Anhedonie, depressieve stemming en hersenstimulatie

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DISCLOSURE

- Relevant Financial Relationship(s)
  - None

- Off-Label Usage
  - None
OUTLINE

I

Anhedonia, brain imaging and Major Depression

II

rTMS, Neuroscience and Major Depression

III

Discussion
Anhedonia, the loss of interest and joy in (nearly) all activities, is a prominent symptom of a lot of psychiatric illnesses, especially in depressive disorders, schizophrenia and addiction.

Anhedonia relates to impairments in brain reward processing.

Anhedonia represents a core symptom of major depression and may be a potential marker for melancholia.
To be diagnosed as **Major Depression with melancholic features**, one must have at least **three** of these symptoms (DSM 5):

1. A distinct quality of depressed mood characterized by profound despondency, despair, or emptiness
2. Depression is **worse in the morning**
3. Early morning waking of at least two hours earlier than normal
4. **Psychomotor disturbances** of either retardation, the slowing of normal movement, or agitation, increased and/or irregular movement
5. Anorexia or **weight loss**
6. Excessive or inappropriate guilt
(An)hedonia

• The reward system
  – The mesolimbic DA pathway
  – The cortico striatal DA pathway

DA: dopamine
Major Depression

'healthy'

Frontal Cortex

'depressed'

Limbic System
High Frequency - rTMS

> 1Hz
‘increase cortical excitability’

Low Frequency - rTMS

≤ 1Hz
‘decrease cortical excitability’

DLPFC: dorsolateral prefrontal cortex

Lefaucheur et al., 2014 Clin Neurophysiology
• TMS action

| • PFC  | • ACC  | • Limbic system |

→ Restores normal communication between mood regulation components
OUTLINE

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Discussion
(r)TMS procedure

Non-invasive, ‘painless’, no anesthesia (ECT)

Conscious

Allows a non-invasive stimulation of well defined neocortical regions

Allows to investigate causal relationships between brain activity and behaviour
(r)TMS mechanisms

CAVE: the effects of cortical TMS on the subcortical structures are indirect…and electrical…
‘Unipolar’ depression

Lefaucheur et al., 2014

Level A evidence

HF-rTMS
Left DLPFC
Multiple sessions

Modest

Brunoni et al., 2017 JAMA Psy

Schutter 2009, Psych Med
Clinical Neuroscience

1. Can brain imaging techniques be used to guide and improve clinical efficacy of rTMS treatment?

2. Focus on anhedonia
The role of the reward system?

\[ \rightarrow \text{rTMS increases dopamine release in the striatum, ACC and OFC} \]

(Cho et al., 2009; Strafella et al., 2001, 2003)
The role of the reward system

- **Probabilistic learning Task** (Pizzagalli et al., 2005)

3 Blocks: B1, B2, B3
100 trials per block

Depressed patients
WAS IT?

the **SHORT** mouth or the **LONG** mouth

?
CORRECT !!
YOU WON
5 CENTS
1. Study 1

2. Study 2

PhD Romain Duprat
1. Study 1

2. Study 2
Study 1: Single Session

- **Cross-over design**

20 participants
mean age: 23 years old

4 task measurements
pre/post 1st stimulation
pre/post 2nd stimulation
Study 1: Results

- **Response Bias**

Significant effect with trait ‘hedonia’
(TEPS: temporal experience of pleasure scale)
Study 1: Summary

1. The more ‘hedonic’ the participant, the faster reward learning after real stimulation

2. The level of hedonic capacity may positively influence the rTMS modulatory effect on the reward system

1. Study 1

2. Study 2
STUDY 2

- Crossover design: Accelerated aiTBS

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td>Monday</td>
<td></td>
</tr>
<tr>
<td>FMRI 1</td>
<td>FMRI 2</td>
</tr>
<tr>
<td>Real aiTBS</td>
<td>Sham</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SHAPS &gt;= 7</td>
<td></td>
</tr>
<tr>
<td>37 TRD patients</td>
<td></td>
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<tr>
<td>18 high Anhedonic</td>
<td></td>
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<tr>
<td>19 low Anhedonic</td>
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<tr>
<th>Follow-up tests</th>
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<tbody>
<tr>
<td>FMRI 3</td>
</tr>
<tr>
<td>Real aiTBS</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>2 weeks</td>
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SHAPS >> 7
Snaith-Hamilton Pleasure Scale

(http://clinicaltrials.gov/show/ NCT01832805)
RESULTS

Repeated measure 3X3X2X2 ANCOVA with Time and Block as within-subject factors; Order and Group as between subject factors and Age, Gender and deltaHDRS as covariates.

Behavioral results:

No significant effect on response bias

- Peak intensity in the right OFC
- The caudate and putamen were also part of the cluster

(k=8929; MNI: x=15, y=30, z=-18; FWE corrected at the cluster level p<0.05)
RESULTS

- Baseline: HighA vs LowA at
  - LowA display more activity in:
    - Putamen
    - Caudate
  - Reward learning deficits in depression; especially in HighA patients
RESULTS

- Pre/post real stimulation

**High anhedonic patients**

**HighA group**
Real vs Baseline

*Increased activity post-aiTBS*
Left rTMS differentially modulates the reward system based in the level of anhedonia

The clinical effects of left rTMS are not via the reward system

Our findings suggest different biological subtypes of depression?

Depression subtypes

Anhedonia
Resting-state connectivity biomarkers define neurophysiological subtypes of depression

Andrew T Drysdale\textsuperscript{1,2,3}, Logan Grosenick\textsuperscript{4,5}, Jonathan Downar\textsuperscript{6}, Katharine Dunlop\textsuperscript{6}, Farrokh Mansouri\textsuperscript{6}, Yue Meng\textsuperscript{1}, Robert N Fetch\textsuperscript{1}, Benjamin Zebley\textsuperscript{7}, Desmond J Oathes\textsuperscript{8}, Amit Etkin\textsuperscript{9,10}, Alan F Schatzberg\textsuperscript{9}, Keith Sudheimer\textsuperscript{9}, Jennifer Keller\textsuperscript{9}, Helen S Mayberg\textsuperscript{11}, Faith M Gunning\textsuperscript{2,12}, George S Alexopoulos\textsuperscript{2,12}, Michael D Fox\textsuperscript{13}, Alvaro Pascual-Leone\textsuperscript{13}, Henning U Voss\textsuperscript{14}, BJ Casey\textsuperscript{15}, Marc J Dubin\textsuperscript{1,2}, and Conor Liston\textsuperscript{1,2,3}

N = 1188

Machine learning

Anxiety related

abnormal in fronto-amygdala connectivity.
Resting-state connectivity biomarkers define neurophysiological subtypes of depression

Andrew T Drysdale¹,²,³, Logan Grosenick⁴,⁵, Jonathan Downar⁶, Katharine Dunlop⁶, Farrokh Mansour⁶, Yue Meng¹, Robert N Fetcho¹, Benjamin Zebley⁷, Desmond J Oathes⁶, Amit Etkin⁹,¹⁰, Alan F Schatzberg⁹, Keith Sudheimer⁹, Jennifer Keller⁹, Helen S Mayberg¹¹, Faith M Gunning²,¹², George S Alexopoulos²,¹², Michael D Fox¹³, Alvaro Pascual-Leone¹³, Henning U Voss¹⁴, BJ Casey¹⁵, Marc J Dubin¹,², and Conor Liston¹,²,³

N= 1188

17-item HDRS

Anergy and fatigue

Machine learning

Reduced connectivity with anterior cingulate and orbitofrontal cortex
Resting-state connectivity biomarkers define neurophysiological subtypes of depression

Andrew T Drysdale1,2,3, Logan Grosenick4,5, Jonathan Downar6, Katharine Dunlop6, Farrokh Mansouri6, Yue Meng1, Robert N Fetcho1, Benjamin Zebley7, Desmond J Oathes6, Amit Etkin9,10, Alan F Schatzberg9, Keith Sudheimer9, Jennifer Keller9, Helen S Mayberg11, Faith M Gunning2,12, George S Alexopoulos2,12, Michael D Fox13, Alvaro Pascual-Leone13, Henning U Voss14, BJ Casey15, Marc J Dubin1,2, and Conor Liston1,2,3

N = 1188

Anhedonia
Psychomotor retardation

17-item HDRS

Machine learning

Increased thalamic and frontostriatal connectivity
Resting-state connectivity biomarkers define neurophysiological subtypes of depression

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N= 154

dmPFC

Anergy

Anhedonia
Resting-state connectivity biomarkers define neurophysiological subtypes of depression

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N=154

dmPFC
Anhedonia, brain imaging and Major Depression

rTMS, Neuroscience and Major Depression

Discussion
1. Longer treatment duration
2. Higher intensities
3. More pulses
4. Accurate localization
5. Personalize parameters

Gershon et al., 2003, Am J Psychiatry
Fitzgerald et al., 2009, Neuropsychopharmacology
Drysdale et al., 2017, Nature Med
Biotypes

Brain biomarkers

Major Depression

RESPONSE

Dorsolateral Prefrontal Cortex

Dorsomedial Prefrontal Cortex

Dorsal ACC

Ventral ACC

BA 25

OFC

Hippocampus

Thalamus
3rd European Conference on Brain Stimulation in Psychiatry

FUTURE PERSPECTIVE FOR A CLINICAL USE

October 18-20th, 2018
Lyon, France

www.brain-stimulation.eu
Multidisciplinary effort

Rudi De Raedt, PhD
Josefien Dedoncker, Msc
Sarah Herremans, MD, PhD
GuoRong Wu, PhD
Peter Van Schuerbeek, PhD
Gilbert Lemmens, MD, PhD
Robrecht Dockx, MD
Linde De Wandel, Msc
Cleo Crunelle, PhD
Karen Caeyenbergs, PhD
Remue Jonathan, PhD
Bernard Sabbe, MD, PhD

Thank you for your attention