Het plastische OCD brein:
nieuwe aanknopingspunten voor preventie, vroeginterventie en innovatieve therapieën

Prof.dr. Odile A. van den Heuvel
Psychiater VUmc

oa.vandenheuvel@vumc.nl
Emotional paradigms in OCD: Meta-Analysis

- 23 studies focusing on emotional processing in OCD
  - 9 symptom provocation (images)
  - 6 emotional faces (images)
  - 8 other (written symptom provocation/cognitive-emotional tasks)

Total number of OCD patients: 514
Total number of healthy controls: 512

OCD > HC

Increased activation in:
- bilateral amygdala
  - symptom provocation > other paradigms
  - unmedicated patients > medicated patients
- right putamen
  - medicated patients > unmedicated patients
- subgenual ACC / OFC

Thorsen et al., Biol Psych CNNI (in press)
Resting state fMRI may be a useful tool in the future to predict response to CBT in OCD patients.

Higher ‘degree centrality’ (= the number of links incident upon a node) in right basolateral amygdala predicts better response to CBT.

Gottlich et al. 2015, Biol Psychology
pre-SMA Hyperactivity in OCD + Siblings

SJ de Wit et al., 2012, Am J Psychiatry
dlPFC Hyperactivity/Inefficiency in OCD + Siblings

FE de Vries*, SJ de Wit* et al., 2014 Biol Psychiatry
Impaired Cognitive Reappraisal

emotion regulation:
main effect over all subjects (N=81) and all stimuli

Contrast: fear regulate > attend

S.J. de Wit et al., 2015 Psychol Med
OCD Brain Imaging Consortium (OBIC)

N=412 OCD
N=368 controls

GM:
decreased volume:
  - dorsomedial PFC
  - IFG/insula
increased volume:
  - cerebellum

WM:
decreased volume:
  - prefrontal WM
  - thalamus

de Wit et al. 2014, Am J Psychiatry
Meta-analysis across Psychiatric Disorders

N=193 studies
= 15,892 subjects
6 disorders:
- Schizophrenia
- Bipolar disorder
- Major depressive disorder
- Addiction
- OCD
- Anxiety

Goodkind et al. JAMA Psych, 2015
Group x Age interactions effects in Striatum and Hippocampus

In OCD patients (with increasing age):

- preservation of striatal volume
- more pronounced hippocampus volume reduction

Meta-analysis across Anxiety Disorders

SDM Signed Differential Mapping
http://www.sdmproject.com/database

A

OCD vs healthy controls
OADs vs healthy controls
OCD vs OADs

(B) Left putamen
Right putamen

Left ACG
Right ACG

(Coronal y=6) (Sagittal x=6)

Radua et al. Arch Gen Psych, 2010
From Anxiety to Compulsivity

Obsessive-compulsive spectrum disorders

- Increased ventral circuit ‘emotion’ / ‘motivation’
- Compulsivity

OCD and other anxiety disorders

- Decreased dorsal circuit ‘cognition’
- Control
- Emotion regulation
- Executive function

OCD = impulsive-compulsive spectrum disorder

- Repetitive behaviour
- Impaired response inhibition
- Impaired cognitive ‘top-down’ control
- Decreased function of frontal-striatal circuits

OCD = anxiety disorder

- Harm avoidance / doubt / uncertainty
- Anxiety / stress
- Hyperresponsive limbic circuit

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ENIGMA
OCD Working Group

http://enigma.ini.usc.edu/

[Map of ENIGMA OCD Working Group locations]

[Logos of Amsterdam Neuroscience, VU University Medical Center, NIH]
ENIGMA-OCD

Subcortical Meta-Analysis - Adults

Boedhoe et al. 2017 (Am J Psychiatry)
ENIGMA-OCD
Subcortical Meta-Analysis- Children

Boedhoe et al. 2017 (Am J Psychiatry)

ICV
Accumbens
Amygdala
Hippocampus
Pallidum
Putamen
Caudate
Thalamus
Lateral Ventricles

Cohen's d effect size [95% CI]
ENIGMA-OCD
Subcortical Volume

![Diagram showing subcortical volume changes in pallidum and thalamus over age from 0 to 65 years.](image)

- Pallidum: OCD > HC
- Thalamus: OCD > HC
Decreased cortical thickness in frontal and temporal areas ($d \approx -0.2$, $P_{FDR} < 0.05$)

Boedhoe et al. 2018, Am J Psychiatry
Decreased surface area
in frontal, parietal, cingulate and occipital regions (d ≈ -0.3, P_{FDR} < 0.05)
ENIGMA-OCD
Effects Medication

\[ \text{Med+ OCD (N=646) vs HC (N=1436)} \]

\[ \downarrow \text{corticale dikte in frontale, temporale, parietale, en occipitale regio's} \]

\[ \text{Unmed OCD (N=831) vs HC (N=1436)} \]

Geen groepsverschil

Boedhoe et al., 2018 Am J Psych
early neurodevelopment → disease onset → neuroplastic changes due to chronic symptomatology and therapeutic interventions

Oorzaak versus Gevolg

‘cause’

‘consequence’
Phenotype over the Lifespan

‘anxiety’ → ‘compulsivity’

inhibition
uncertainty
obsessions

goal-directed
compulsions

habits
Modellen voor OCD

van den Heuvel et al. 2016, Eur Neuropsychopharmacology
Global OCD project (funded by NIMH)

PI: H. Blair Simpson, Columbia University, New York, USA
PI Netherlands: Odile van den Heuvel

Role NL: 1 of 5 sites worldwide, coordination of imaging

PhD student: Niels de Joode
Project members NL: Ton van Balkom, Neeltje Batelaan, Petra Pouwels, Chris Vriend, Merijn Eikelenboom

Aim: to identify reproducible neuroimaging signatures those distinguish cognitive and clinical profiles of OCD

Design: multi-center harmonized data-collection on clinical phenotype, neurocognitive profile and neuroimaging markers in 250 OCD patients, 250 healthy controls and 125 unaffected siblings

Start: January 2018
Inclusion criteria:
Ages 18-50
Current DSM-5 criteria for OCD, with both obsessions and compulsions;
OCD is the principal psychiatric problem (YBOCS score ≥16);
Not on psychotropic medication (for at least 6 weeks; benzodiazepines / sleeping medication at least 1 week)
No current cognitive behavioral therapy (exposure in vivo with response prevention) for their OCD symptoms (last 6 weeks)

Project participation:
3 days assessment (2 clinical assessments and 1 MRI session) within 2 weeks time
+ 1 FU measurement (questionnaires only)

More information:
Niels de Joode > n.dejoode@vumc.nl
Emotion regulation training

‘prevention’

Concentrated ET Neuromodulation (rTMS/tDCS/DBS/surgery)

‘limit chronicity’

‘early and effective treatment’

Prediction treatment response
Based on Gogtay et al. PNAS 2004;101:8174-79
The dorsal prefrontal cortex (as part of the dorsal ‘cognitive control’ circuit) is the last part of the brain reaching mature state.
Project 2 Generation R (funded by NWO-ZonMW vidi)

PI: Odile van den Heuvel  
PhD student: Cees Weeland  
Project members: Tonya White, Henning Tiemeier, Manon Hilligers

Aims:
> Identify the neural correlates of impaired cognitive control and early OCD symptoms in children  
> Identify the pre/perinatal environmental factors contributing to vulnerability and resilience

Design: longitudinal design within Generation R study  

Start: May 2018  

Inclusion: data already collected
Environmental and Genetic factors in Brain Development

Generation R cohort

Planned analyses in Generation R study (Rotterdam, The Netherlands), population-based birth cohort N>9000 pregnant women, N=350 children scanned at 6-8 yr, N>5000 children scanned at age 10 yr
Aanknopingspunten voor Innovatie

‘prevention’
Emotion regulation training

‘early and effective treatment’
Prediction treatment response

‘limit chronicity’
Concentrated ET Neuromodulation (rTMS/tDCS/DBS/surgery)
PI: Odile van den Heuvel  
PhD student: Niels de Joode  
Project members: Chris Vriend, Anouk Schrantee, Ton van Balkom, Chaim Huyser

Aim: to understand the variation in thalamus and pallidum volume during the different stages of development and disease and how this relates to fluctuations in glutamate concentration.

Design: cross-sectional lifespan approach, using high-resolution (7 Tesla) structural MRI (regions-of-interest: thalamus and pallidum) combined with dynamic MRS to measure state-dependent fluctuations in glutamate concentration and brain activation

Start: mid 2018

Inclusion: broad range in developmental age (10-55 yr) and disease duration
Project 4

Inference Based Approach (funded by NWO)

PI: Henny Visser (GGZ Centraal)
PhD students: Emma Koenen (imaging) & Nadja Wolf (clinical)
Project members: Ton van Balkom, Harold van Megen, Odile van den Heuvel, Patricia van Oppen

Aim: who responds best to what?

Design: multi-center randomized controlled non-inferiority trial comparing 20 sessions CBT to 20 sessions IBA with pre-posttreatment MRI

Start: Autumn 2018

Inclusion: 200 OCD patients
Project 5
Intensive Exposure Therapy (funded by Norwegian grant)

PI: Gerd Kvale & Bjarne Hansen (Bergen, Norway)
PhD student: Anders Lillevik Thorsen
Project members: Odile van den Heuvel, Stella de Wit, e.a.

Question: which neural biomarkers predict good treatment response and maintained remission?

Design: pre-post intensive ET MRI + 3 months FU MRI

Start: data collection completed (2014-2018)

Analyses starting (2018-2019)
Emotion regulation training

‘prevention’

‘early and effective treatment’

Prediction treatment response

Concentrated ET Neuromodulation (rTMS/tDCS/DBS/surgery)

‘limit chronicity’
Transcranial Magnetic Stimulation
Modulation Treatment Response

Emotion / Motivation  Cognition

Ventral ↑ ventral frontal-striatal & limbic circuits

Dorsal ↓ dorsal frontal-striatal circuit

OCD patients: High-frequency rTMS vs. placebo (= stimulation)

Controls: Low-frequency rTMS vs. placebo (= inhibition)
repetitive Transcranial Magnetic Stimulation (rTMS)

day 1
fMRI during emotion regulation paradigm version 1

SPM:
Single subject analysis reappraise > attend stimulation coordinates

day 2
20 min rTMS treatment (1 Hz, 10 Hz or sham) using neuronavigation

fMRI during emotion regulation paradigm version 2

repeated measures analyses day 1 versus day 2, 1st level

2nd level group analysis
Effect of rTMS on Habituation

OCD patients:

Sham:
No decrease in state anxiety (day 2 vs day 1) in response to exposure

10 Hz DLPFC:
Decreased state anxiety at day 2 (habituation)

controls:

Sham:
Decreased state anxiety at day 2 (vs day 1) in response to exposure

1 Hz DLPFC:
Less habituation

S.J. de Wit et al., 2015, Psychol Med
PI: Odile van den Heuvel
PhD student: Sophie Fitzsimmons
Project members: Ysbrand van der Werf, Dilene van Campen, Neeltje Batelaan

Aim:
- to compare the mechanisms of effect between two different stimulation protocols, i.e., targeting the dorsal ‘cognitive control’ circuit (DLPFC-rTMS) and the sensorimotor circuit (SMA-rTMS)
- to determine the role of glutamate in the rTMS-induced changes
- to establish the effects of rTMS on the ability to profit from behavioural therapy (exploratory analysis)

Design: RCT (3 stimulation conditions) with pre-post EEG and MRI
- low-frequency SMA-rTMS (n=25), high-frequency DLPFC-rTMS (n=25), and placebo stimulation (n=25)

Start: Summer 2018

Inclusion: 75 adult OCD patients who did not respond sufficiently to behavioural therapy and medication.
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