The search for novel treatment targets for Obsessive Compulsive Disorder

BBRF Webinar
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Abnormal repetitive thoughts and behaviors are central to neuropsychiatric disorders including OCD.
What OCD isn’t
What OCD is

**DSM-V criteria**

A. Either obsessions
   - A. Recurrent, persistent intrusive thoughts, impulses, or images
   - B. Not simply excessive worries about real-life problems
   - C. Attempts at neutralization via thought or action
   - D. Recognition of obsessions as a product of own mind

B. or compulsions
   - A. Repetitive behaviors or mental acts
   - B. Behaviors/acts reduce distress or prevent dread
What OCD is

I'm so O.C.D. that...

A COMIC SERIES BY: Lily Williams

I must do everything 8 times in a row

If I lose count or mess up...

I have to start over...

and if I don't do this...

my parents will die.

these intrusive thoughts repeat over and over and over and over...

LILYWILLIAMSArt.COM
What OCD is

I'm so O.C.D. that...

A comic series by: Lily Williams

I think all food is poisoned

Rules* for if food is contaminated:

1. The top came off too easily
2. It just "seems" odd
3. Touched something else suspicious
4. Suspicious bruise equals drugs
5. Remember that one episode of that one show where a candy bar was poisoned?

*Rules can change at any time for any reason...

I made these
no thanks

I throw away half of the food
I get even though I feel guilty and cannot afford this

Regardless of if I trust someone, I do not trust there aren't drugs in all food

If I do end up consuming something that I believe is contaminated...
1. Shut down.
2. I can't breathe.
3. I can't function.
4. I can't stop thinking...

LILYWILLIAMSART.COM
OCD is common and severe

Prevalence

- 1-3% lifetime prevalence
- OCD does not discriminate across cultures and countries
- 2 onset peaks

Severity

- Patients can spend many hours/day consumed by symptoms
- Can interfere with education, work, and independent living
- Can be difficult to treat

Kessler et al., 2005; Ruscio et al, 2010
OCD symptoms are heterogeneous

- In addition, other proposed subdivisions
  - obsessive slowness, tic-related OCD, pure obsessional, etc
- Need neurobiological studies to identify shared vs distinct elements
Pharmacotherapy for OCD

The serotonin system

- SRIs only proven monotherapy
- Full remission
  - 10-15%
- Partial responders
  - 20-40% symptom reduction
- Only 20% remission at >10 year follow-up (Bloch et al, 2003)

- Multiple augmentation strategies
    - ketamine, riluzole, N-Ac
  - dopaminergic blockade
    - “antipsychotics” (Simpson et al, 2013)
Exposure therapy with response prevention

- Can be highly effective (Foa et al, 2005)
- But can be difficult for patients to complete
- Hard to find skilled treatment providers

100% SUDS

~30% SUDS

0% SUDS
Is there an App for that?

<table>
<thead>
<tr>
<th>Mobile Apps for Obsessive-Compulsive Disorder</th>
<th>GGOC: OCD Relief</th>
<th>nOCD</th>
<th>OCD Understood</th>
<th>iCounselor: OCD</th>
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To learn more about these scores, visit PsyberGuide.org
Neurosurgical treatments

**Ablative neurosurgery**
- Precise lesions of connections between cortex and striatum
- ~50-70% treatment response
- Non-reversible

**Deep Brain Stimulation**
- Can be obtained through Humanitarian Device Exemption
- High frequency stimulation
- Targets:
  - VC/VS: ~50-60% efficacy (reviewed Greenberg et al, 2010; Alonso et al, 2015)
  - Limbic STN (Tyagi et al, 2019)
Repetitive transcranial magnetic stimulation

- Still investigational
- Non-invasive treatment
- Electromagnetic field changes electrical currents in underlying cortex
- Brain activity can be stimulated or inhibited depending on protocol used
- Investigational targets
  - Pre-supplementary motor area (pre-SMA) (Montavani et al, 2006)
  - mPFC and anterior cingulate (20Hz) (Carmi et al, 2019, AJP)
  - OFC + habit override: Dr. Rebecca Price, University of Pittsburgh
Translational strategies to develop new treatments
People with OCD have dysfunction in behavior transitions

Adapted from Pauls, (2014) Nat Rev Neuro
"It's like a broken machine. Thoughts go in your head, get stuck and keep going around and around."

— Megan Flynn
Translational strategies in OCD research

- Translating imaging findings from OCD patients into mice
- Identifying OCD-related molecular changes using human post-mortem brain
- Probing mechanisms underlying OCD-relevant behaviors in relevant transgenic model systems
circuits
Evidence for cortical-basal ganglia circuit abnormalities in OCD

Can’t test cause and effect in humans
Using optogenetics in mice to simulate hyperactivity in OFC and striatum in OCD
Using optogenetics in mice to simulate hyperactivity in OFC and striatum in OCD
Using optogenetics in mice to simulate hyperactivity in OFC and striatum in OCD
Challenge: Assessing OCD-relevant behaviors in mice

"The drug has, however, proved more effective than traditional psychoanalysis."
Challenge: Assessing OCD-relevant behaviors in mice

**OCD-relevant behaviors**
- Perseverative Grooming
- Impaired sensorimotor gating
- Perseverative Locomotion
- Impaired reversal learning

**Anxiety-related behavior**
- Open Field
- Elevated Plus Maze
Repeated cortico-striatal stimulation leads to abnormal behavior and pathologic plasticity

Ahmari et al, Science, 2013
Repeated cortico-striatal stimulation leads to abnormal behavior and pathologic plasticity

? Mechanisms?

? Treatment applications?

Ahmari et al, Science, 2013
Repeated cortico-striatal stimulation leads to abnormal behavior and pathologic plasticity.

Ahmari et al, Science, 2013
Can circuit hubs be leveraged for non-invasive treatment?

TMS

- Regulate
- ACA

DBS

- VS
- rl-GPi, VP
- rd-SNR
- pm-MD

cortex

striatum
Using new tools to examine brain activity while mice are performing repetitive behaviors

Multi-site recording

In vivo microscopy

optical fiber

OFC

VMS

tetrodes

nVista microscopes
*In vivo* microscopy allows examination of local network activity in freely moving mice.
In vivo microscopy allows tracking of brain networks over time.
Outline: Translational strategies in OCD research

- Translating imaging findings from OCD patients into mice
- Identifying OCD-related molecular changes using human post-mortem brain
- Probing mechanisms underlying OCD-relevant behaviors in relevant transgenic model systems
Genetics of OCD

- Twin and family studies have revealed a significant genetic component to the etiology of OCD
  - Heritability of OCD ~ 40-60%
    - Higher in children than adults
- Genome-wide association studies are used to identify common genetic risk factors
  - IOCDF Genetics Collaborative (Mol Psych, 2018)
    - 2688 cases and 7037 controls
    - **Zero statistically significant risk genes**
  - Schizophrenia (Nature 2014)
    - 36,989 cases and 113,075 controls
    - 108 significant risk genes
- Ongoing studies are attempting to find rare OCD genes
Parallel approach: post-mortem OCD studies

**BRAIN TISSUE DONATION PROGRAM**

University of Pittsburgh Medical Center
Center for the Neuroscience of Mental Disorders and Translational Neuroscience Program

- OFC
- caudate
- Nucleus accumbens

Identification of pathological findings
Post-synaptic density may be a vulnerable molecular compartment in OCD

Sean Piantadosi
Brittany Chamberlain
Identification of donated brains from people with OCD and matched unaffected comparison subjects

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<tr>
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<th>COMPARISON SUBJECTS</th>
<th>OCD SUBJECTS</th>
<th>P-VALUE</th>
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<td>Brain pH (±SD)</td>
<td>6.6 (0.2)</td>
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<td>Suicide, n (%)</td>
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Identifying molecular changes in OCD

8 people with OCD; 8 comparison subjects

Brain regions
- medial OFC
- lateral OFC
- Caudate
- Nucleus accumbens

Step 1:
Slice fresh frozen tissue

Step 2:
Extract RNA from sample

Step 3:
Perform qPCR

Sample Preparation
RNA Binding
Wash
Elution

Fluorescence
Cycle number
10 15 20 25 30
Downregulation of transcripts that make up the structure of excitatory synapses

**A** Discs Large Associated Protein 1 (DLGAP1)

**B** Discs Large Associated Protein 2 (DLGAP2)

**C** Discs Large Associated Protein 3 (DLGAP3)

**D** Discs Large Associated Protein 4 (DLGAP4)

**E** SLIT and NTRK-like protein 1 (SLITRK1)

**F** SLIT and NTRK-like protein 3 (SLITRK3)

**Figure 1** Piantadosi et al., Molecular Psychiatry, 2019
Downregulation of transcripts encoding excitatory synapse transporters

A. Glutamate ionotropic receptor AMPA type subunit 1 (GRIA1)
   - BA11: -44%
   - BA47: -34%
   - Caudate: -6%
   - NAc: -14%

   Diagnosis: $F_{1,8} = 9.0, p = .02$
   Brain region: $F_{3,24} = 1.0, p = .39$
   Diagnosis x Region: $F_{3,24} = 1.6, p = .21$

B. Glutamate ionotropic receptor NMDA type subunit 2B (GRIN2B)
   - BA11: -45%
   - BA47: -35%
   - Caudate: -25%
   - NAc: -25%

   Diagnosis: $F_{1,8} = 6.9, p = .03$
   Brain region: $F_{3,24} = 1.8, p = .17$
   Diagnosis x Region: $F_{3,24} = 1.1, p = .36$

C. Solute carrier family 1 member 1 (SLC1A1)
   - BA11: -37%
   - BA47: -34%
   - Caudate: -10%
   - NAc: -12%

   Diagnosis: $F_{1,10} = 5.0, p = .05$
   Brain region: $F_{3,30} = 3.2, p = .04$
   Diagnosis x Region: $F_{3,30} = 3.7, p = .02$

D. Solute carrier family 17 member 7 (SLC17A7)
   - BA11: -45%
   - BA47: -43%
   - Caudate: -10%
   - NAc: -12%

   Diagnosis: $F_{1,10} = 12.4, p = .005$
   Brain region: $F_{3,10} = 0.02, p = .89$
   Diagnosis x Region: $F_{1,10} = .02, p = .89$

Piantadosi et al., *Molecular Psychiatry*, 2019
Little change in inhibitory synapse transcripts

![Graphs showing changes in mRNA expression for various proteins in different brain regions.](#)

**Figure 3**

Piantadosi et al., *Molecular Psychiatry*, 2019
Most robust decrease in excitatory gene expression in OFC, not striatum

Piantadosi et al., *Molecular Psychiatry*, 2019
OCD post-mortem studies suggest altered regulation of excitatory synapse genes in OFC

- OFC is possible ‘molecular hub’
- May also suggest upstream thalamic pathology
Outline: Translational strategies in OCD research

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Investigating striatal mechanisms underlying compulsive behavior using Sapap3-knockout mice

Compulsive Grooming

Persists despite negative consequences

Welch et al. 2007, Burguiere et al., 2013
Striatum receives strong projections from OFC and M2

Corbit et al., J. Neuroscience, 2019
Strengthened M2 projections might be causing striatal hyperactivity in knockout mice

Corbit et al., J. Neuroscience, 2019
Investigating heterogeneity of compulsive behavior using Sapap3-knockout mice

Reversal learning

Learning the rule
Inactive  Active

Early reversal 1 (perseverative)
Active  Inactive

Late reversal 1 (flexible)
Active  Inactive

Lizzie Manning
Reversal learning is impaired in SAPAP3 KOs

~40% of SAPAP3-KOs fail reversal

Manning et al., 2018, Neuropsychopharmacology
Reversal is not predicted by grooming severity or task acquisition

- Striking but variable deficit in reversal learning
- Underlying circuit mechanisms are unclear

Manning et al., 2018, Neuropsychopharmacology
Longitudinal imaging allows tracking of neurons during different OCD-relevant behaviors.
Translational strategies to develop new treatments
Overall goal: develop improved, neuroscience-based treatments for OCD

New stimulation programs?

Prediction of treatment response?
The benefits of including people with lived experience in research
Consider participating in studies

https://pittplusme.org/studyarms/publicdetails?
Guid=7d12d093-8987-43ff-acb5-48b34f9f82c3

https://iocdf.org/research/research-participants-sought/

https://iocdf.org/research/research-participants-sought/
Please consider brain donation!!!
Many thanks to the patients and their families for their generous gift.