- Rumination
- Suppression
- Avoidance

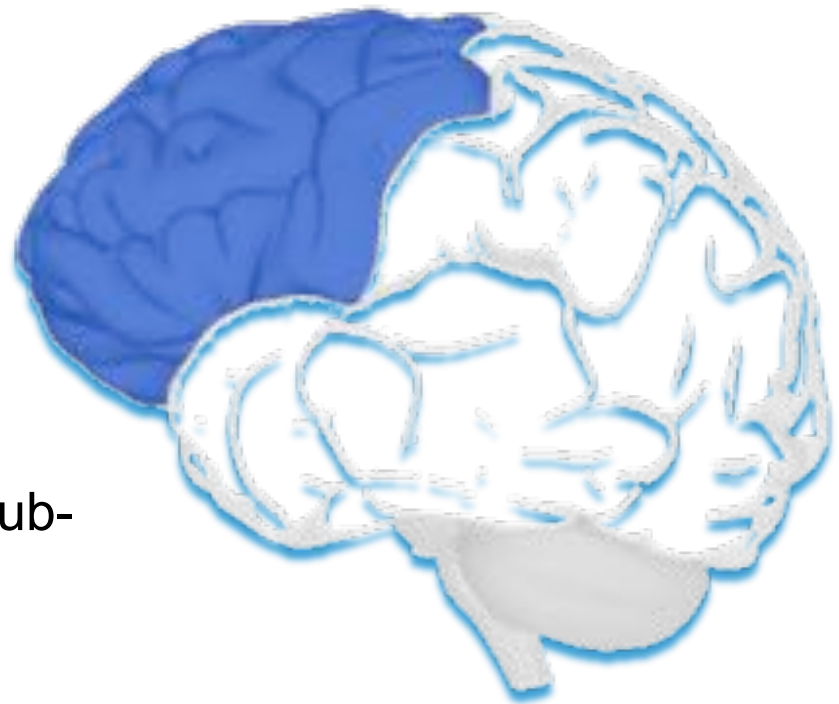


Frontal circuits and executive functions

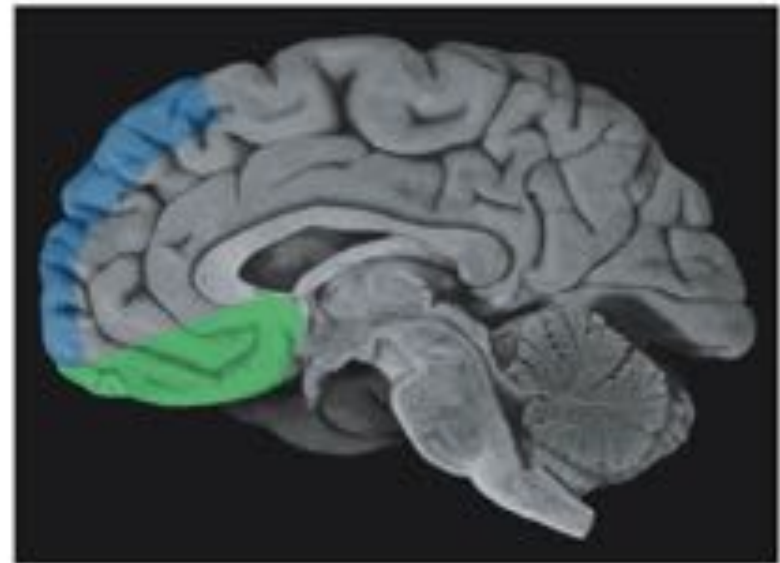
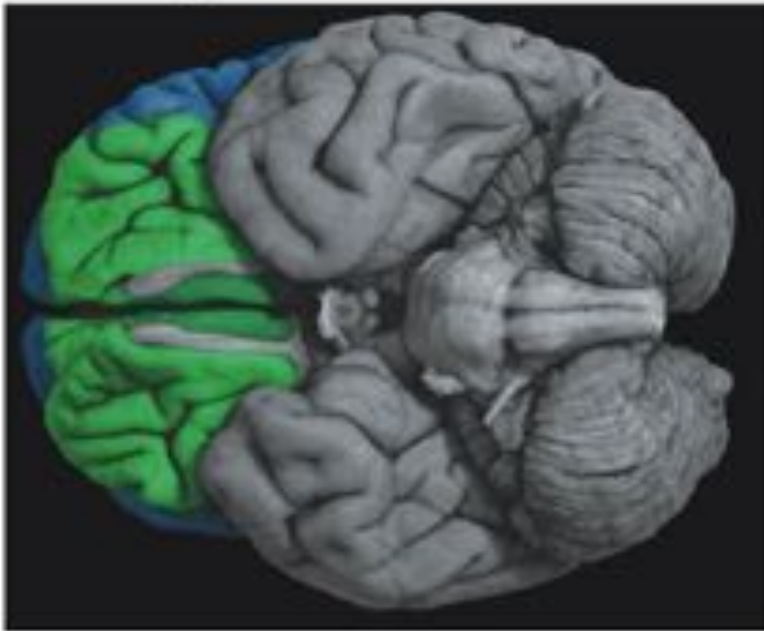
Prefrontal cortex is necessary for these functions:

- *Orbitofrontal cortex*
- *Dorsolateral prefrontal cortex*
- *Anterior cingulate*

Also circuits with posterior cortical and sub-cortical structures



(a) The prefrontal cortex in humans



Orbitofrontal cortex

Executive control of
Emotion
Emotional behavior

Dorsolateral prefrontal cortex

Cognitive control
Attentional control

Anterior cingulum

Motivation, drive, initiation,
monitoring behavior



Circuits involved in depression

Dorsal components related to motor and cognitive symptoms in depression

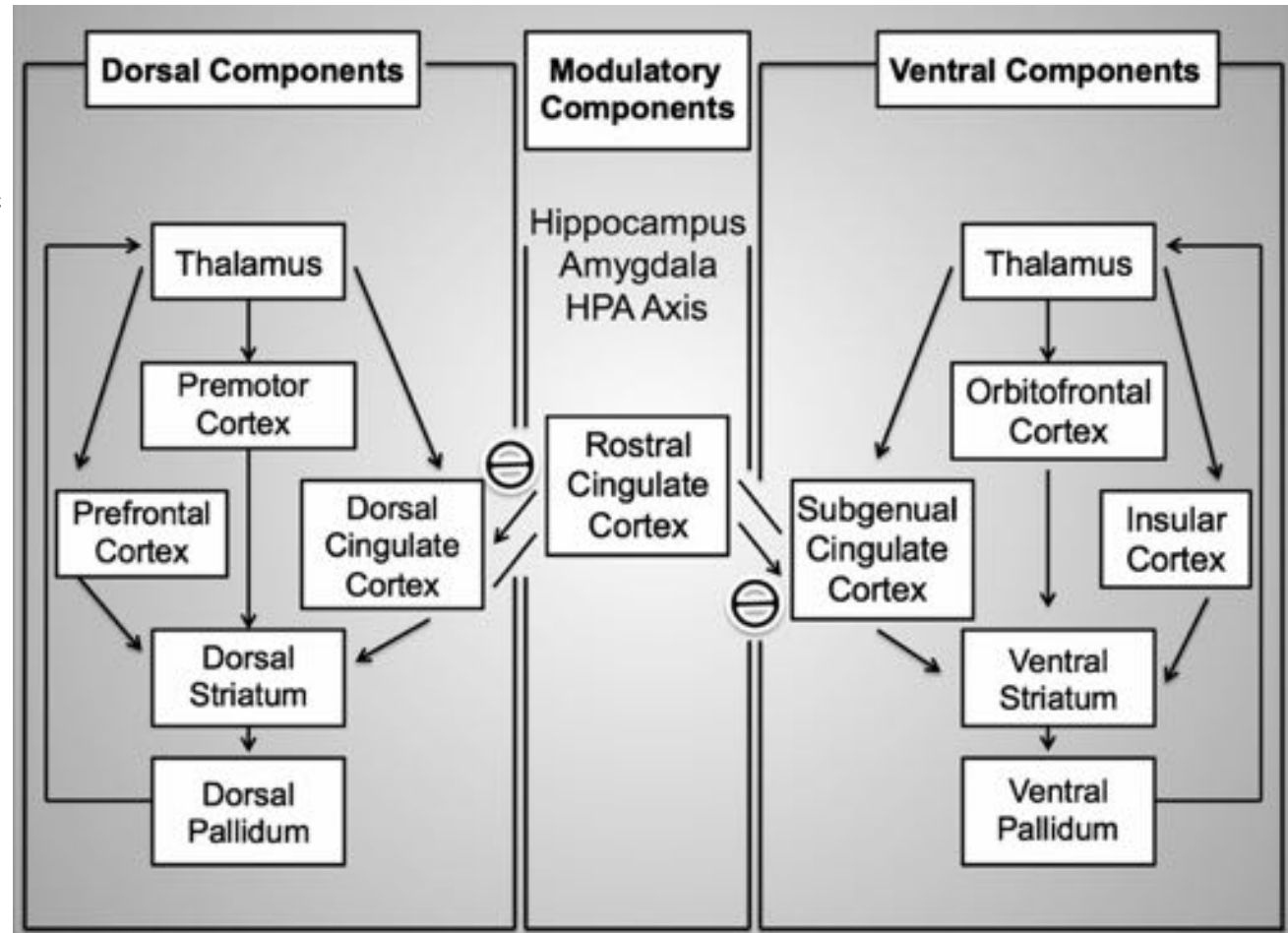
Ventral component related to somatic and vegetative symptoms in depression

Modulatory part balances the dorsal and ventral components

Circuits derived from neuroimaging experiments

Hypo- and hyper activity in depression

- Hypoactivity in the dorsal part
- Hyperactivity in the ventral part



Depression and Executive Functions

Depression has been linked with

- hypoactivity in the dorsolateral prefrontal cortex
- deficits in Executive Functions

Impairment has been found in all key EF processes

- working memory, inhibition, shifting

Two-thirds of depressed patients and one-third, one-half of remitted depressed patients suffer from cognitive impairment

Cognitive impairment is an important aspect of MDD

Impaired ability to think, concentrate or make decisions is a diagnostic criterion for MDD

It is thought that cognitive impairment is a core feature of depression, not just an epiphenomenon of depression or entirely secondary to lower mood

(Meta-analysis and Review by Rock et al 2014 in Psychological Medicine, Snyder 2013 in Psychol Bulletin)

MDD and emotion attention interaction

Depressed individuals

- Attentional bias to negative stimuli
 - *Attend faster and longer to negative emotional stimuli*
- Interpret environmental and social stimuli more negatively than healthy peers
- Remember negative material better



Leads to negative cognitive triad with

- negative view about themselves,
- the environment and
- the future

ECT and Cognition

Most acutely effective treatment of depression

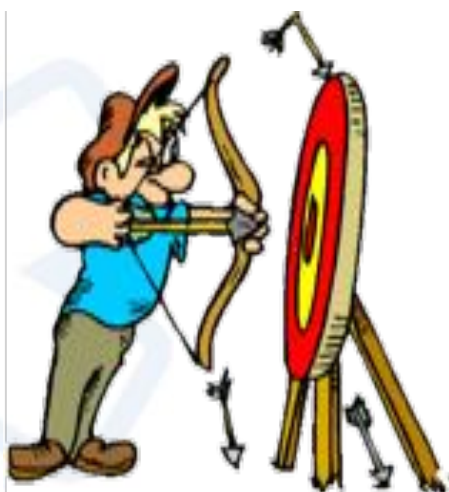
Use limited by cognitive side effects, mainly memory problems

Safety vs. Tolerability

Cognitive side effects (episodic memory and executive functions) mostly limited to 3 days post-ECT, return to baseline or improvement noted after 15 days (Semkovska and McLoughlin in Biol Psychiatry 2010)



Aims of the Study



1. Effect of ECT on higher cognitive control functions i.e. executive functions
2. Effect of ECT on emotion-attention and emotion-executive function interaction
3. Suitability of computerized Executive functions test to assess changes in executive functions before and after ECT treatment
4. Applicability of BRIEF-A questionnaire on assessing executive functions before and after ECT

Methods

17/32 subjects with pharmaco-resistant depression treated with ECT

Subjects were tested with computer based Executive Reaction Time (RT) Test before and 3-7 days after ECT treatment.

- Treatment included ~10 ECT (bilateral) sessions during 3 weeks according to Tampere University Hospital ECT protocol

Subjects and their informant also filled in BRIEF-A questionnaire assessing executive functions before and after treatment



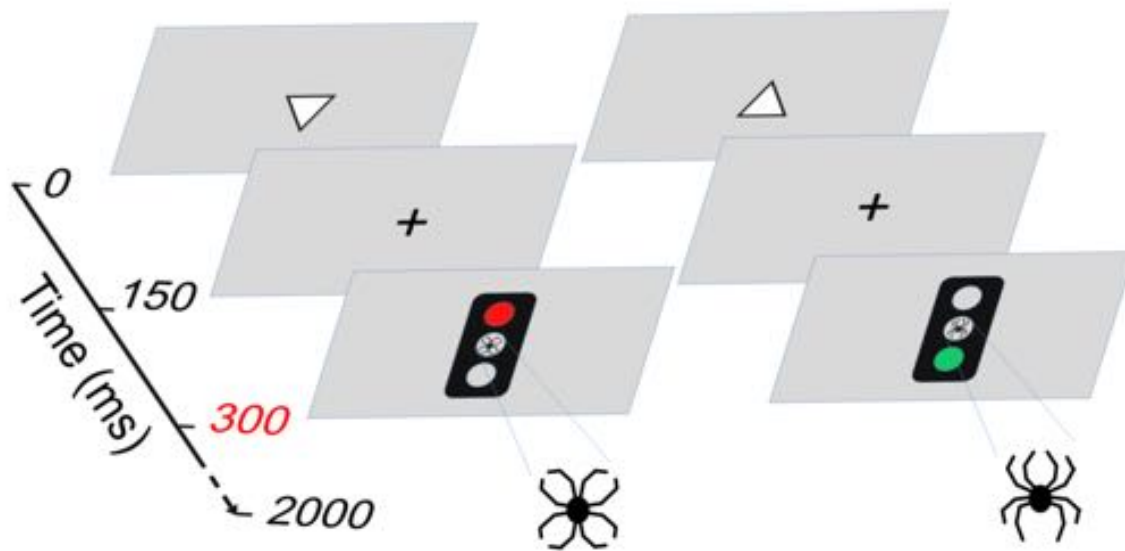
Standardized neuropsychological tests

Not sensitive to mild executive dysfunction/alteration in efficacy of executive functions

- Test that assesses one cognitive domain such as language, memory, attention at a time do not challenge executive function
- Structured testing environment: Neuropsychologists give the structure i.e. provides the executive control "what to do and when" thus patients' executive control functions are not challenged
- Learning effect, long testing, bottleneck trained neuropsychologist
- Everyday life challenges executive control with multiple cognitive processes required at any given moment, unexpected and novel situations, need to suppress impulses and distractors in order to stay on goal or behave socially appropriately, need to switch goals or ways of behavior when context or circumstances change (work, home, safe environment, potential danger)

Executive-RT test

Test of Executive Functions



Performance measures

Reaction Time

Total errors – Overall Performance

Incorrect Responses – Working Memory

Missing Responses – Sustained Attention

Commission Errors – Inhibition

Hartikainen K.M., Wäljas M., Isoviita T., Dastidar P., Liimatainen S., Solbakk A.K., Ogawa KH, Soimakallio S., Ylinen A., Öhman J. Persistent symptoms in mild to moderate traumatic brain injury associated with executive dysfunction. *Journal of Clinical and Experimental Neuropsychology*. 2010; 32 (7), 767-774

Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)

BRIEF: A standardized questionnaire originally developed to assess impairment of executive functions in children and adolescents (5-18 years)

- Parent and teacher input
- Self report

BRIEF-A: Adult version (18-90 years)

- Self report form
- Informant form

Consists of

- Generic Executive Composite
- Metacognition Index
- Behavioral Regulation Index
- Eight behavioral indices

General Executive Composite

Meta-Cognition

Monitor

Plan/Organize

Organization of Materials

Working Memory

Initiate

Behavioral Regulation

Shift

Inhibit

Emotional Control

Results

Depression was alleviated

- BDI: dropped from 35.2 points (Severe depression) to 17.8 points (Mild depression)
- MADRS: dropped from 36.4 points (Severe depression) to 11.9 points (Mild depression)

Executive functions improved

- Executive-RT test: Inhibitory top-down control, shielding working memory from emotional distraction, attention control
- BRIEF-A: Subjective improvement of executive functions

Discussion

ECT is effective in alleviating depression

ECT improved executive functions

- Patients working memory, attention and inhibition/top-down control improved

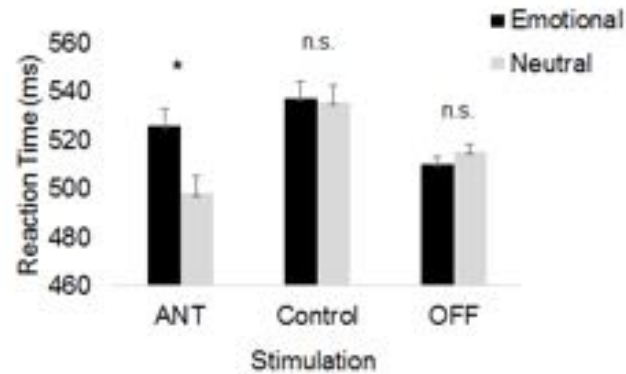
Improved mood -> improved cognition, causal relation uncertain

Upregulation of trophic factors?

After ECT treatment Emotional reactivity to threat was altered

-Behavioral Biomarker?

Behavioral and Electrophysiological biomarkers of emotion-attention interaction and their alteration due to neuromodulation

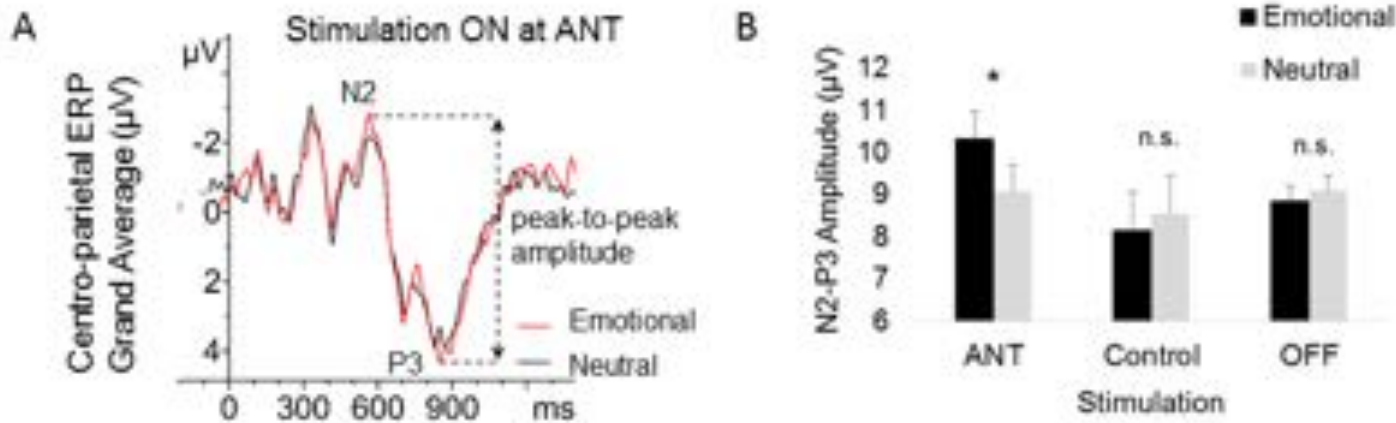


Emotional distractor



Neutral distractor

ANT-DBS enhances attention allocation to threat



Sun, Lihua; Peräkylä, Jari; Polvivaara Markus; Öhman Juha, Peltola, Jukka; Lehtimäki, Kai; Huhtala, Heini; Hartikainen, Kaisa. [Human anterior thalamic nuclei are involved in emotion-attention interaction](#). *Neuropsychologia*, 2015 Oct 3. pii: S0028-3932(15)30179-2. doi: 10.1016/j.neuropsychologia.2015.10.001.

Studies going on in Tampere



The immediate impact of TDCS on cognition, specifically on emotion-executive function interaction in healthy subjects

The efficacy of TDCS in treatment of depression and impact on cognition

Impact of DBS in treatment of OCD, MDD and epilepsy on brain circuits underlying mental functions

Summary

- Sensitive and objective methods for detecting alterations in cognitive and emotional functions are needed to
 - To better understand the alterations of basic affective and cognitive functions due to mental disorders
 - To better understand the mechanisms of action of neuromodulatory treatment
 - Detecting effects of neuromodulation affective and cognitive brain functions
 - Optimizing neuromodulation treatment



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