Neurobiology of OCD & Novel Treatment options

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Outline

• Snapshots on Etiology and Pathophysiology
• Cognitive deficits of OCD
• Circuitry Models and Compulsivity
• OCD and the role of anxiety
• Cortical-Subcortical interaction studies
• Neuromodulation: working on the interacting brain networks
NEUROBIOLOGY OF OCD

- Neurotransmitters: Glutamate/Serotonin
- Neuroimmune: Cytokines
- Neurocognitive aberrations
- OCD SYMPTOMS
- Vulnerability/genetic
Neurocognitive deficits might form a basis and a template for symptoms
SALIENT NEUROCOGNITIVE DEFICITS IN OCD

• Stroop task

Say the **COLOR**, not the word:

- PURPLE
- ORANGE
- BLUE
- RED
- GREEN
- YELLOW

• Wisconsin Card Sorting Test

Complex figure test
SALIENT NEUROCOGNITIVE DEFICITS IN OCD

• Overactive conflict and error detection (cause of obsessions)
  - Stroop task

• Response inhibition/Motor output suppression
  - Go/No-Go, Stop Signal Reaction Time (SSRT) (involves motor suppression in addition to conflict monitoring)

• Set shifting (cognitive inflexibility)
  - attentional switching (WCST, CANTAB ID/ED)
  - affective switching

• Decision making
  - Risk & Uncertainty (IGT)

• Non-verbal memory
  - RCFT
  - Intact copying, poor recall because of executive failure of organizational strategies during encoding

Kuelz, 2004; Nakao 2014
Neuropsychological Deficits in OCD

Meta-analysis – Mean effect sizes (Cohen’s d)

- Non verbal memory: -0.76
- Response inhibition: -0.49
- Set shifting: -0.51

Abramovitch et al. 2013

Shin et al. Psychological Medicine 2014
Enhanced error related negativity amplitude in medication-naïve, comorbidity-free obsessive compulsive disorder

Hema Nawani\textsuperscript{a,b}, Janardhanan.C. Narayanawamy\textsuperscript{a,b,c}, Shrinivasa Basavaraju\textsuperscript{a,b}, Anushree Bose\textsuperscript{b}, Sri Mahavir Agarwal\textsuperscript{b}, Ganesan Venkatasubramanian\textsuperscript{a,b}, Y.C. Janardhan Reddy\textsuperscript{a}

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**Graphs:**

- **Cz**
  - **ERN**: Showing amplitude changes over time.

- **FCz**
  - **ERN**: Showing amplitude changes over time.

**Diagrams:**

- **Error related negativity amplitude at Cz (micro volts):**
  - **Healthy Controls**
  - **Medication naive OCD patients**

**Legend:**

- **Medication naive OCD patients**
- **Healthy controls**

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Error monitoring and oculomotor functions

1. Target in the centre of the screen. Eye is looking at target.

2. Target moves from centre to one side of the screen. Eye should move an equal distance from the centre to the opposite side (mirror image location - direction of arrow).

a - position of the target on the screen
b - correct eye position during an antisaccade
Error monitoring and oculomotor functions

• **AS error** describes an oculomotor paradigm designed to evaluate the inhibitory capacity of the brain.

• Subjects with OCD made greater number of antisaccade errors which could reflect the fronto-striatal abnormality seen in this condition.

(Narayanaswamy JC, under review)
Neurobiological Models to understand OCD

OCD as a compulsive (impulsive) disorder

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

OCD as an anxiety disorder

- harm avoidance / doubt / uncertainty
- anxiety / stress
- Hyper-responsive limbic circuit

Exposure & response prevention

![Graph showing anxiety levels over time for different sessions](image-url)
Cortico-Striatal circuitry

Pauls et al, Nature Neuroscience Reviews, 2014
Affective and reward processing

Executive functions - working memory/planning

Motor preparation and response inhibition

Affective

Dorsal cognitive

Ventral cognitive

Milad and Rauch, 2012; Menzies, 2008
Partially segregated circuits

- **Hyperactive ventral – emotional/motivational circuit** - increased anxiety and repetitive behaviors

- **Hypoactive dorsal executive circuit** - cognitive control deficits and inability to modulate emotional and behavioral responses

(Phillips et al., 2003; MataixCols & van den Heuvel, 2006)
OCD: CSTC CIRCUITS

van den Heuvel et al. 2016, Eur Neuropsychopharmacology
Anxiety in OCD

Brain Structures Involved in Dealing with Fear and Stress
DISEASE SPECIFIC STIMULI

OCD

PHOBIA

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OCD – SYMPTOM PROVOCATION

controls > OCD: activation dorsal system

OCD > controls: activation limbic system


van den Heuvel et al., 2004 *Psych Res*
Patients were found to have deficient activation in the following areas – bilateral anterior prefrontal, dorsolateral prefrontal, orbitofrontal, anterior cingulate, insular and parietal cortices, precuneus, and caudate.

Agarwal SM, 2012
Emotional interference and error monitoring

- Emotional interference is observed in OCD
- This fMRI study examines endophenotype status of emotional interference
- Prefrontal and insular BOLD changes during the task might be an endophenotype

Janardhanan Narayanaswamy et al, Asian Journal of Psychiatry, 2018
Key Neuroimaging findings on Brain Structure in OCD
ENIGMA-OCD working group
PI’s: Odile van den Heuvel / Dan Stein / co-PI: Premika Boedhoe

http://enigma.ini.usc.edu/
Distinct subcortical volume alterations in pediatric and adult OCD:
A worldwide meta- and mega-analysis


the American Journal of Psychiatry (January 2017)

1,830 OCD patients (N=335 children, N=1,495 adults) and 1,759 controls (N=287 children, N=1,472 adults)
Distinct Subcortical volume alterations in Pediatric and Adult OCD

Boedhoe et al. 2017 (Am J Psych)

Adult OCD vs HC:
- Smaller hippocampus
  (could be related to comorbid depression)
- Larger pallidum
  (related to early disease onset - chronicity)

Juvenile OCD vs HC:
- Larger thalamus
  (unmedicated kids)
CORTICAL ABNORMALITIES

Figure 1. Statistical parametric t map (SPM12a) of gray matter volume reduction in obsessive-compulsive disorder. Clusters of more than 1000 voxels showing uncorrected P<.001 are displayed. The 3 orthogonal planes on the left side represent a typical maximum intensity projection “glass brain,” and the set of images on the right side illustrates results superimposed on normalized structural images in selected planes. R indicates the right hemisphere, and the color bar represents the t-score. Significant voxels were found in the orbitofrontal cortex, medial frontal gyrus, and left insulo-opercular region (corrected P<.05). Note that right insular and retrosplenial changes, showing a tendency toward significance, are also displayed.

Figure 2. Statistical parametric t map (SPM12a) showing relative increases in gray matter volume in obsessive-compulsive disorder. Clusters of more than 1000 voxels at P<.001 are displayed. R indicates the right hemisphere, and the color bar represents the t-score. Significant voxels were found in the ventral part of the striatum, including the ventral striatum proper area, and in the anterior cingulum (corrected P<.05).

Decreased gray matter volume

72 OCD Vs. 72 HC

Increased gray matter volume

Pujol et al. 2004; Arch Gen Psych
CORTICAL ABNORMALITIES

Data from OCD Clinic, NIMHANS (Unpublished):
221 DSM-IV OCD patients with the Y-BOCS ≥ 16 [Unmedicated = 142 (drug-naive = 94, drug-free for at least 2 months = 48)] and 194 HC

1.

<table>
<thead>
<tr>
<th>Contrast</th>
<th>MNI Coordinate</th>
<th>Cluster Extent ( (K_e) )</th>
<th>T</th>
<th>( P_{FWE} )</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Controls &gt; Medicate dOCD Patients</td>
<td>-8 44 6</td>
<td>50</td>
<td>5.0</td>
<td>0.006</td>
<td>Left ACC (Brodmann area 32)</td>
</tr>
<tr>
<td></td>
<td>-5 48 36</td>
<td>91</td>
<td>5</td>
<td>0.011</td>
<td>Left Medial Frontal Gyrus (Brodmann area 8)</td>
</tr>
</tbody>
</table>

2. Unmedicated OCD vs. HC = No differences
Cortical Abnormalities Associated With Pediatric and Adult Obsessive-Compulsive Disorder: Findings From the ENIGMA Obsessive-Compulsive Disorder Working Group.

Boedhoe PSW¹, Schmaal L¹, Abe Y¹, Alonso P¹, Ameis SH¹, Anticevic A¹, Arnold PD¹, Batistuzzo MC¹, Benedetti F¹, Beucke JC¹, Bollettini I¹, Bose A¹, Brem S¹, Calvo A¹, Calvo R¹, Cheng Y¹, Cho KIK¹, Ciullo V¹, Dallaspezia S¹, Denys D¹, Feusner JD¹, Fitzgerald KD¹, Fouche JP¹, Fridgeirsson EA¹, Gruner P¹, Hanna GL¹, Hibar DP¹, Hoexter MQ¹, Hu H¹, Huyser C¹, Jahanshad N¹, James A¹, Kathmann N¹, Kaufmann C¹, Koch K¹, Kwon JS¹, Lazaro L¹, Lochner C¹, Marsh R¹, Martínez-Zalacain I¹, Mataix-Cols D¹, Menchón JM¹, Minuzzi L¹, Morer A¹, Nakamae T¹, Nakao T¹, Narayanaswamy JC¹, Nishida S¹, Nurmi E¹, O'Neill J¹, Piacentini J¹, Piras F¹, Piras F¹, Reddy YCJ¹, Reess TJ¹, Sakai Y¹, Sato JR¹, Simpson HB¹, Soreni N¹, Soriano-Mas C¹, Spalletta G¹, Stevens MC¹, Szyszko PR¹, Tolin DF¹, van Wingen GA¹, Venkatasubramanian G¹, Walitza S¹, Wang Z¹, Yun JY¹; ENIGMA-OCD Working Group¹, Thompson PM¹, Stein DJ¹, van den Heuvel OA¹; ENIGMA OCD Working Group.

American Journal of Psychiatry, 2018
ENIGMA-OCD Cortical Analysis
adult OCD (N=1498) vs HC (N=1436)

↓ cortical thickness of bilateral inferior parietal cortex
↓ surface area of left transverse temporal cortex

Bodhoe et al., 2018
SUMMARY

**Cortical:**
- smaller volume in dorsomedial PFC, bilateral insula, and parietal cortex
- bigger volume in cerebellum
- cortical effects seem to be dependent on medication status

**Subcortical:**
- bigger pallidum in adults, mostly in case of disease chronicity
- smaller hippocampus in adults, mostly related to comorbid depression
- bigger thalamus in (unmedicated) children, not in adults

Changes due to chronic compulsivity? Due to medication?

Boedhoe et al., 2018
CORTICAL – SUBCORTICAL REGULATORY EFFECTS?
Cognitive Appraisal during Symptom Provocation

During symptom provocation ---- Reductions in positive coupling between amygdala and orbitofrontal cortex were observed in OCD patients relative to healthy control participants.

During appraisal and passive viewing of OCD-relevant stimuli - abnormally high Amygdala-ventromedial prefrontal cortex coupling was found when appraisal was distracted by a secondary task.

No group differences in amygdala connectivity at rest.
Fear reversal paradigm:
Maladaptive vmPFC combined with increased connectivity with areas involved in salience processing undermines accurate safety learning in OCD patients, resulting in inflexible threat beliefs.

Apergis-Schoute et al., *Neural basis of impaired safety signaling in Obsessive Compulsive Disorder* Proc Natl Acad Sci U S A. 2017
Identifying reproducible bio-signatures of OCD

Aim #1: To identify neuroimaging signatures using data-driven approaches.

Aim #2: To link these signatures to neurocognitive function and clinical dimensions.

R01 MH113250 – PI- Prof. Blair Simpson (USA)
Role of neuroplasticity in treatment – Modulating effect of glutamate
Evidence for glutamatergic abnormalities in OCD

- Elevated CSF glutamate
- In vivo studies – MRS
- Genetic studies
In a subset of OCD patients – excessive glutamate in CSF

(Chakrabarty et al, 2005; Bhattacharya et al., 2009)

Only a subset of cases of OCD?

Global / region specific alterations?
Evidence for glutamatergic abnormalities in OCD
Magnetic Resonance Spectroscopy Studies

- Early MRS studies in unmedicated pediatric OCD - glutamate and related compounds elevated in the basal ganglia; reduced in the ACC (Rosenberg et al., 2000 & 2004)

- Recent studies have reported variable results, with the majority reporting no significant differences between patients and controls (review - Brennan et al., 2013)
Evidence for glutamatergic abnormalities in OCD

Genetics

- Attempts to demonstrate etiological role for glutamate dysregulation in OCD
- Slc1a1, which encodes the principle neuronal glutamate transporter, EAAT3
- Recent focus of interest:
  - Genes that are highly expressed in cortico-striatal circuits
  - Sapap3 knockout mouse (Welch 2007);
    Slitrk5 knockout mouse (Shmelkov, Nat Med 2014)
- Key components of the postsynaptic complex that anchors and spatially organizes glutamate receptors
Comparison between regional gray matter volume in OCD patients and Healthy controls: Modulated by SLC1A1 rs3056 (A/G) Genotype (N=160) and healthy controls (N=152)

Significantly less gray matter volume in Right Middle Frontal Gyrus in G allele carriers in patients

Jose et al., unpublished
TRANSLATING EVIDENCE FROM NEURAL CIRCUITRY MODELS OF OCD
Neuromodulatory approaches

• Repetitive transcranial magnetic stimulation (rTMS)
• Transcranial direct current stimulation (tDCS)
rTMS

- **Advantages** - More focal stimulation, non-invasive, no need for anesthesia
- **Disadvantages** - most available systems target superficial targets

High frequency – excitatory & Low frequency - inhibitory
## Obsessive Compulsive Disorder - rTMS targets

<table>
<thead>
<tr>
<th>Targets</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsolateral prefrontal cortex (DLPFC)</td>
<td>• Rationale: positive studies in depression and imaging studies • Inconsistent responses for both HF and LF rTMS on either side</td>
</tr>
<tr>
<td>Pre-Supplementary motor Area (Pre-SMA)</td>
<td>• Hyperactivity noticed in functional imaging studies • Early positive studies with LF rTMS • Later studies with larger sample size were not encouraging • Interest in high frequency – ? hyperactivity is compensatory</td>
</tr>
<tr>
<td>Orbitofrontal cortex (OFC)</td>
<td>• Hyperactivity of orbitofrontal cortex- more consistently seen in OCD • Pilot studies have shown positive findings • Targets ill-defined</td>
</tr>
<tr>
<td>Dorsomedial prefrontal cortex (DMPFC)</td>
<td>• Recent evidence from imaging studies • Open-label trials with both HF and LF • Needs special coils</td>
</tr>
</tbody>
</table>
Current evidence for rTMS in OCD

• Most meta-analyses have demonstrated significant short term efficacy in comparison to placebo
  – 18 RCTs with Hedge’s g of 0.79 (0.43 – 1.15)
  – Pre-SMA generally showing the best response
    Rehn et al, 2018

• However inconsistent results from recent studies
• Long term efficacy not established
• Should be considered an experimental treatment and can be tried in SSRI non-responsive patients
Transcranial direct current stimulation (tDCS)

- Battery and 2 electrodes
  - weak current passed between anode and cathode
- **Anode** - increases excitability and spontaneous neural activity
- **Cathode** - decreases excitability and spontaneous neural activity
- Cheap, portable, non-invasive and minimal adverse effects
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Anode</th>
<th>Cathode</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bation et al, 2015</td>
<td>8</td>
<td>Right cerebellum</td>
<td>Left OFC</td>
<td>5/8 had ≥ 25% decrease in YBOCS scores</td>
</tr>
<tr>
<td>Mondno et al, 2015</td>
<td>1</td>
<td>Right occipital</td>
<td>Left OFC</td>
<td>26% reduction in YBOCS</td>
</tr>
<tr>
<td>Narayanaswamy et al, 2015</td>
<td>2</td>
<td>Left pre-SMA</td>
<td>Right supra-orbital</td>
<td>Around 50% reduction in YBOCS</td>
</tr>
<tr>
<td>D’Urso et al, 2015</td>
<td>1</td>
<td>Deltoid</td>
<td>Bilateral Pre-SMA</td>
<td>30% reduction in YBOCS</td>
</tr>
</tbody>
</table>
Efficacy of pre-supplementary motor area transcranial direct current stimulation for treatment resistant obsessive compulsive disorder: a randomized, double blinded, sham controlled trial
(Shayanth et al, under review in Brain Stimulation)
Shayanth et al., under review
High Definition tDCS
(HD-tDCS)

- A technical enhancement over conventional tDCS
- Optimized electrodes and montages configurations
- Substantially increase in stimulation focality
- Maintains the same low intensity of current density to the brain
Center electrode overlying the target cortical region surrounded by four return electrodes.
High Definition tDCS for OCD

- First-time application of add-on HD-tDCS in SSRI-resistant OCD patients

- 14 patients OCD having persistent symptoms despite adequate and stable treatment with SSRIs were administered HD-tDCS (anodal 2mA, right Pre-SMA).

- Two sessions of 20 minutes each per day, scheduled 20 minutes apart were administered for 5 consecutive days.

- There was a significant reduction in YBOCS total score after HD-tDCS sessions [Baseline vs. Post HD-tDCS= 27.6±5.7 vs. 19.4±8.0, t=3.9, p=0.002].

- Median percentage reduction in YBOCS total score was 25.8 and there were 8 (57.1%) responders.

  (Narayanaswamy et al., manuscript under preparation)
Neurosurgical Approaches

Ablative Procedures

- Thermal coagulation
- Gamma-knife radiosurgery

Deep brain stimulation

1. Ventral capsule/Ventral striatum (VC/VS)
2. Nucleus Accumbens (NAcc)
3. Bed nucleus of stria terminalis
4. Sub-thalamic nucleus (STN)
5. Inferior thalamic peduncle (ITP)

1. Capsulotomy
2. Anterior Cingulotomy
3. Subcaudate Tractotomy
4. Limbic Leucotomy
Deep Brain stimulation

3 stages
1. Image guided insertion of electrodes (1mm) inserted
2. Subdermal implantation of neurostimulator
3. Programming of electrical parameters
   – Polarity, amplitude, frequency and pulse duration
Effects observed 3-6 months post-surgery

Mechanism of action
• Functional lesion
• Disruption of dysfunctional circuits
• Inhibiting as well as activating network effects
• Modulates oscillatory activity
Targets in OCD

- Anterior limb of the internal capsule
- Ventral capsule/ventral striatum (VC/VS)
- Nucleus Accumbens
- Bed nucleus of stria terminalis
- Subthalamic nucleus

Others
- Inferior thalamic peduncle

Kohl et al, 2014
Forest Plot for percentage of responders according to standardized criteria (35% reduction in post-treatment Y-BOCS scores)

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Proportion</th>
<th>95%-CI</th>
<th>W(fixed)</th>
<th>W(random)</th>
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<tbody>
<tr>
<td>Mallet et al., 2002</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
<td>[0.16; 1.00]</td>
<td>1.9%</td>
<td>1.9%</td>
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<tr>
<td>Nuttin et al., 2003</td>
<td>4</td>
<td>8</td>
<td>0.50</td>
<td>[0.16; 0.84]</td>
<td>9.2%</td>
<td>9.2%</td>
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<tr>
<td>Sturm et al., 2003</td>
<td>3</td>
<td>4</td>
<td>0.75</td>
<td>[0.19; 0.99]</td>
<td>3.5%</td>
<td>3.5%</td>
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<tr>
<td>Aouizerale et al., 2004</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
<td>[0.16; 1.00]</td>
<td>1.9%</td>
<td>1.9%</td>
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<tr>
<td>Abelson et al., 2005</td>
<td>2</td>
<td>4</td>
<td>0.50</td>
<td>[0.07; 0.93]</td>
<td>4.6%</td>
<td>4.6%</td>
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<tr>
<td>Greenberg et al., 2006</td>
<td>6</td>
<td>10</td>
<td>0.80</td>
<td>[0.26; 0.88]</td>
<td>11.1%</td>
<td>11.1%</td>
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<tr>
<td>Mallet et al., 2008</td>
<td>12</td>
<td>16</td>
<td>0.75</td>
<td>[0.48; 0.93]</td>
<td>13.9%</td>
<td>13.9%</td>
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<tr>
<td>Jiménez et al., 2009</td>
<td>5</td>
<td>5</td>
<td>1.00</td>
<td>[0.48; 1.00]</td>
<td>2.1%</td>
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<tr>
<td>Servello et al., 2009</td>
<td>2</td>
<td>4</td>
<td>0.50</td>
<td>[0.07; 0.93]</td>
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<td>4.6%</td>
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<td>Huff et al., 2010</td>
<td>1</td>
<td>10</td>
<td>0.10</td>
<td>[0.00; 0.45]</td>
<td>4.2%</td>
<td>4.2%</td>
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<tr>
<td>Greenberg et al., 2010 (UF)</td>
<td>3</td>
<td>5</td>
<td>0.50</td>
<td>[0.15; 0.95]</td>
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<tr>
<td>Greenberg et al., 2010 (LV)</td>
<td>4</td>
<td>7</td>
<td>0.57</td>
<td>[0.18; 0.90]</td>
<td>7.9%</td>
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<td>Denys et al., 2010</td>
<td>9</td>
<td>16</td>
<td>0.56</td>
<td>[0.30; 0.80]</td>
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<td>Franzini et al., 2010</td>
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<td>2</td>
<td>0.50</td>
<td>[0.01; 0.99]</td>
<td>2.3%</td>
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<td>Tsai et al., 2012</td>
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<td>0.50</td>
<td>[0.07; 0.93]</td>
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<td>4.6%</td>
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<td>Chabardès et al., 2012</td>
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<td>2</td>
<td>0.50</td>
<td>[0.01; 0.99]</td>
<td>2.3%</td>
<td>2.3%</td>
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<td>Roh et al., 2012</td>
<td>4</td>
<td>4</td>
<td>1.00</td>
<td>[0.40; 1.00]</td>
<td>2.1%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

Fixed effect model: 105
Random effects model

Heterogeneity: I²=0%, t²-squared=0, p=0.8381

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0133591
Summary

• Neural Circuitry Models generate potential treatment strategies
• Chronicity of compulsions seem to be producing neuroplastic changes- hence need for early interventions
• Potential utility of neuromodulation to target specific domains of symptoms (eg: Disgust)
• Role of neuromodulation to aid faster fear extinction (with CBT?)
• Psychosurgical options - DBS
Acknowledgements

OCD clinic team at NIMHANS,

- WISER neuromodulation program, NIMHANS
- Wellcome trust/DBT India Alliance fellowship grant
  - NIMH RO1 grant
- ENIGMA OCD Working group
EDITORIAL

Obsessive-compulsive disorder: Mimicking journey of psychiatry
Om Prakash Singh
DOI: 10.4103/psychiatry.indianjpsychiatry_3_19
[HTML Full text] [PDF] [Mobile Full text] [EPub] [Sword Plugin for Repository] 

GUEST EDITORIAL

Recent advances in obsessive compulsive and related disorders
Janardhanan C Narayanaswamy, Shyam Sundar Arumugham, TS Jaisoorya, Y C Janardhan Reddy
DOI: 10.4103/psychiatry.indianjpsychiatry_587_18
[HTML Full text] [PDF] [Mobile Full text] [EPub] [Sword Plugin for Repository] 

REVIEW ARTICLES