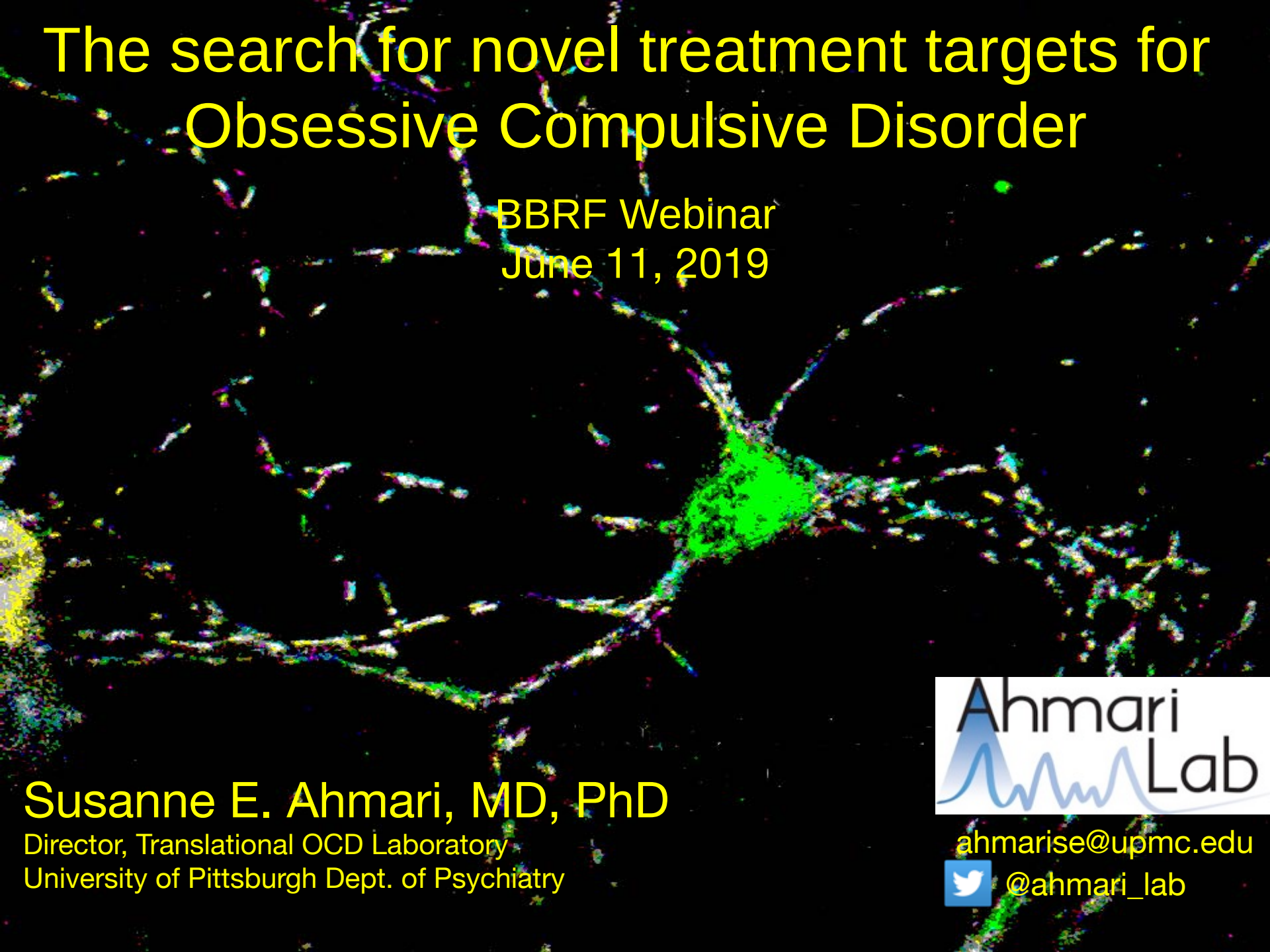
The search for novel treatment targets for Obsessive Compulsive Disorder

BBRF Webinar
June 11, 2019



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Ahmari Lab

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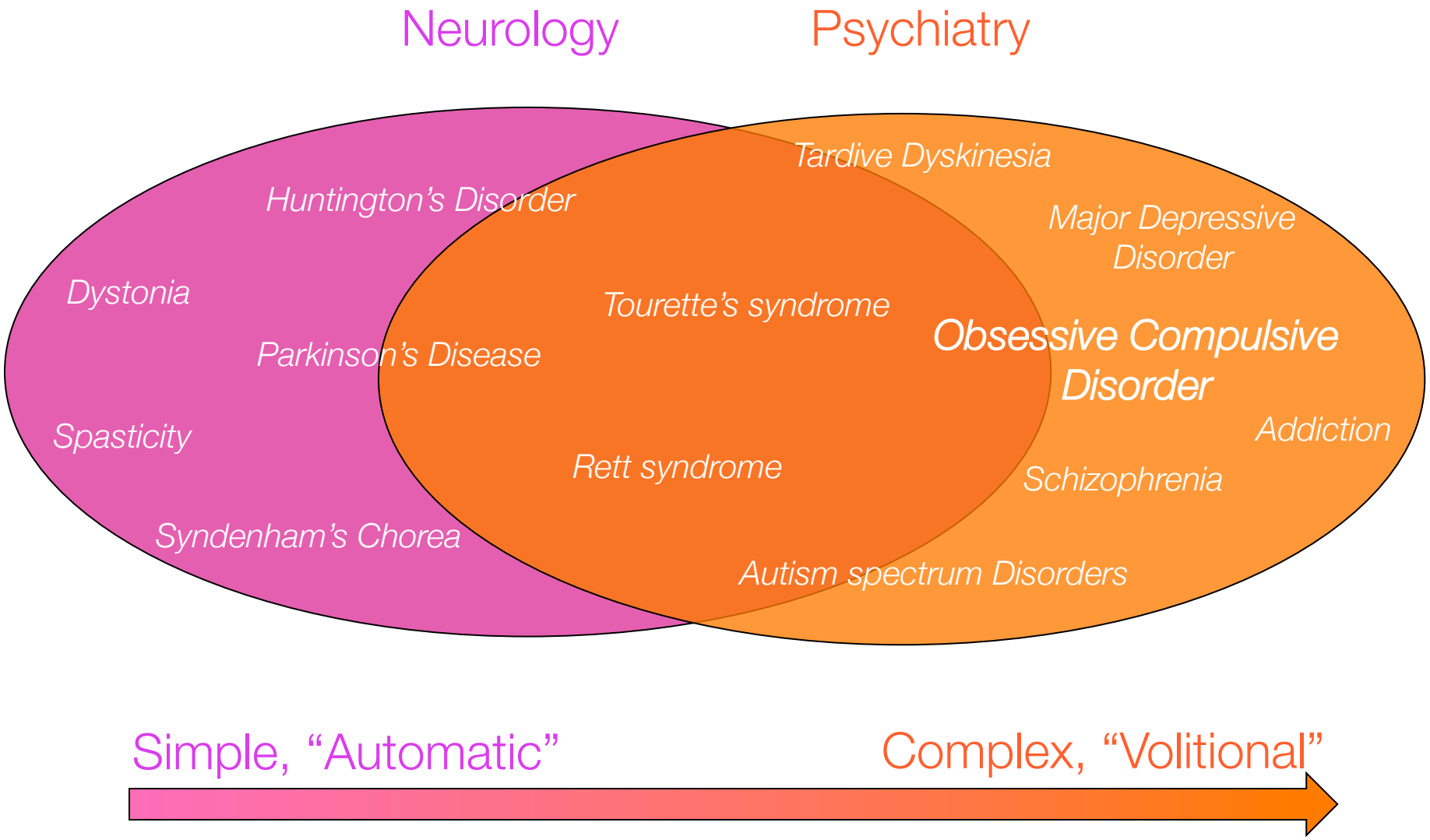
Abnormal repetitive thoughts and behaviors are central to neuropsychiatric disorders including OCD



What OCD *isn't*

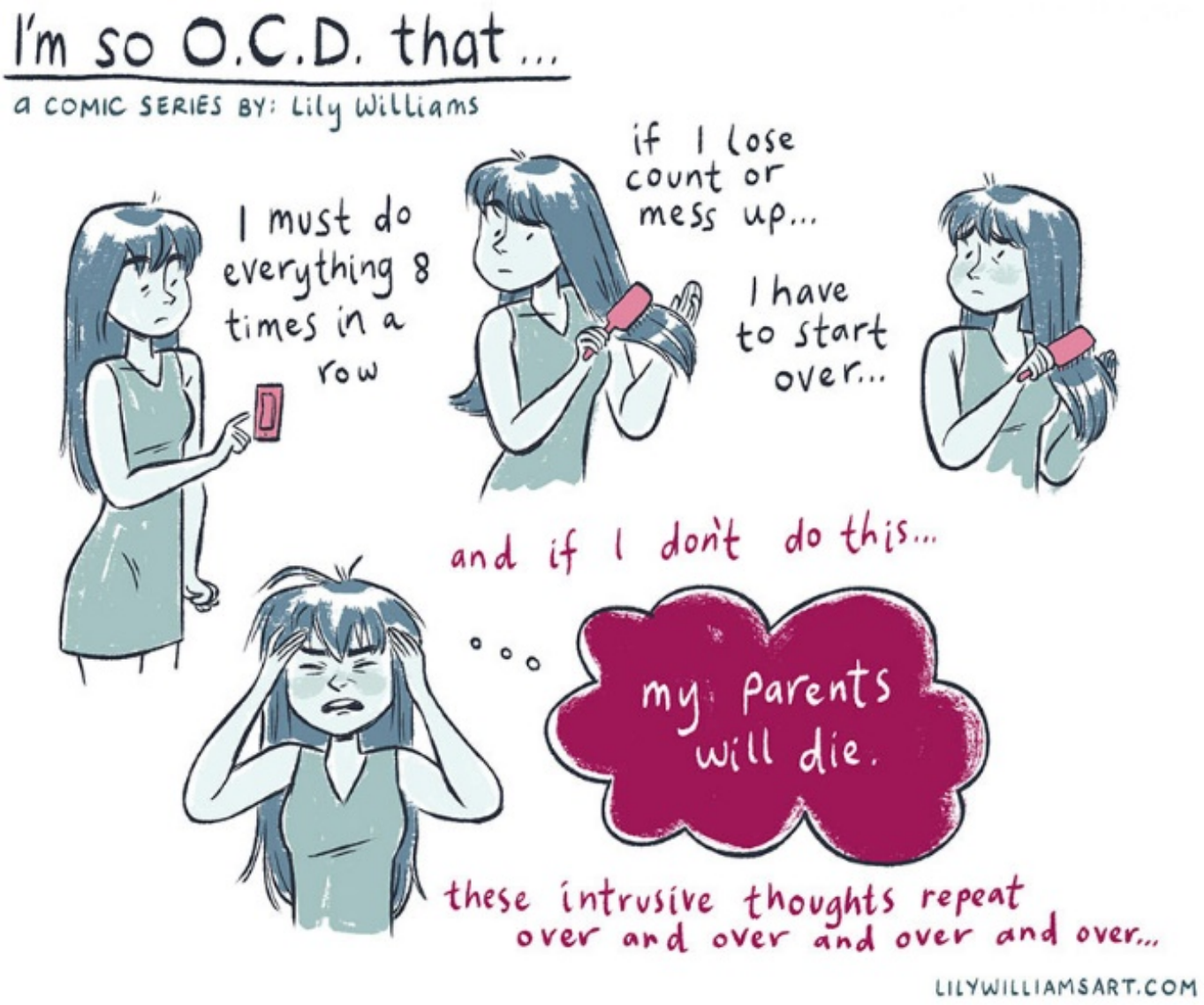
What OCD *is*

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
YOGURT
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
regardless of if I trust someone, I do not trust there aren't drugs in all food
I throw away half of the food I get even though I feel guilty and cannot afford this
If I do end up consuming something that I believe is contaminated...
I Shut down.
I can't breathe
I can't function.
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

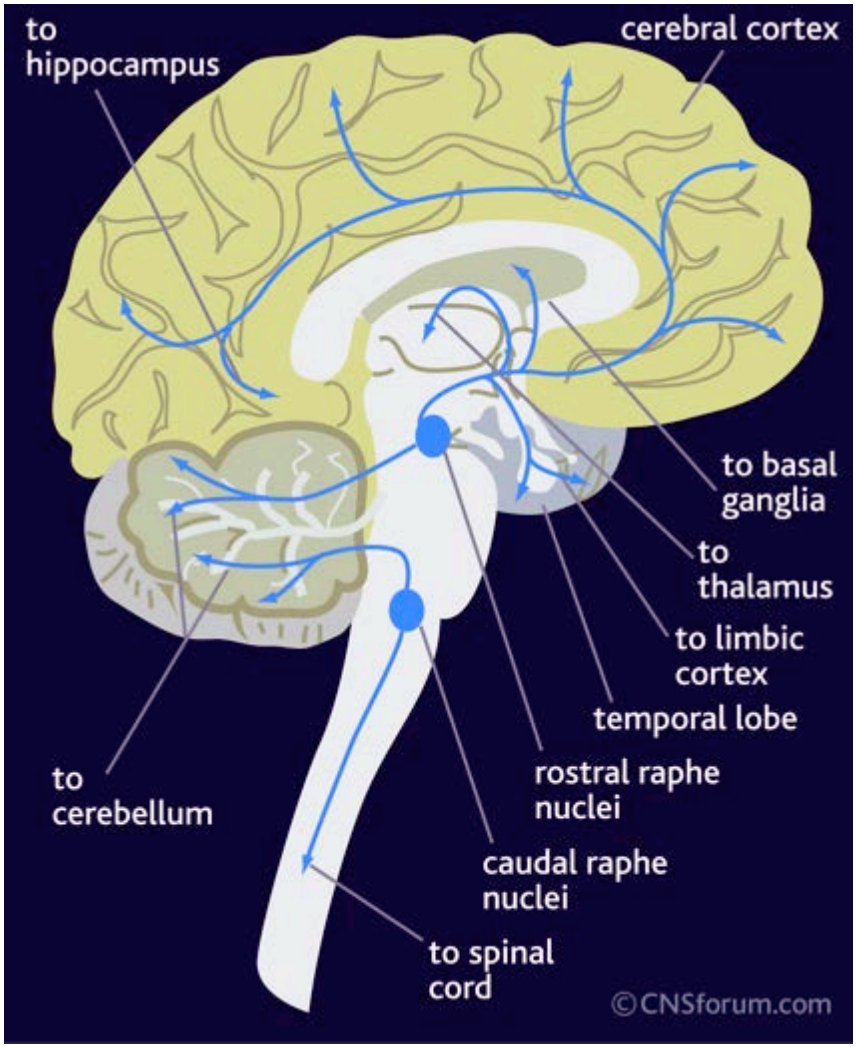
- In addition, other proposed subdivisions

  -obsessive slowness, tic-related OCD, pure obsessional, etc

- Need neurobiological studies to identify shared vs distinct elements

Pharmacotherapy for OCD

The serotonin system



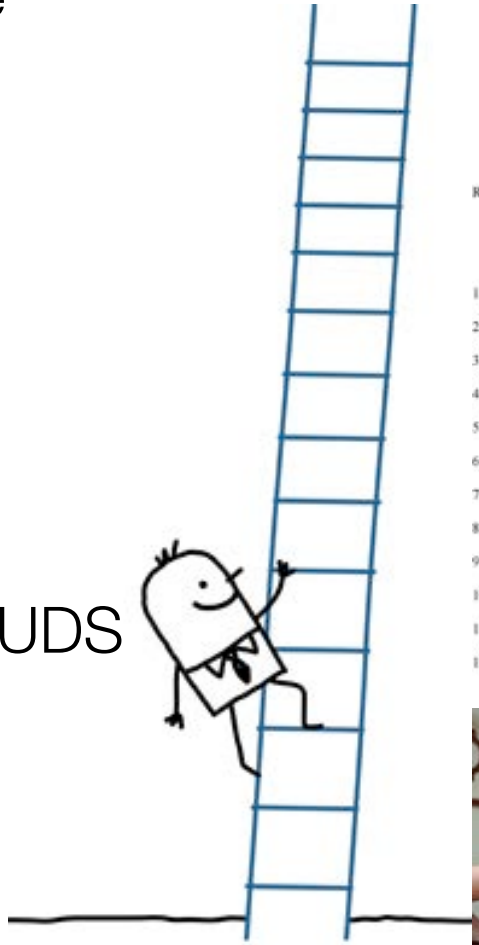
- SRIs only proven monotherapy
- Full remission
  - 10-15%
- Partial responders
  - 20- 40% symptom reduction
- Only 20% remission at >10 year follow-up (Bloch et al, 2003)

- Multiple augmentation strategies
  - glutamatergic agents (Rodriguez et al, 201, Bloch et al, 2012, Pittenger, 2015)
    - 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

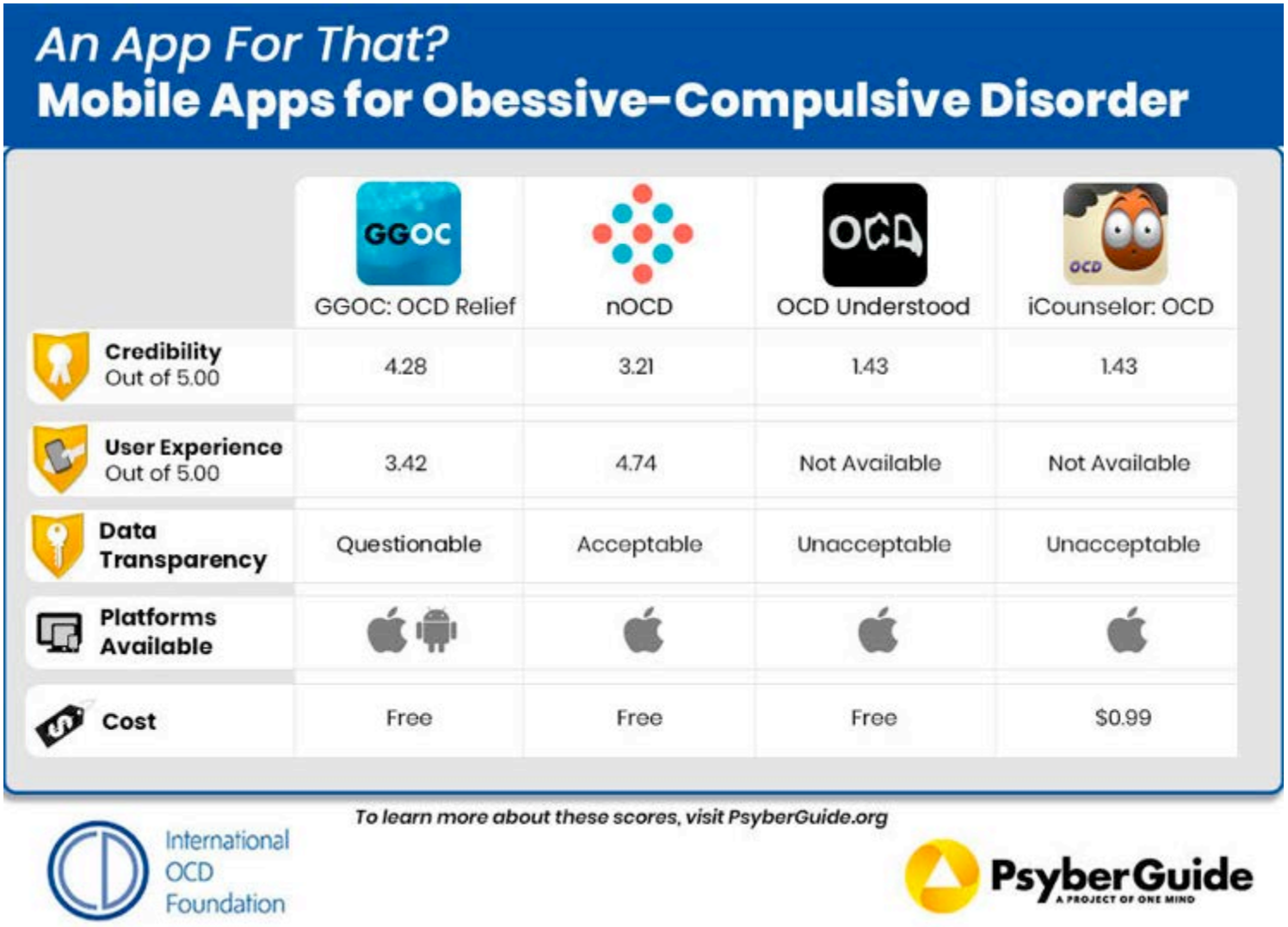
0% SUDS

Exposure Hierarchy

Rate your anxiety from 0-10 and rank your symptoms from easiest to most challenging to face or change.

Symptom	Subjective Unites of Distress (SUDS)						
Week	0	2	4	6	8	10	12
1. *Inhaling someone else's breath who I don't like*	10	10	9	8	8	6	4
2. *Eating off of plates, table, or silverware cleaned by unknown products*	9	8	8	7	7	4	3
3. *Conversation with someone I don't like without washing my face hands*	9	9	8	8	5	6	5
4. *Shower for less than 30 minutes in the evening*	8	8	6	6	5	4	2
5. *Not washing my face hands after a conversation with someone I like*	7	7	6	5	4	3	2
6. *Cleaning with non-organic cleaning products*	7	6	5	5	4	4	4
7. *Not washing my hands and feet after cleaning the shower*	5	5	5	4	2	2	1
8. *Not rinsing off the shower before getting into it*	5	6	5	4	2	0	0
9. *Eating at a new restaurant*	4	5	5	4	3	2	2
10. *Eating food in someone else's home*	4	4	3	3	2	1	0
11. *Shower for less than 30 minutes in the morning*	3	3	2	2	1	0	0
12. *Not wiping my workbag, laptop and phone at the end of the day*	3	5	5	4	3	2	1

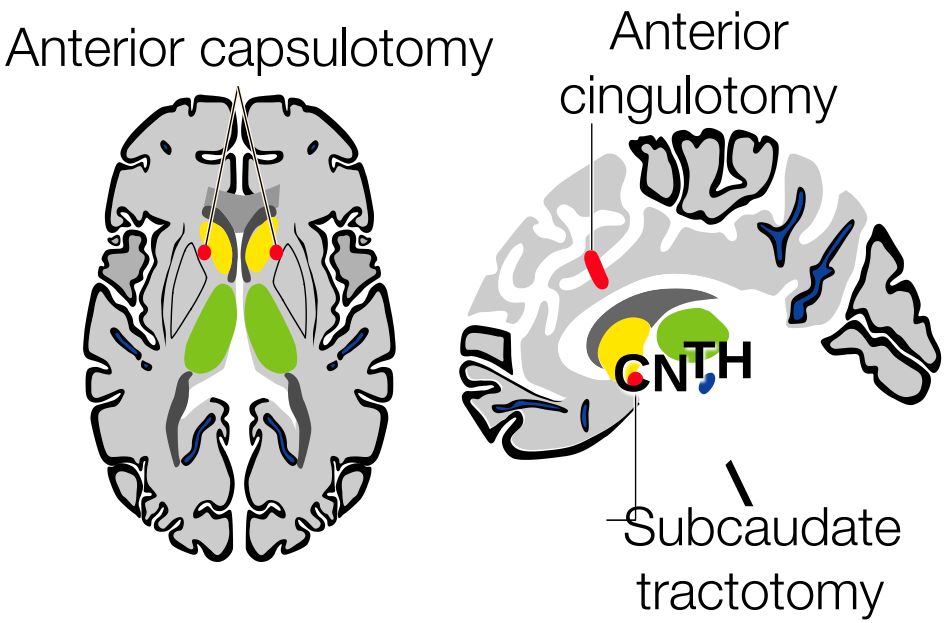
Is there an App for that?



Neurosurgical treatments

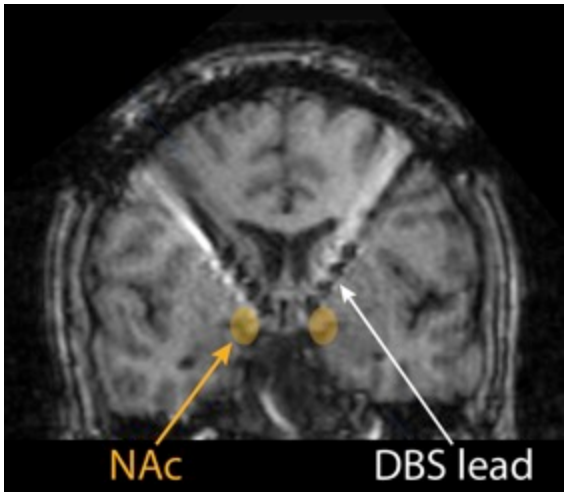
Ablative neurosurgery

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



Deep Brain Stimulation

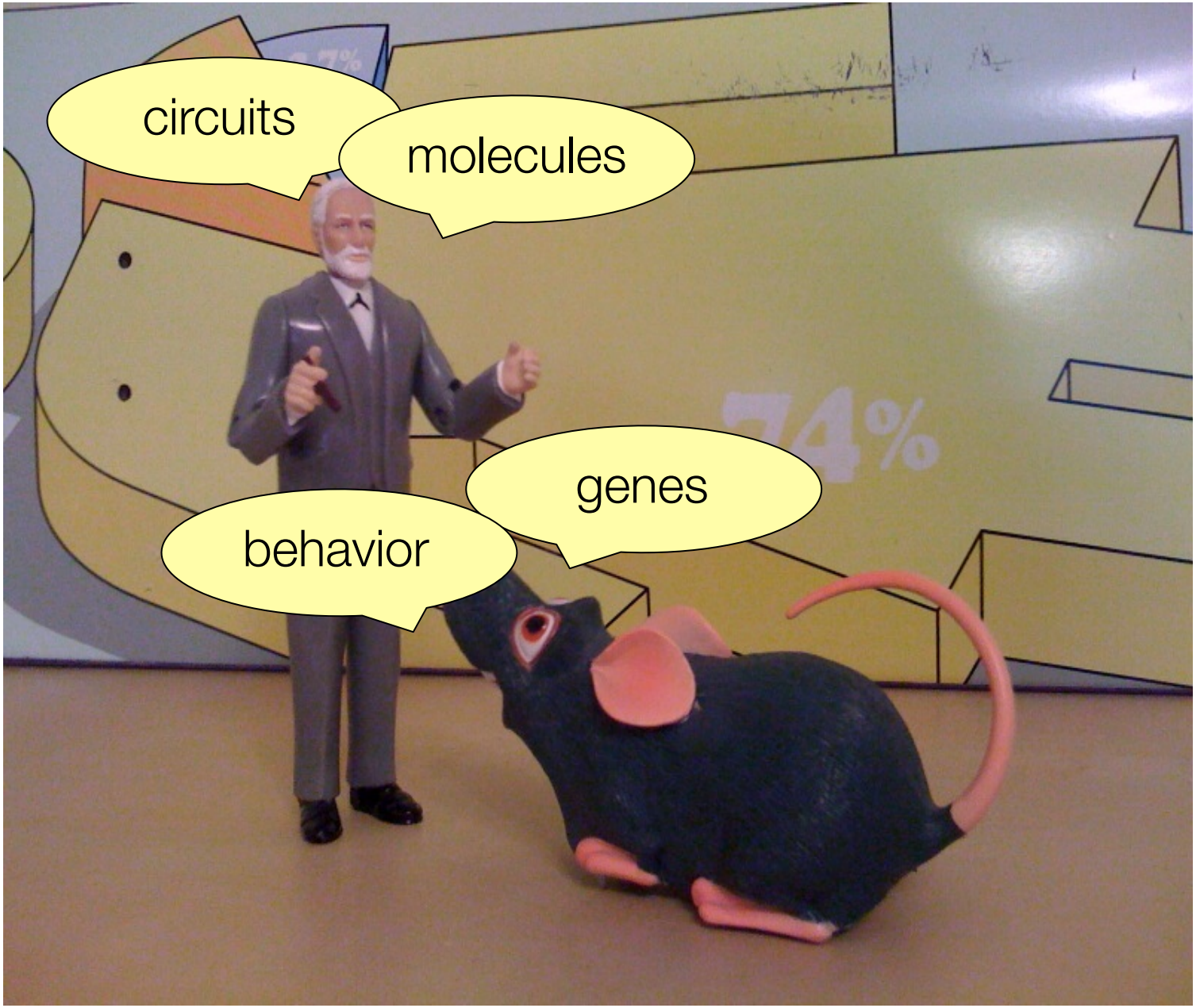
- Can be obtained through Humantarian Device Exemption
- High frequency stimulation
- Targets:
  - VC/VS: ~50-60% efficacy (reviewed Greenberg et al, 2010; Alonso et al, 2015)
  - Limbic STN (Tyagi et al, 2019)



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

Stimulus
(internal or external)

Inappropriate
fear

Uncertainty

Obsession

Distress and anxiety

Drives rituals
to avoid/
decrease
anxiety

Negative
reinforcement

Temporary relief from
distress and anxiety

Ritualized behaviour
(compulsions)

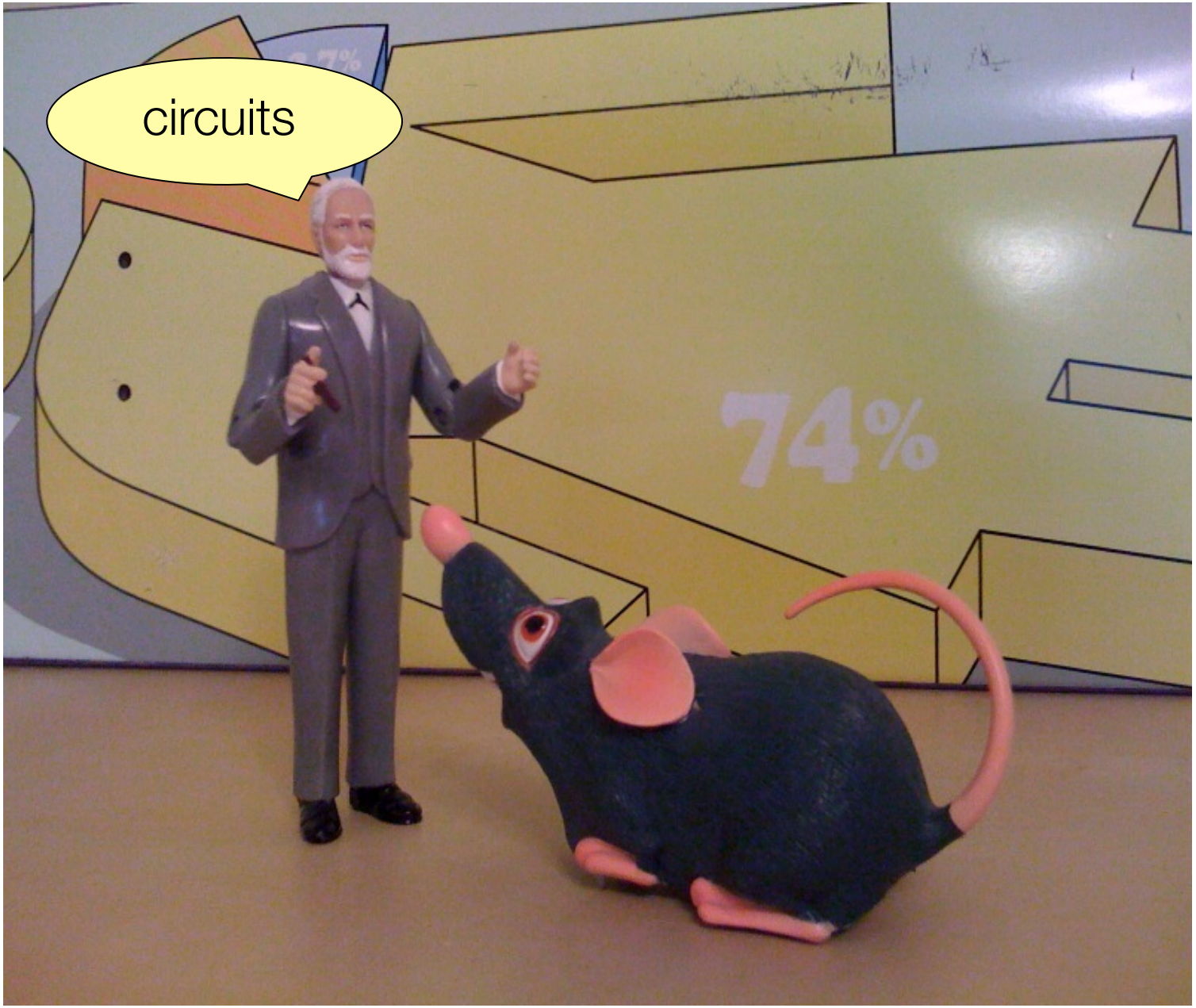
Exit?

Adapted from Pauls, (2014) *Nat Rev Neuro*

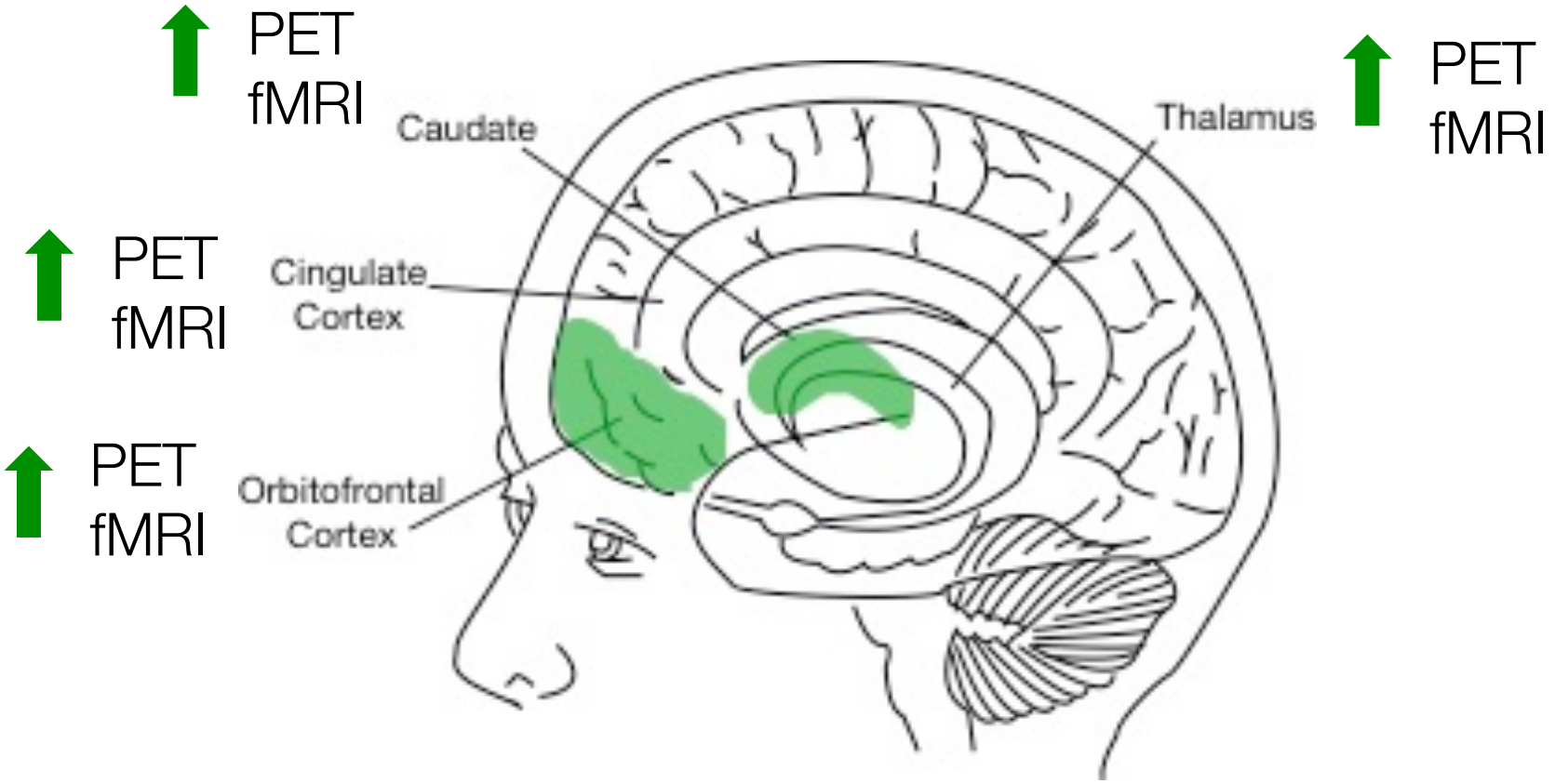

“It's like a broken machine. Thoughts go in your head, get stuck and keep going around and around.”
— Megan Flynn
The MIGHTY

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

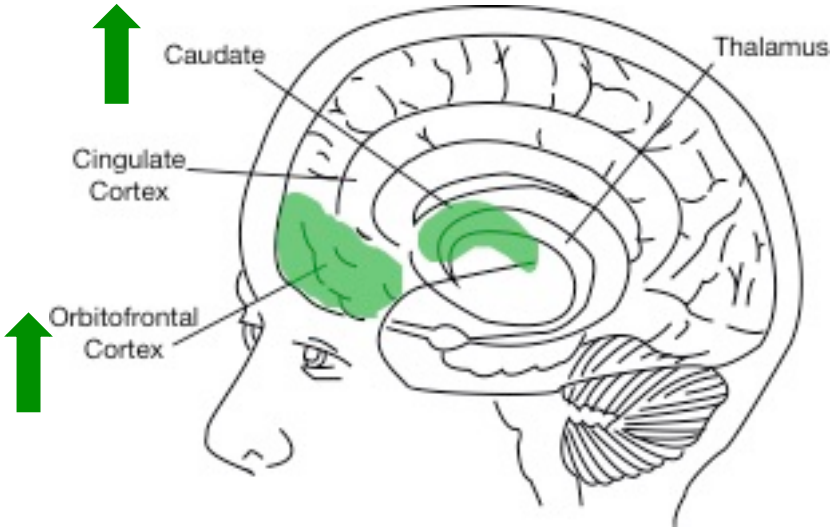

circuits
74%

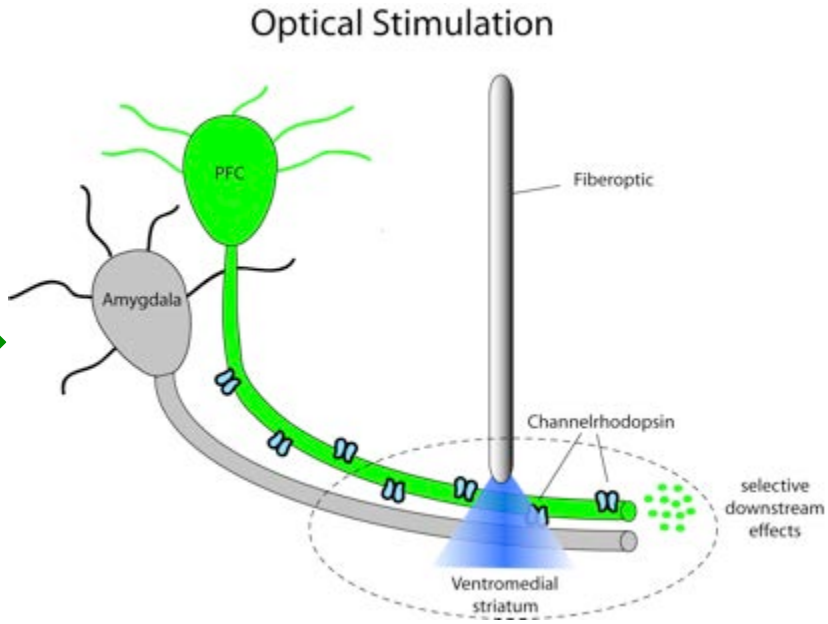
Evidence for cortical-basal ganglia circuit abnormalities in OCD



Can’t test cause and effect in humans

Using optogenetics in mice to simulate hyperactivity in OFC and striatum in OCD





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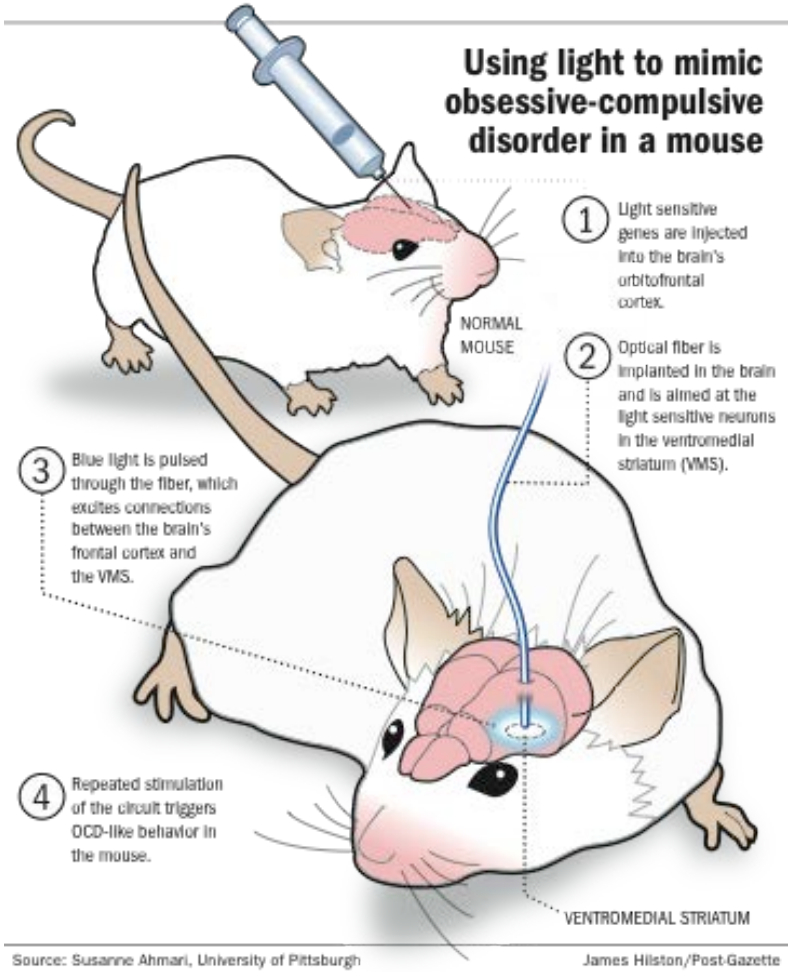

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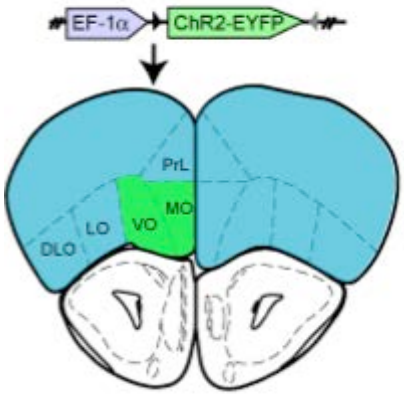
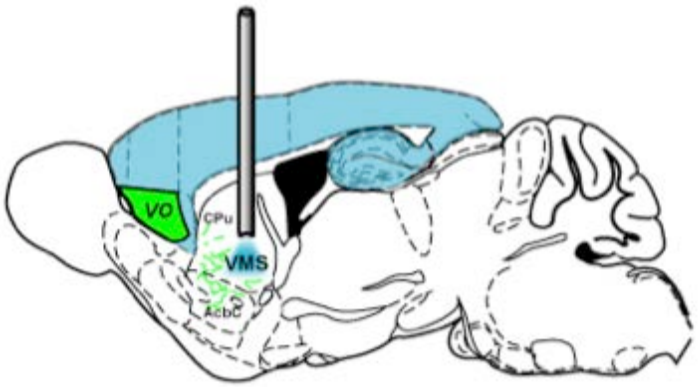
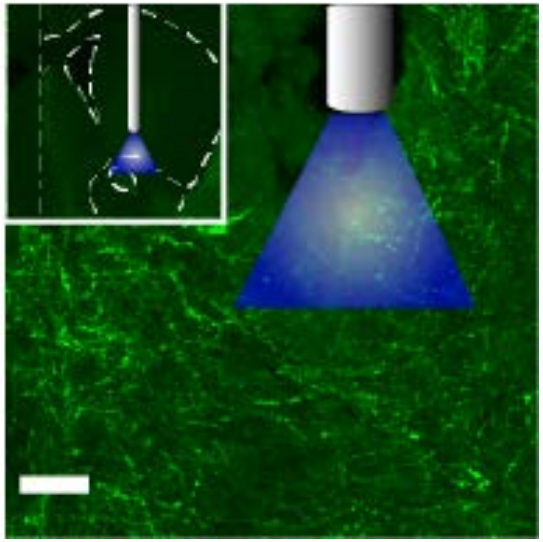
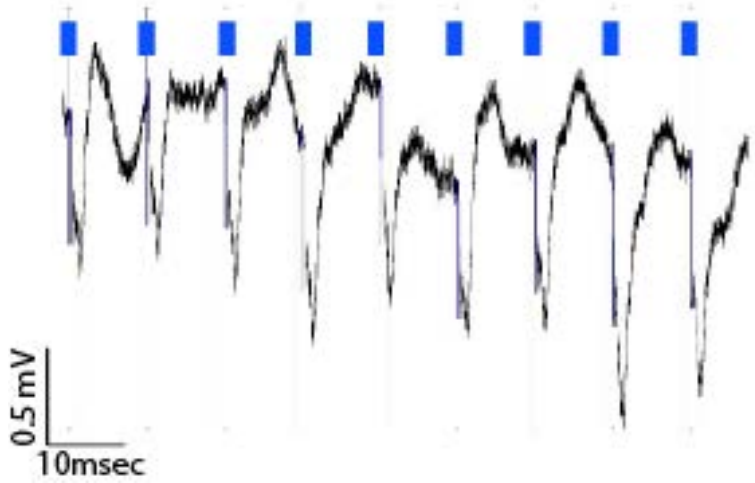


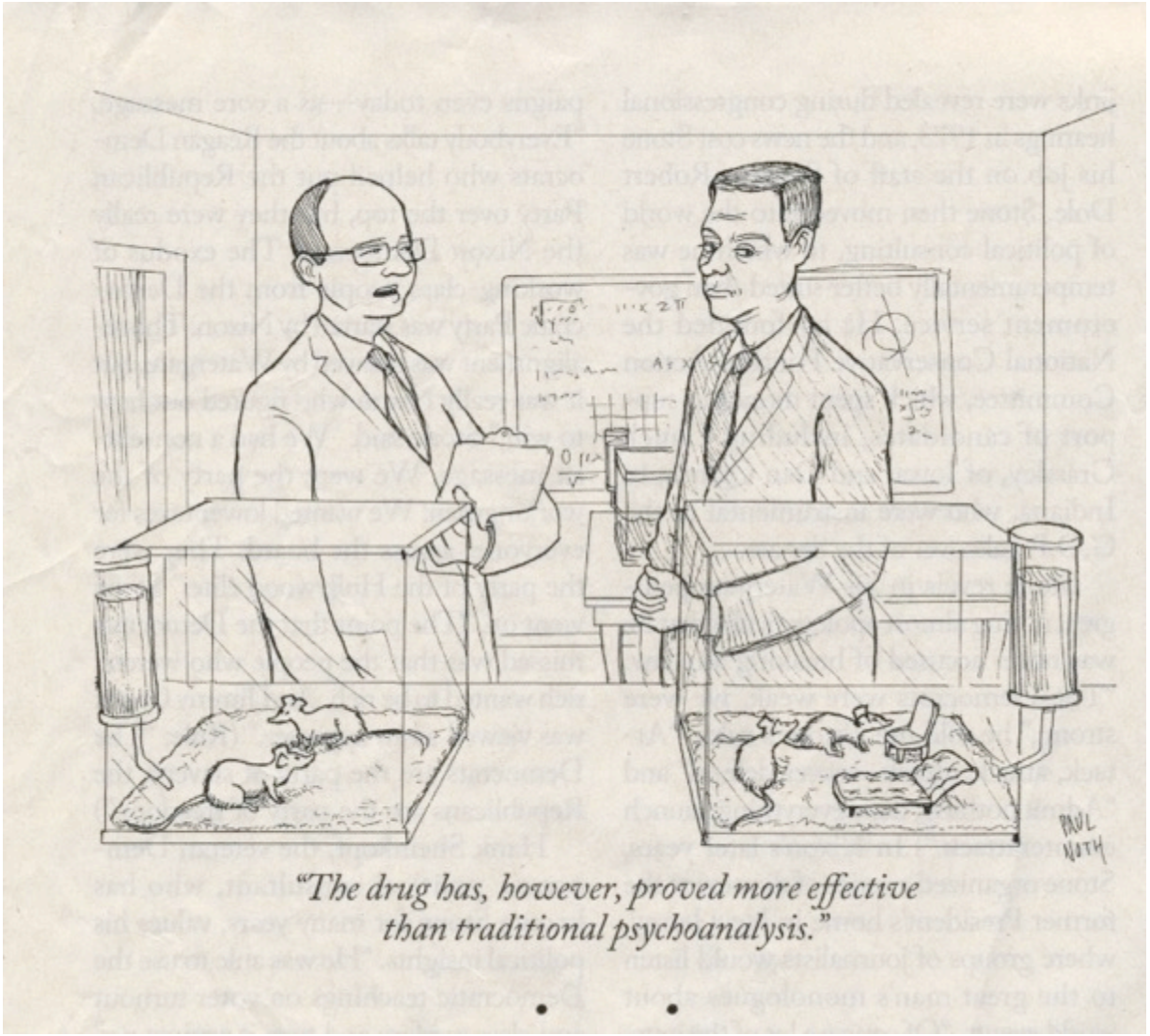






Ahmari et al, Science, 2013

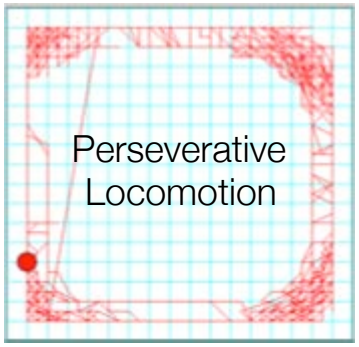
Challenge: Assessing OCD-relevant behaviors in mice



"The drug has, however, proved more effective than traditional psychoanalysis."

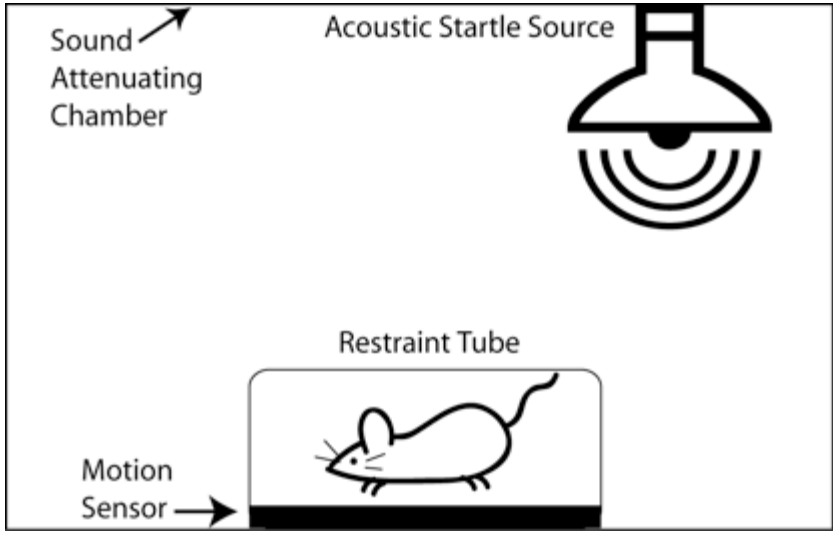
Challenge: Assessing OCD-relevant behaviors in mice

OCD-relevant behaviors



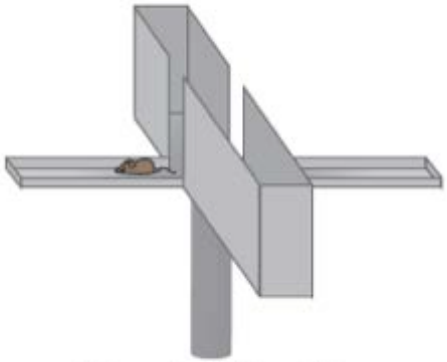
Impaired reversal learning

Impaired sensorimotor gating



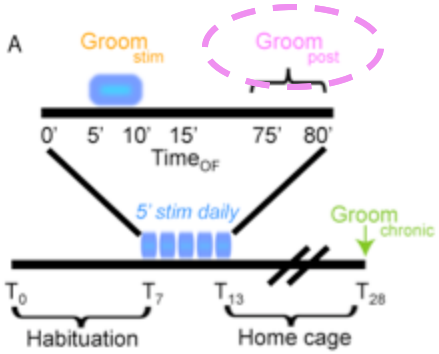
Anxiety-related behavior

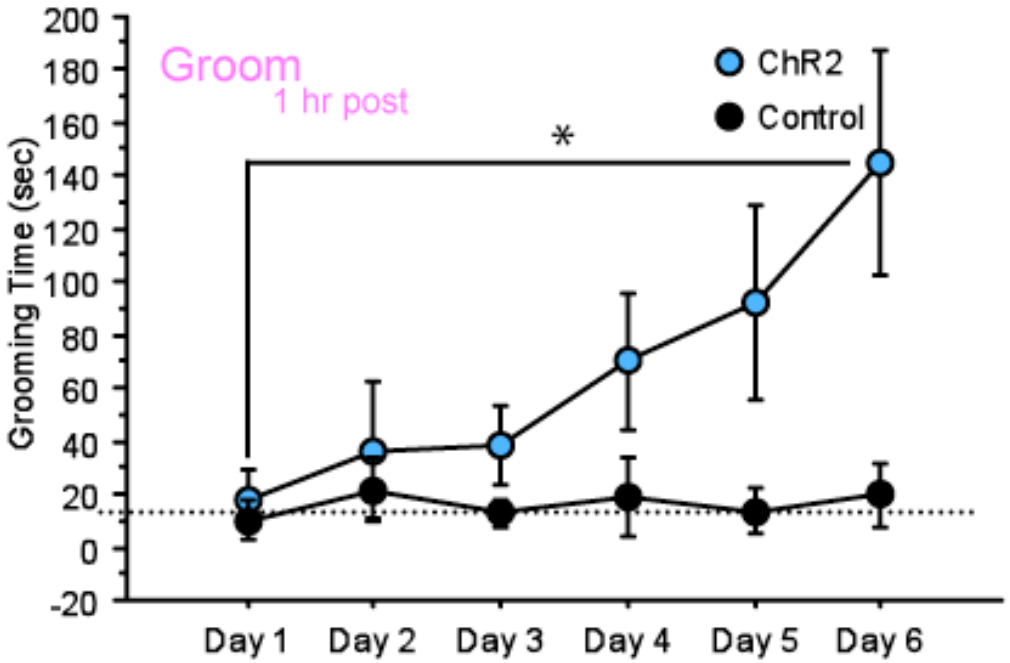
Open Field



Elevated Plus Maze

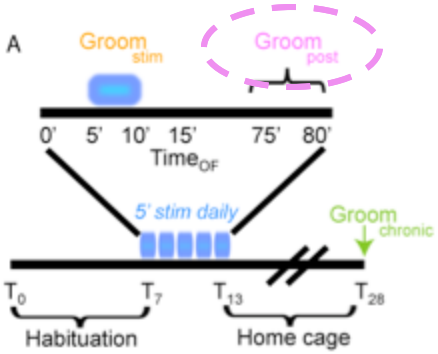
Repeated cortico-striatal stimulation leads to abnormal behavior and pathologic plasticity

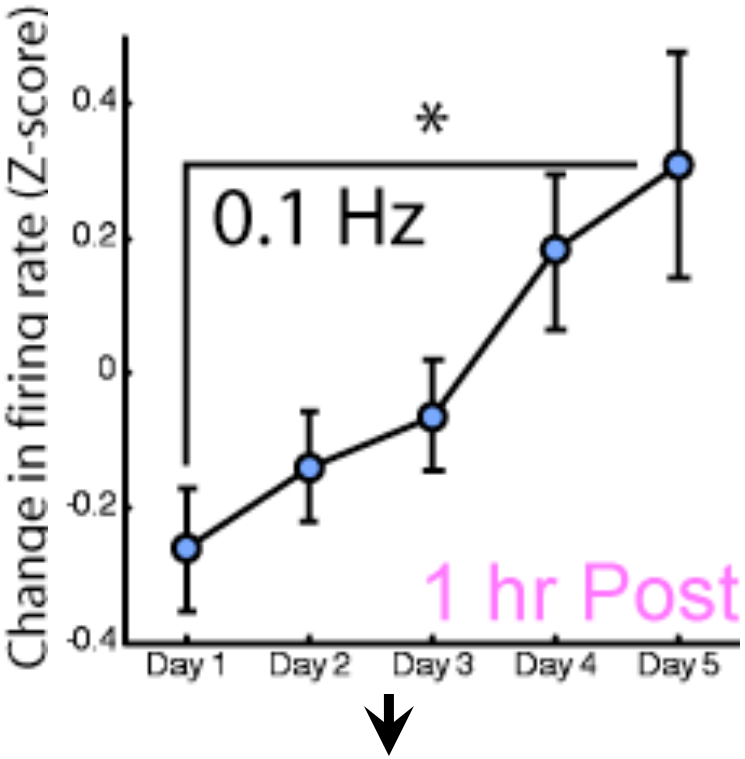




Ahmari et al, Science, 2013

Repeated cortico-striatal stimulation leads to abnormal behavior and pathologic plasticity

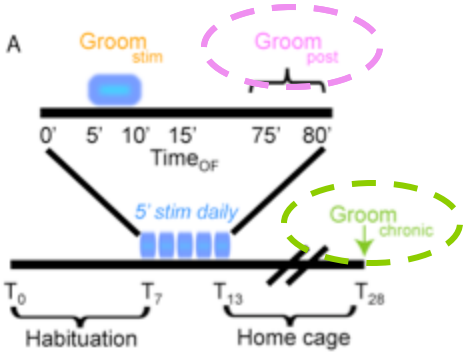


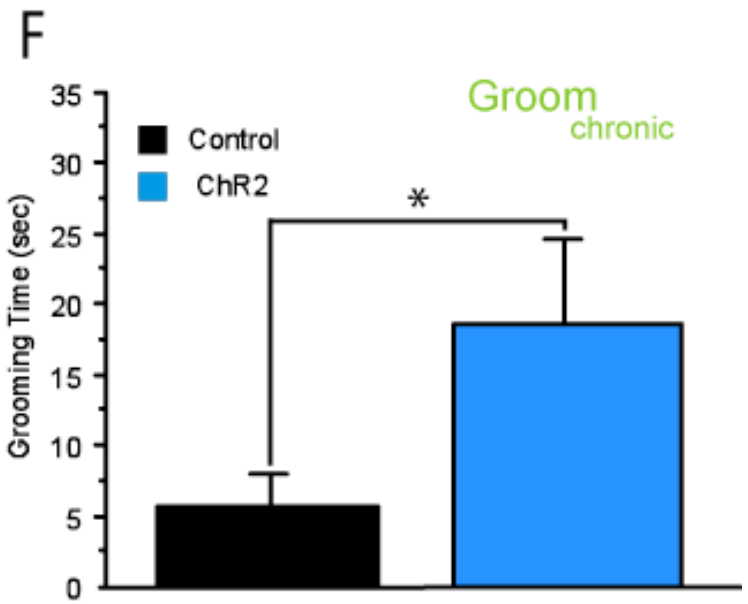


? Mechanisms ?
? Treatment applications?

Ahmari et al, Science, 2013

Repeated cortico-striatal stimulation leads to abnormal behavior and pathologic plasticity





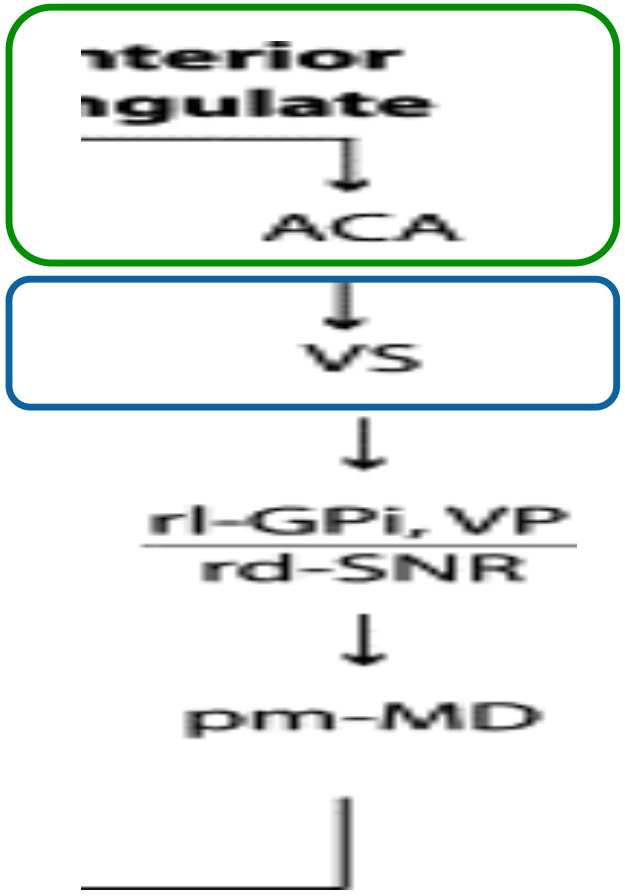
? Mechanisms ?

Ahmari et al, Science, 2013

Can circuit hubs be leveraged for non-invasive treatment?

TMS

DBS

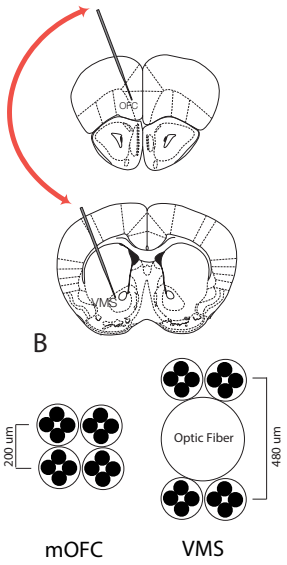


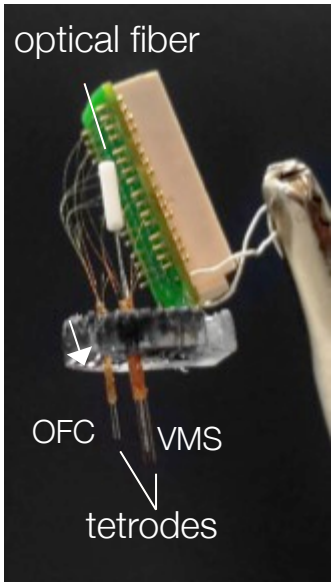
cortex

striatum

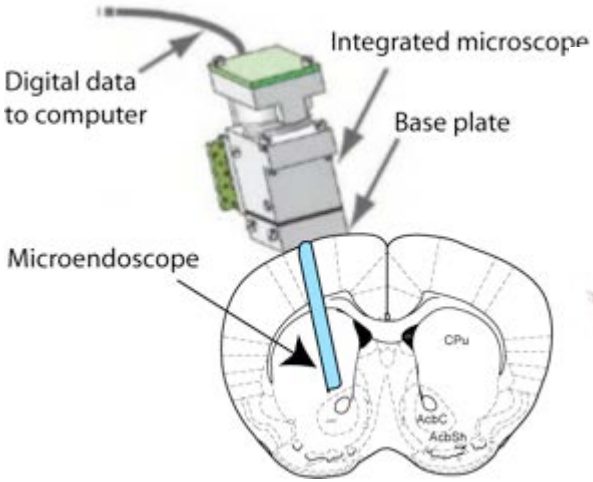
Using new tools to examine brain activity while mice are performing repetitive behaviors

Multi-site recording

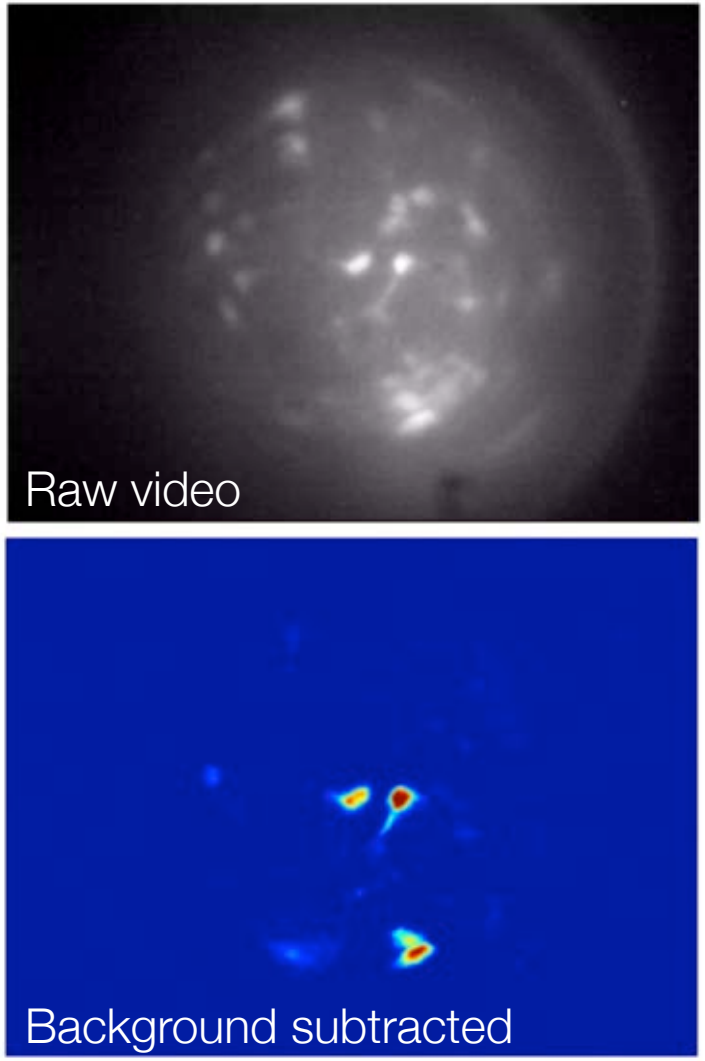




In vivo microscopy



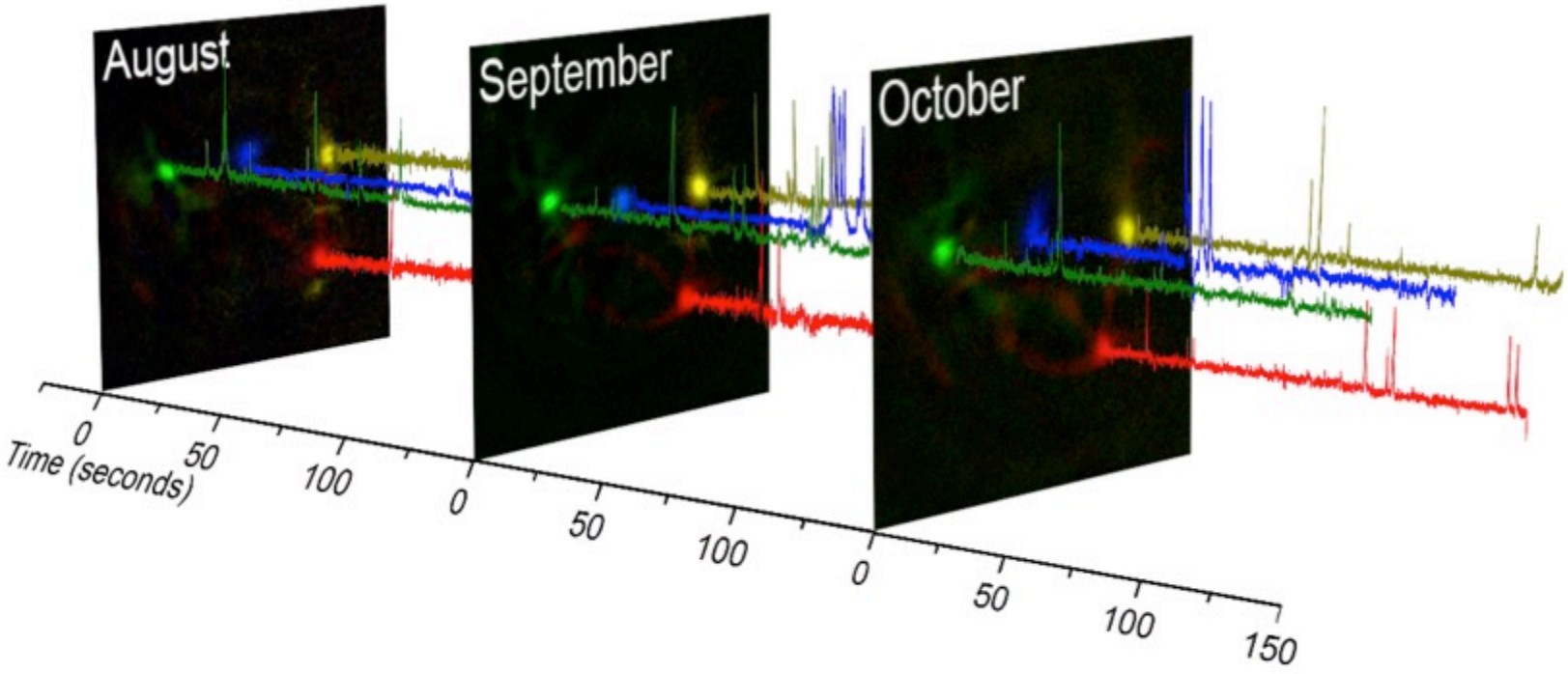
In vivo microscopy allows examination of local network activity in freely moving mice



Pengcheng Zhou

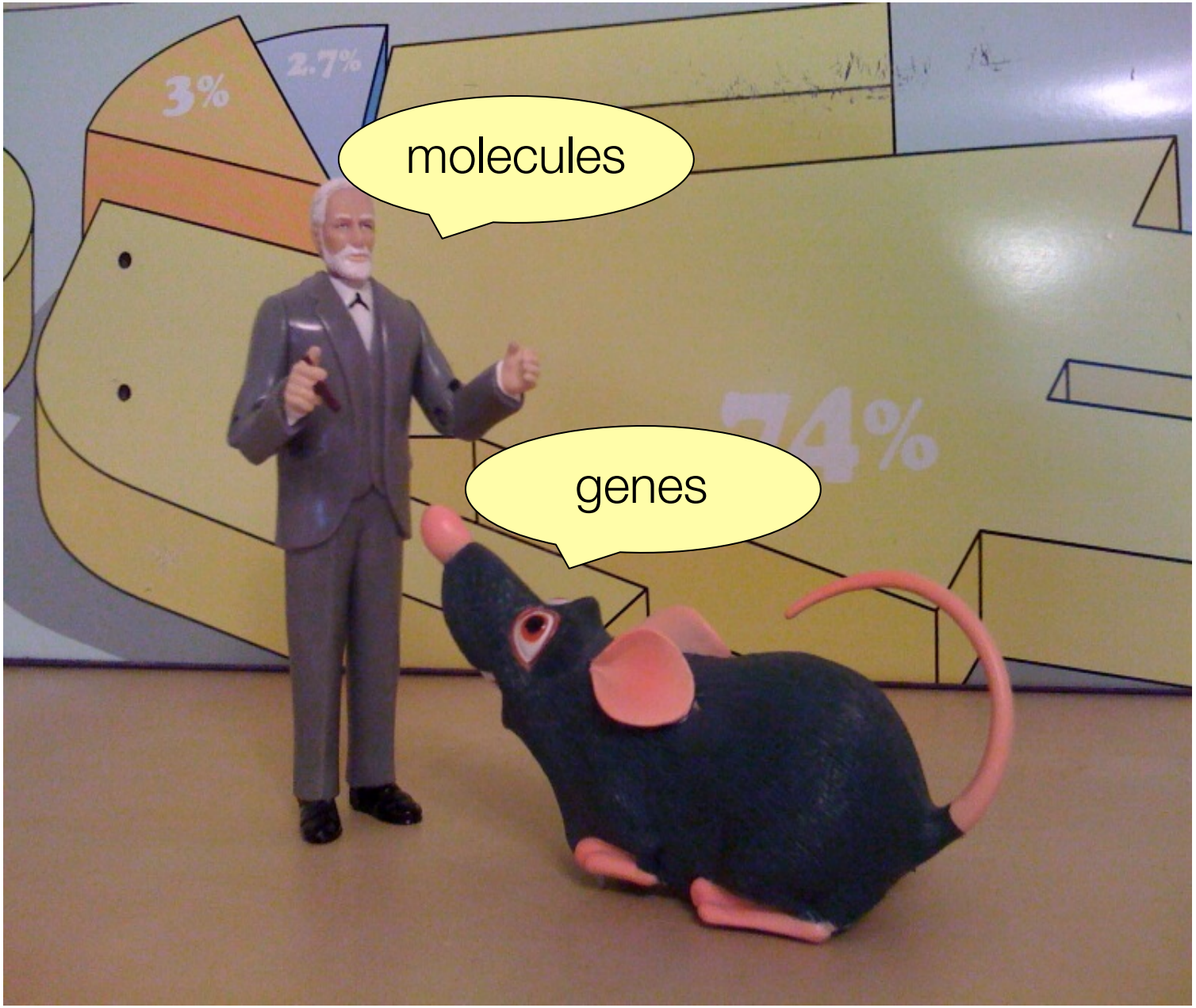
Rob Kass., Ph.D.

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

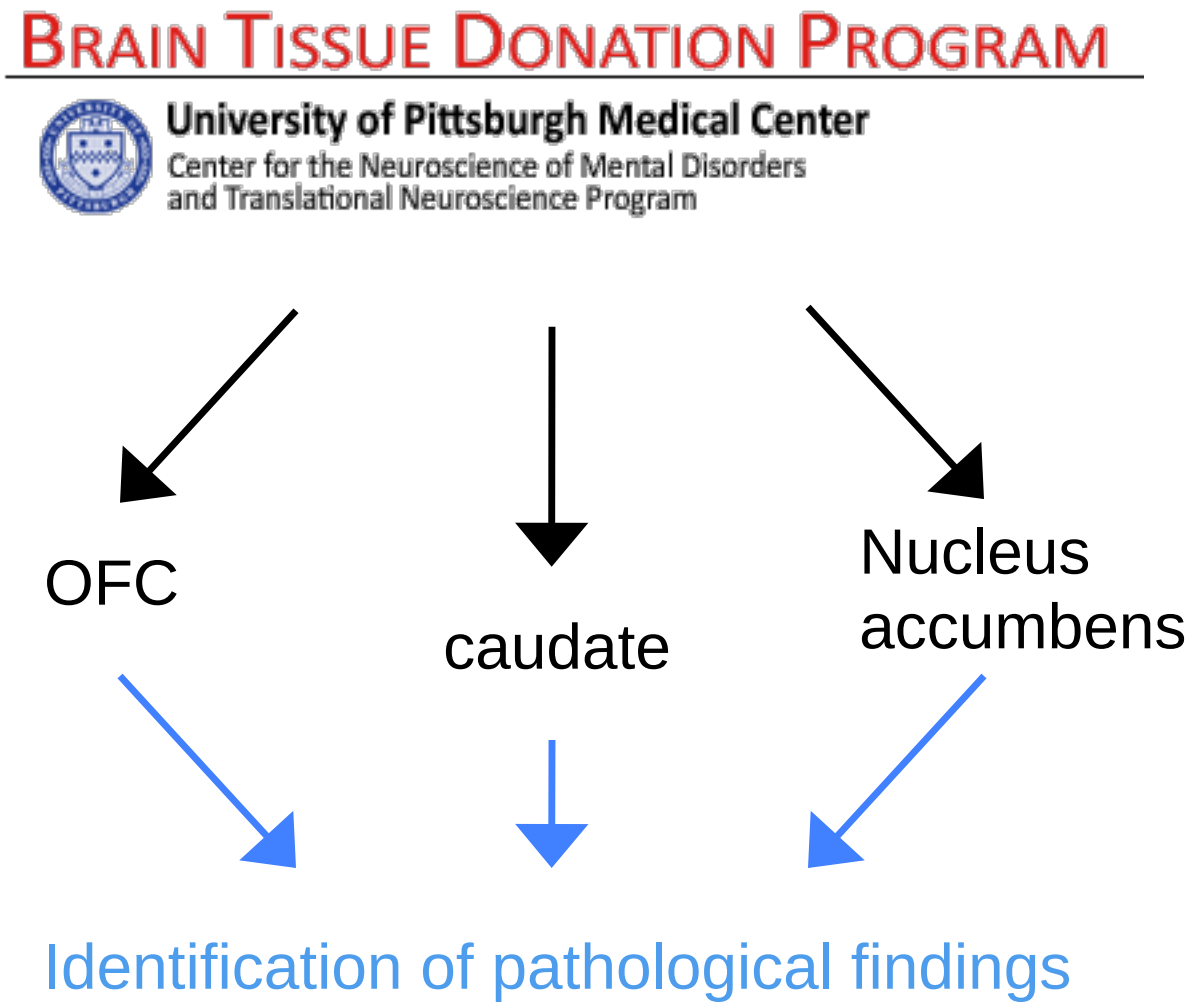

3%
2.7%
molecules
genes

Genetics of OCD

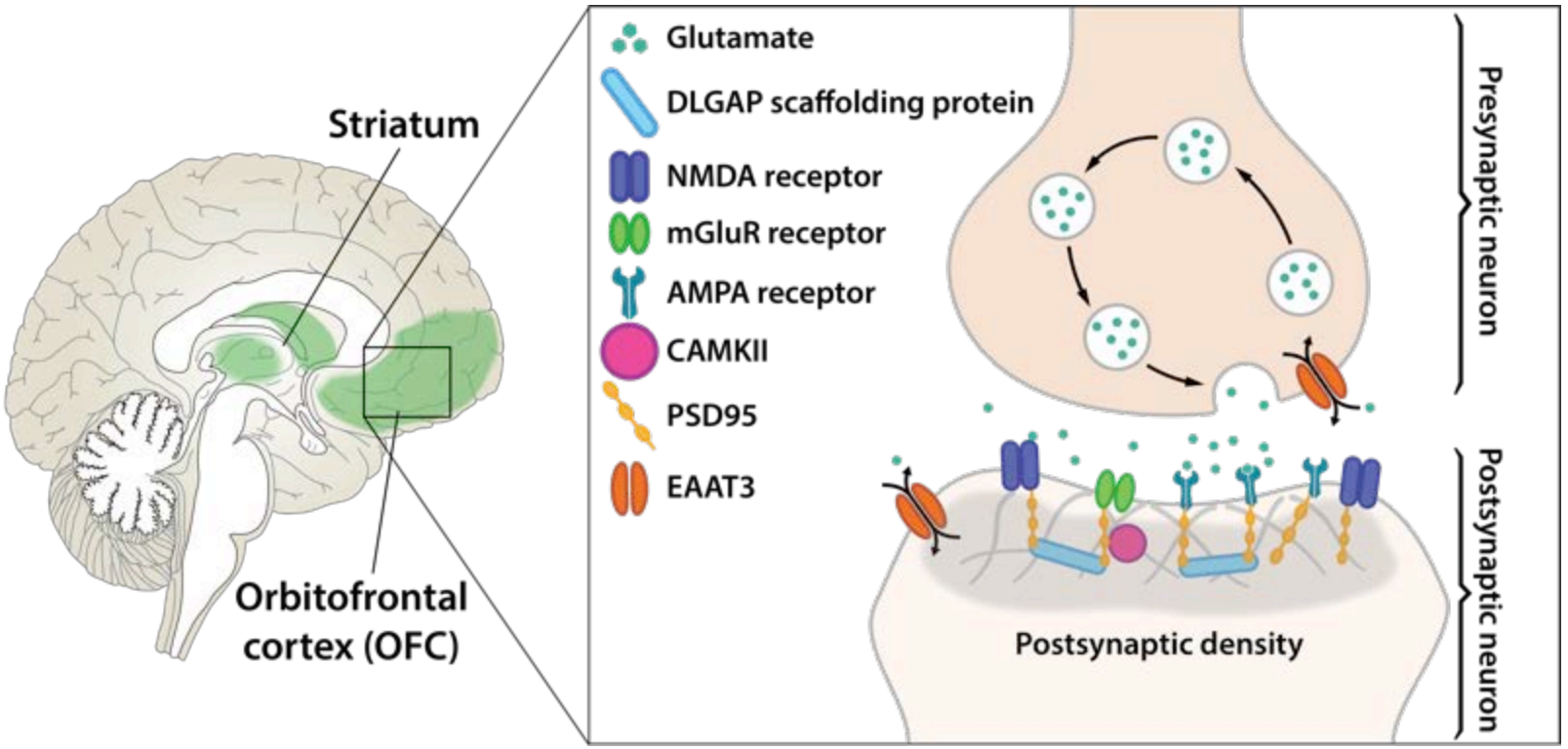
- Twin and family studies have revealed a significant genetic component to the etiology of OCD

- 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

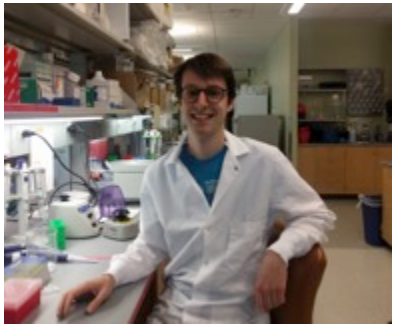
Parallel approach: post-mortem OCD studies



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

8 people with OCD; 8 comparison subjects

	COMPARISON SUBJECTS	**OCD SUBJECTS**	***P*-VALUE**
Number of subjects (*n*)	8	8	
Mean age (±SD)	45.1 (14.6)	46.6 (14.5)	*0.176*
Range	25-65	20-69	
Sex (F/M)	4/4	4/4	
PMI (±SD)	16.0 (4.8)	18.0 (7.3)	*0.31*
Brain pH (±SD)	6.6 (0.2)	6.7 (0.2)	*0.236*
RNA ratio	1.6 (0.25)	1.6 (0.22)	*0.783*
RNA integrity number	7.7 (0.65)	7.8 (0.44)	*0.630*
Suicide, *n* (%)	0 (0%)	3 (38%)	
Antidepressants ATOD, *n* (%)	0 (0%)	5 (63%)	

Pair	***OCPD***	***MDD***	***BPD***	***GAD***	***PD***	***PTSD***
1	Yes	Yes	-	-	-	-
2	Yes	-	-	-	-	-
3	-	-	-	-	-	-
4	-	-	-	-	Yes	Yes
5	-	-	Yes	-	-	-
6	Yes	-	-	-	Yes	Yes
7	-	Yes	-	-	-	-
8	-	Yes	-	Yes	-	-

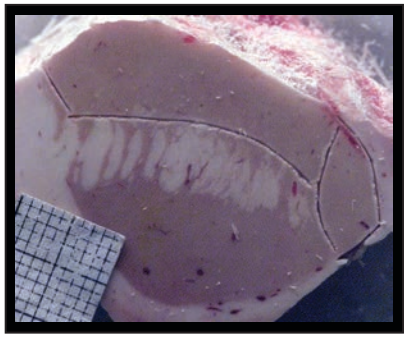
Identifying molecular changes in OCD

8 people with OCD; 8 comparison subjects

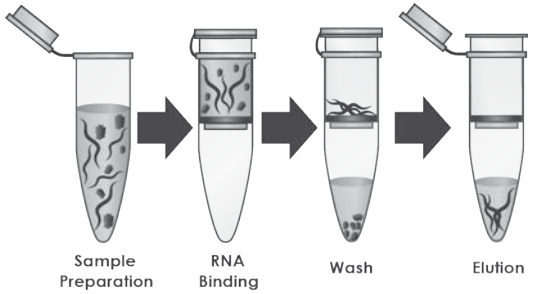
Brain regions

- medial OFC
- lateral OFC
- Caudate
- Nucleus accumbens

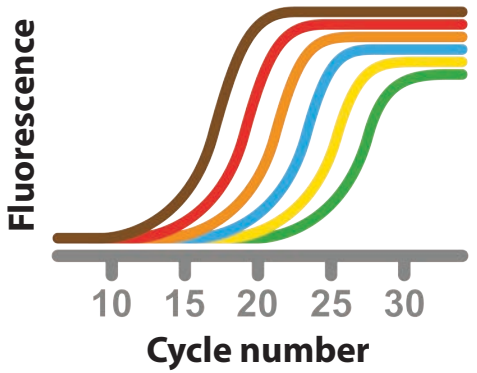
Step 1:
Slice fresh frozen tissue



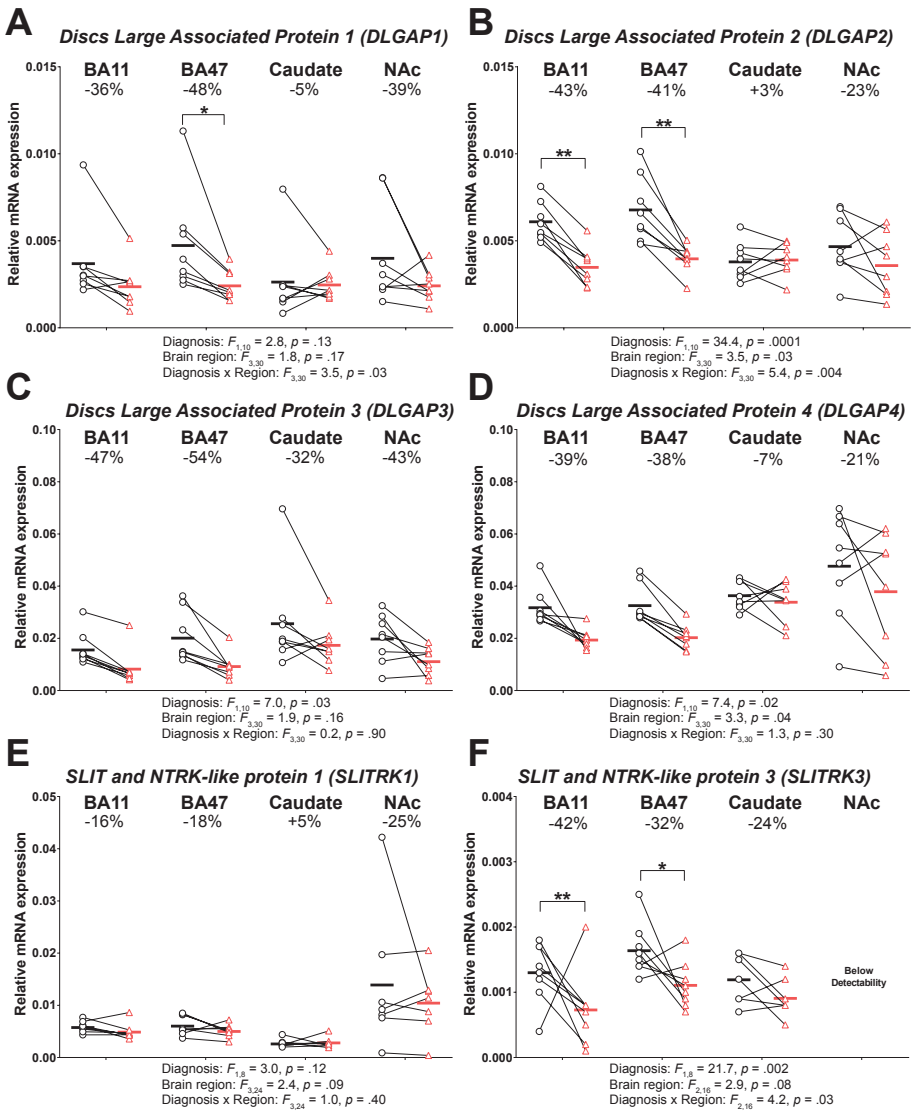
Step 2:
Extract RNA from sample



Step 3:
Perform qPCR

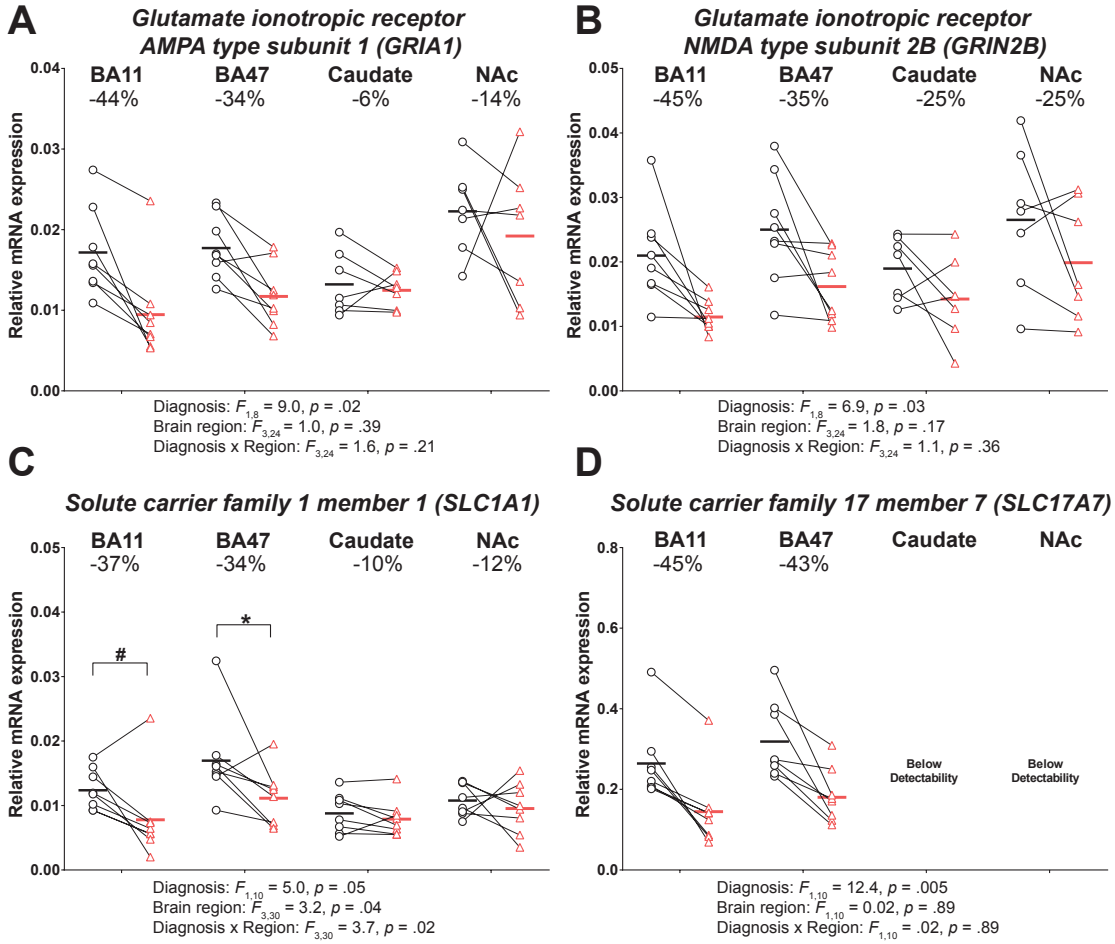


Downregulation of transcripts that make up the structure of excitatory synapses



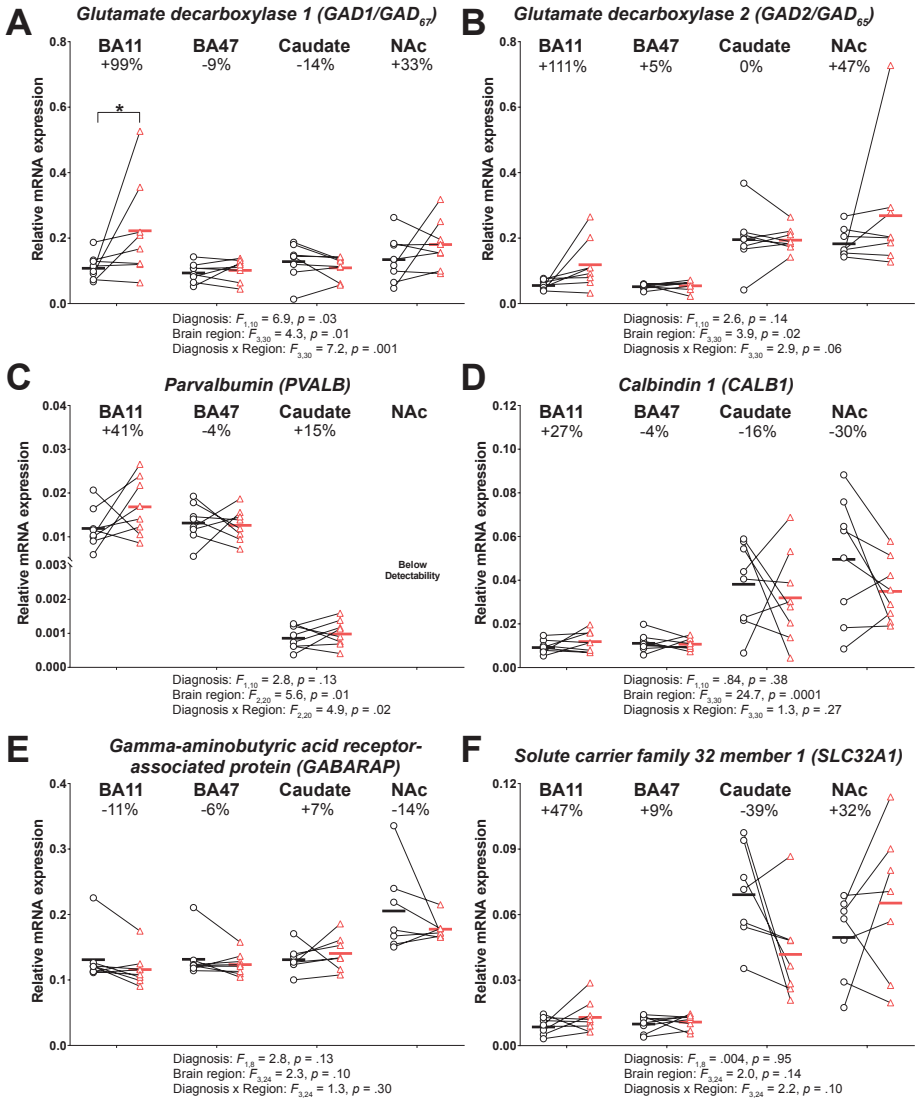
Piantadosi et al., *Molecular Psychiatry, 2019*

Downregulation of transcripts encoding excitatory synapse transporters



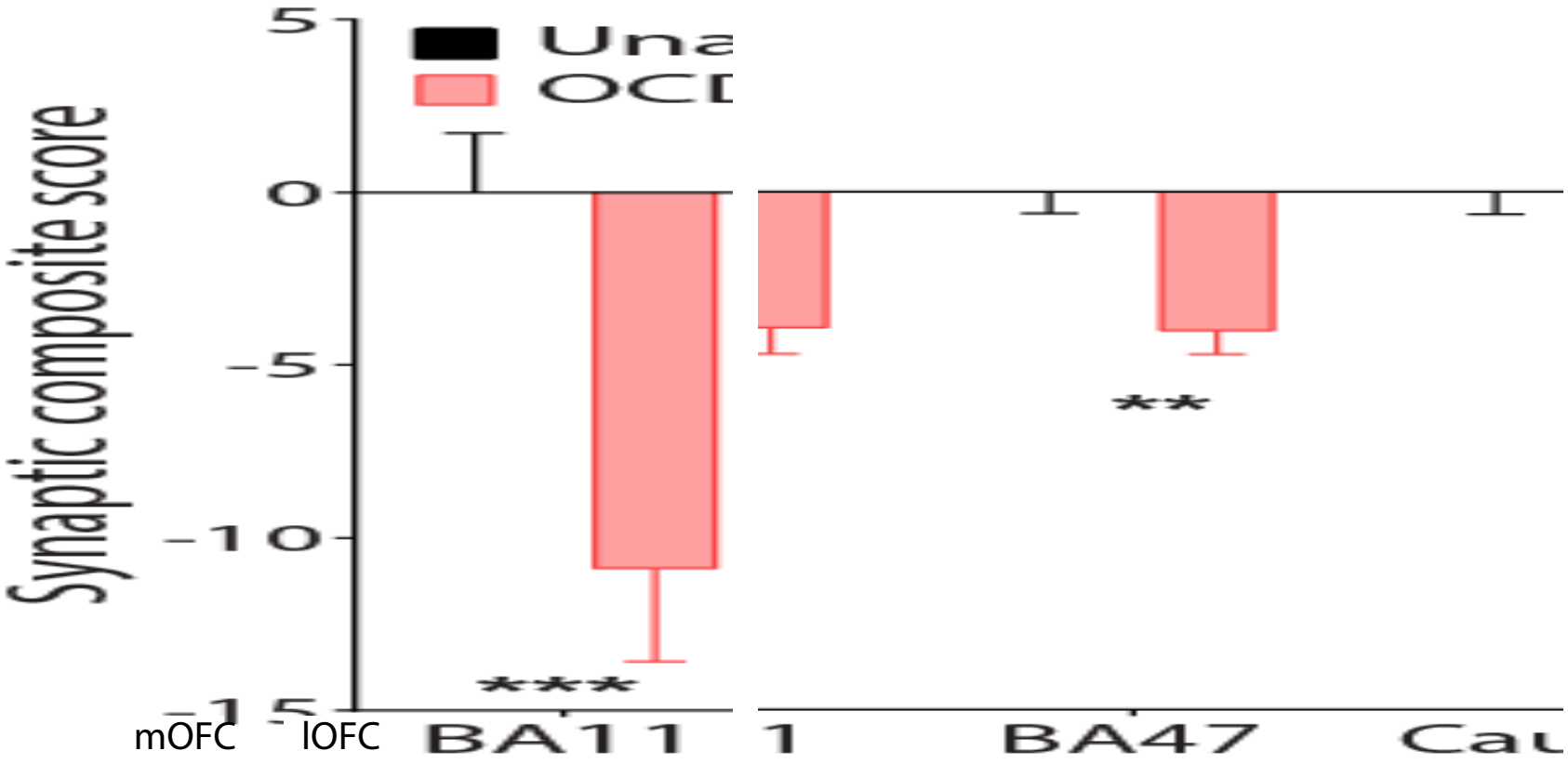
Piantadosi et al., *Molecular Psychiatry, 2019*

Little change in inhibitory synapse transcripts



Piantadosi et al., *Molecular Psychiatry, 2019*

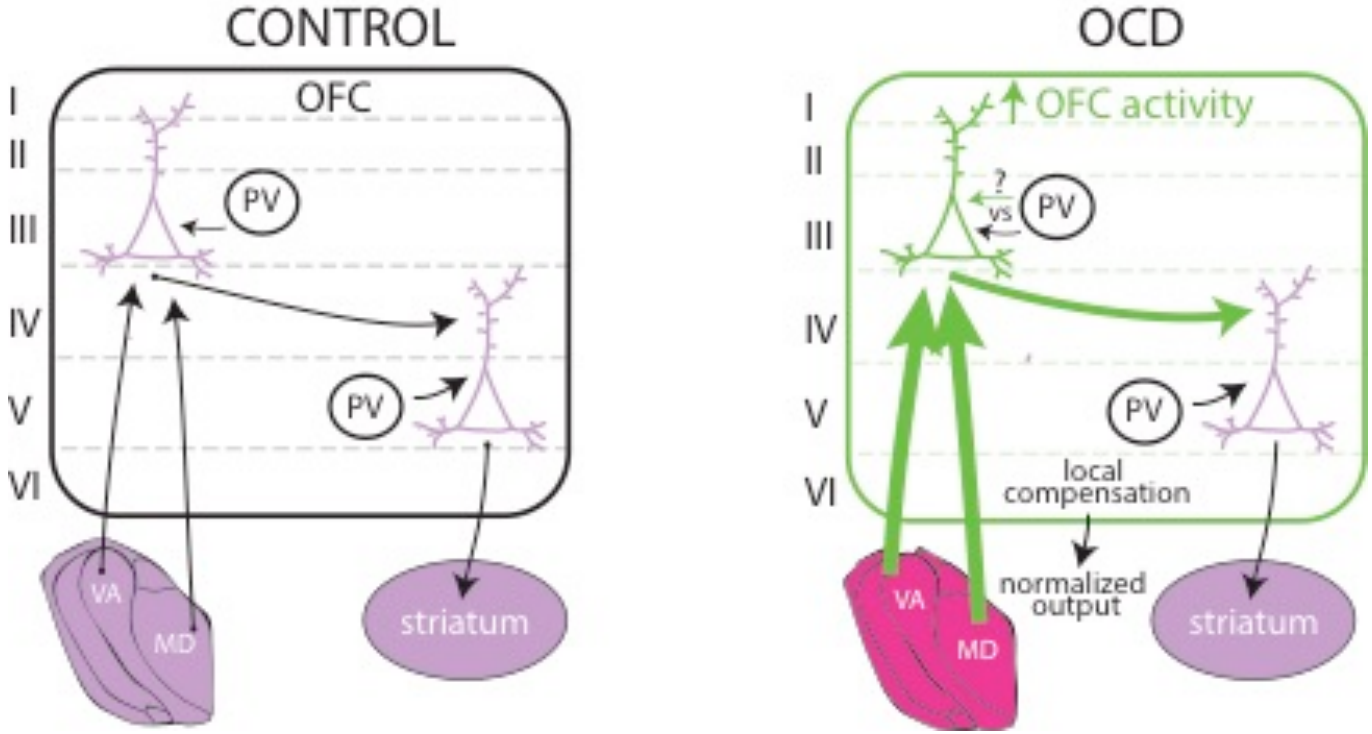
Most robust decrease in excitatory gene expression in OFC, not striatum



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



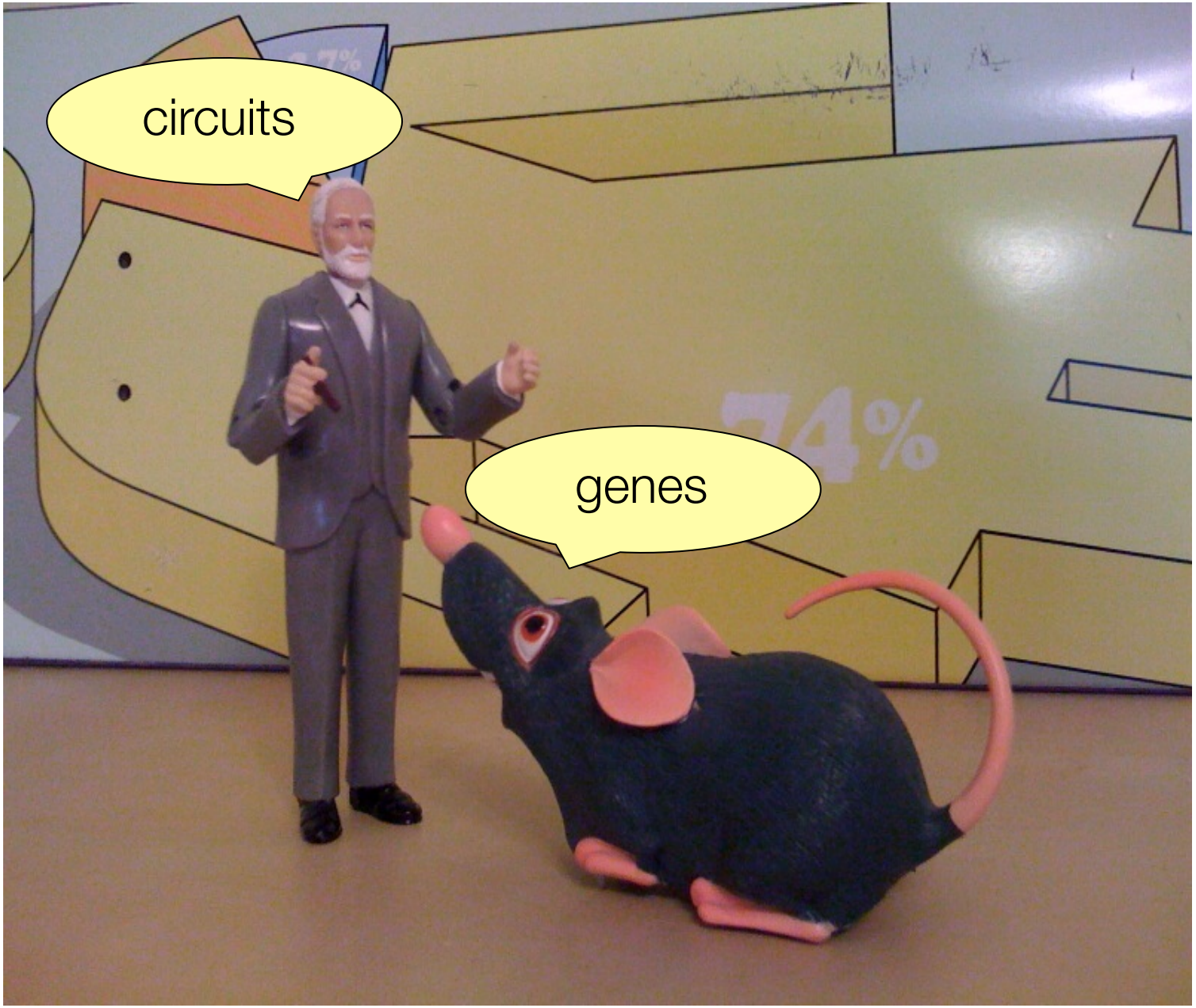
International OCD Foundation

ONE MIND

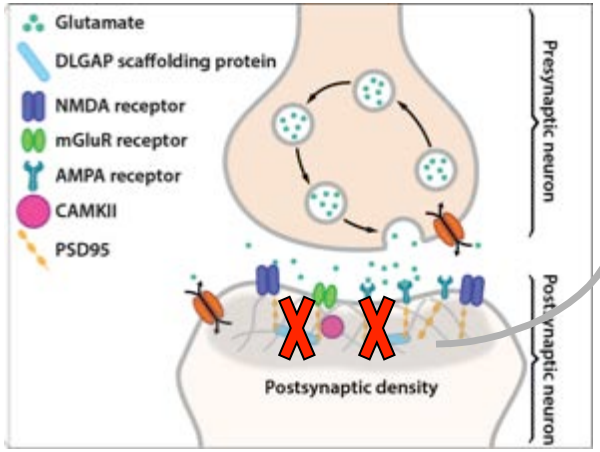
RISING STAR AWARDS

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

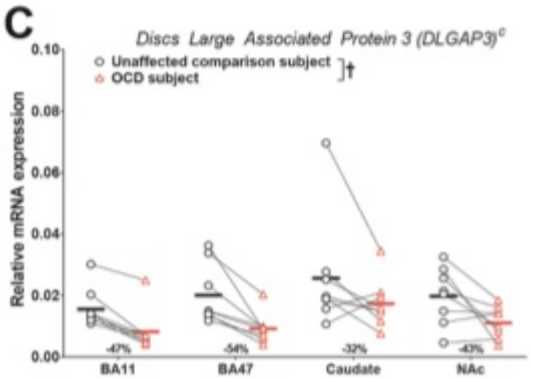

circuits
genes

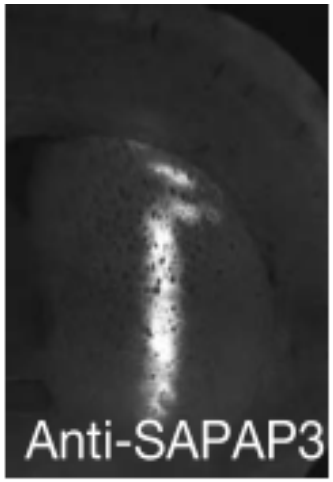
Investigating striatal mechanisms underlying compulsive behavior using *Sapap3*-knockout mice

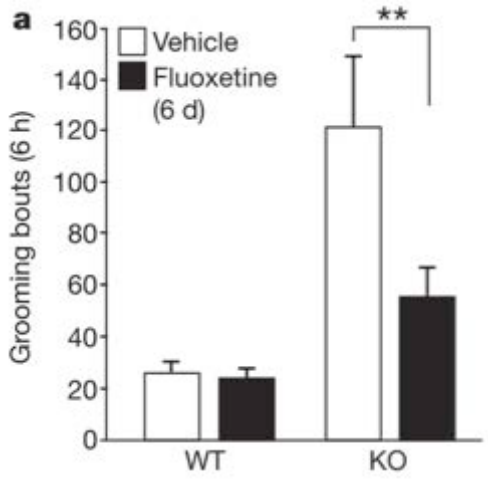


Compulsive Grooming

Persists despite negative consequences

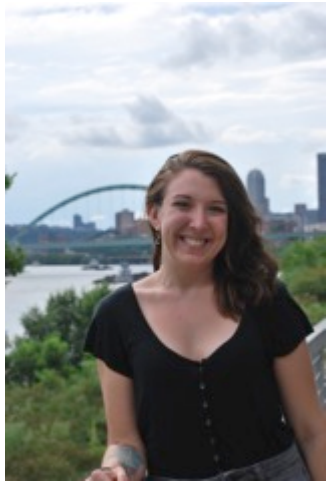




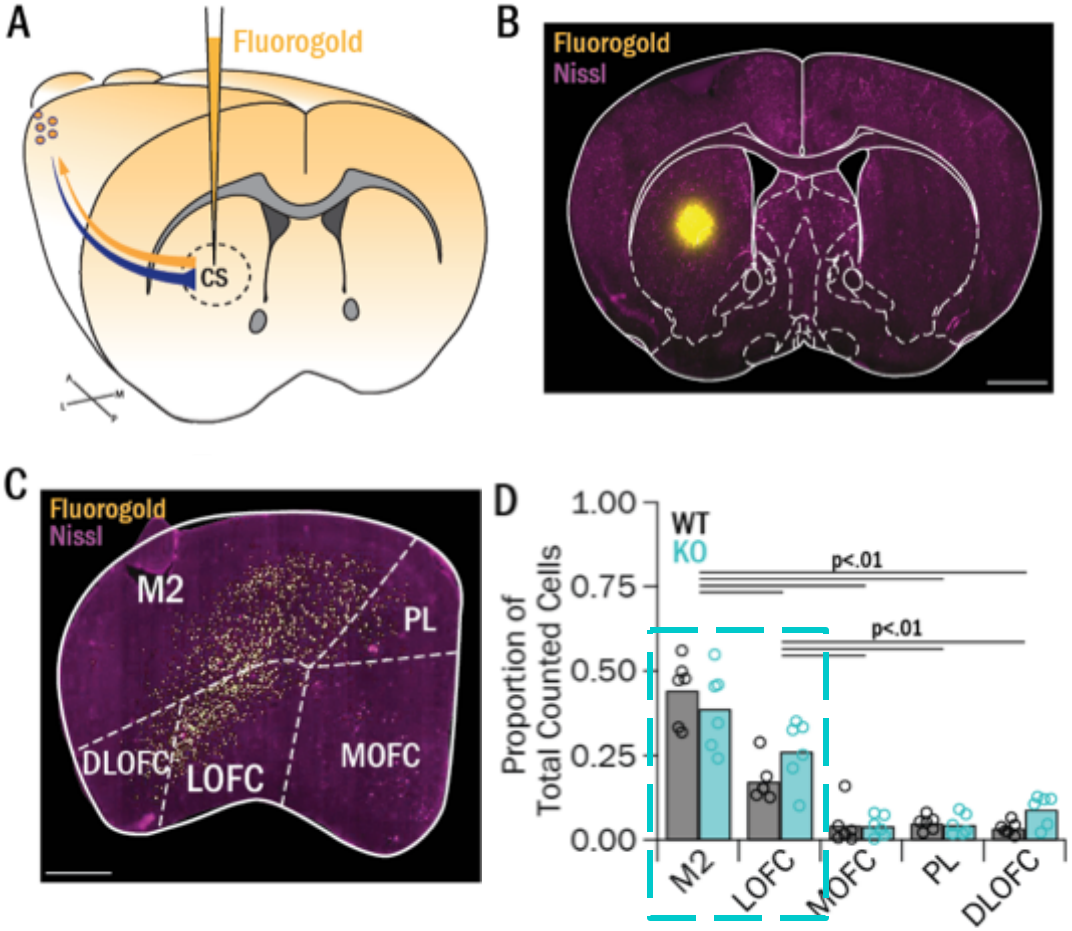


Welch et al. 2007, Burguiere et al., 2013

Striatum receives strong projections from OFC and M2

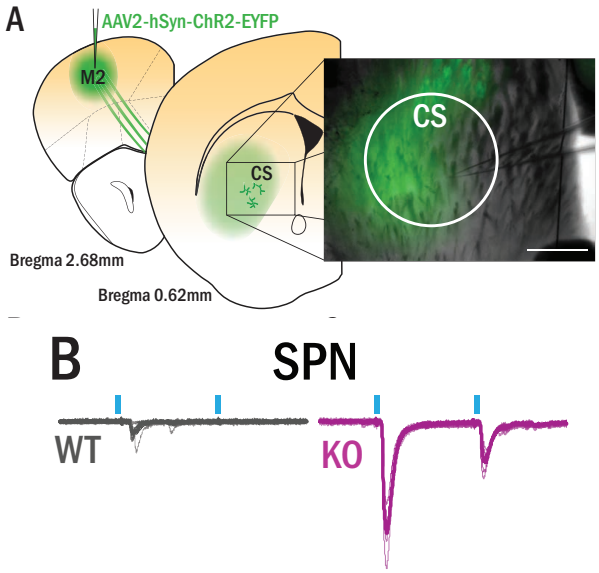


Victoria Corbit



Corbit et al., *J. Neuroscience,* 2019

Strengthened M2 projections might be causing striatal hyperactivity in knockout mice

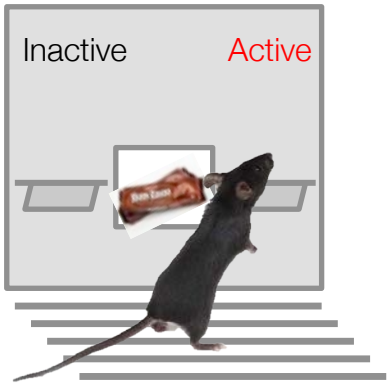


Corbit et al., *J. Neuroscience,* 2019

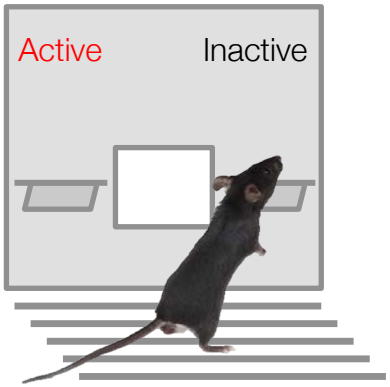
Investigating heterogeneity of compulsive behavior using *Sapap3*-knockout mice

Reversal learning

Learning the rule



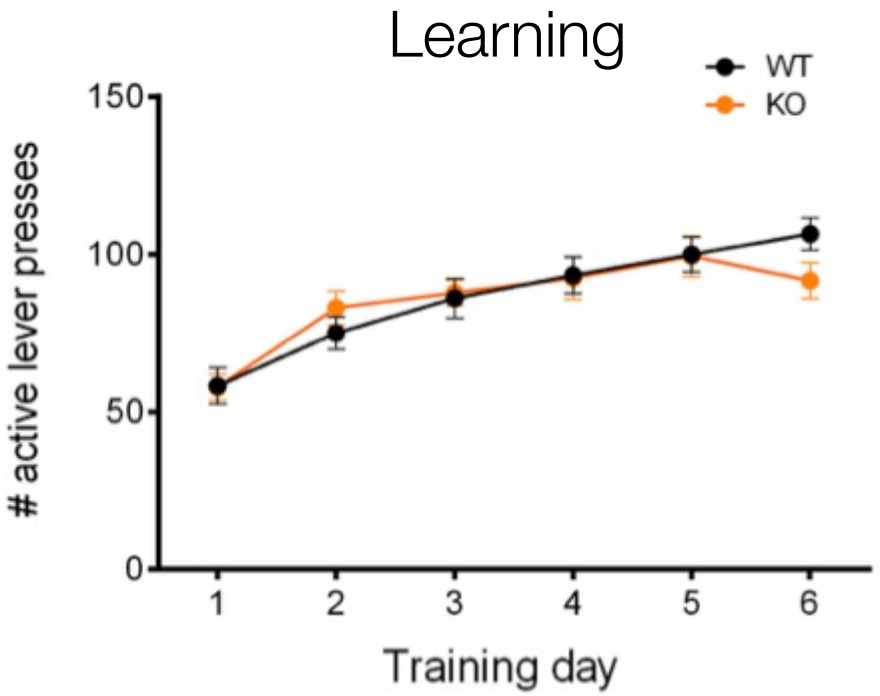
Early reversal 1
(perseverative)

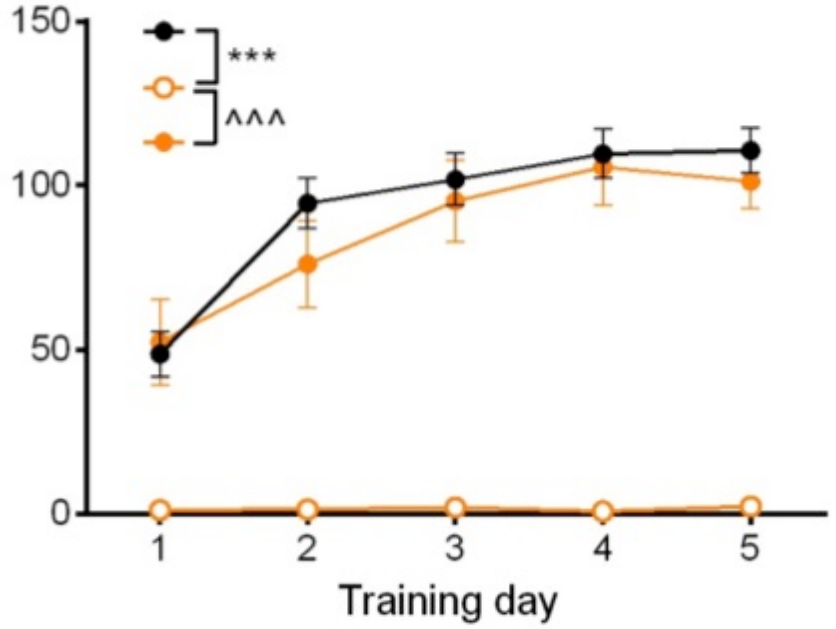


Late reversal 1
(flexible)

Lizzie Manning

Reversal learning is impaired in SAPAP3 KOs

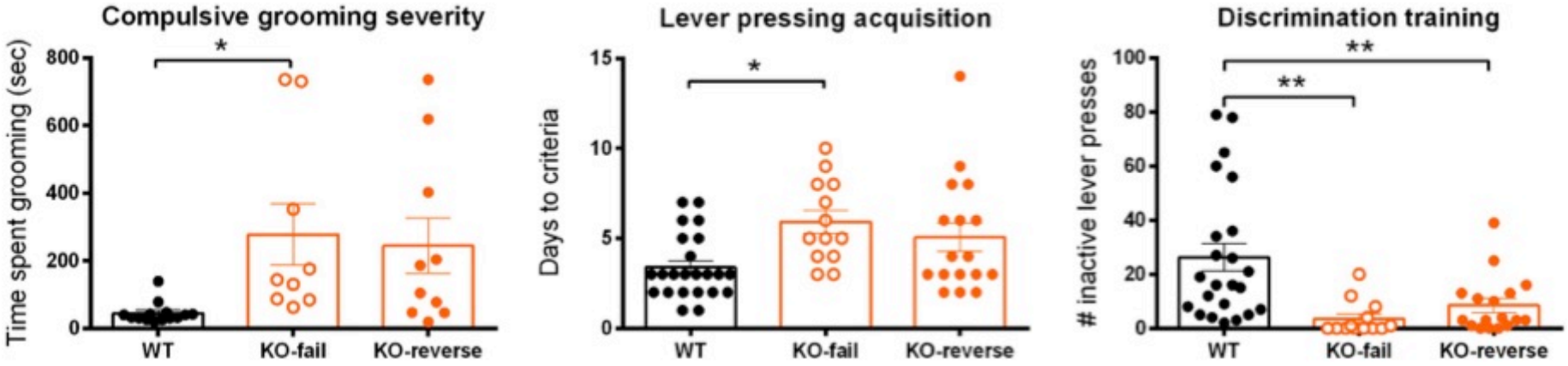




~40% of SAPAP3-KOs fail reversal

Manning et al., 2018, *Neuropsychopharmacology*

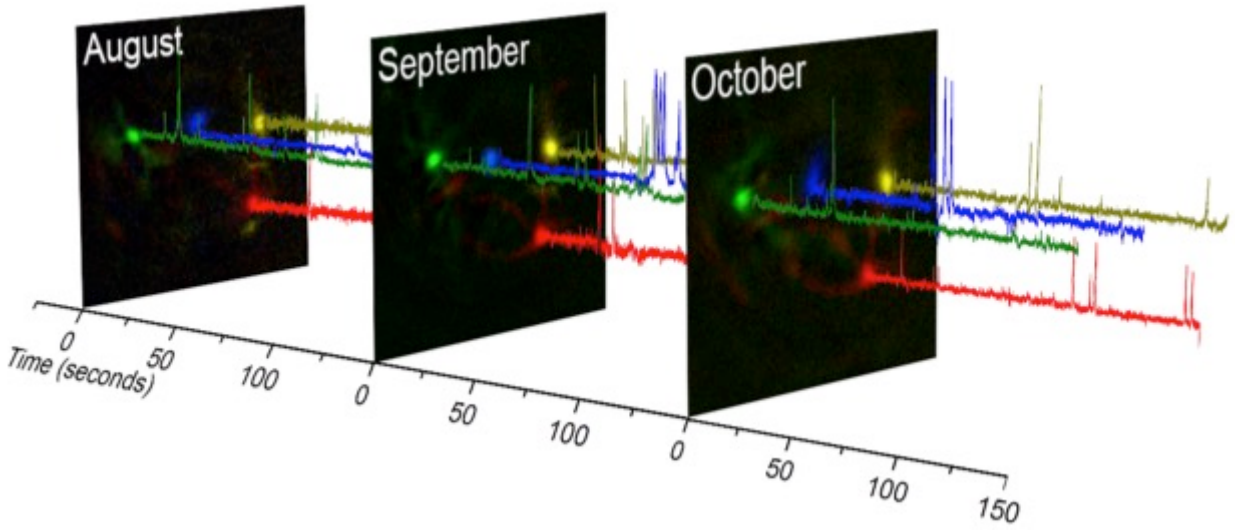
Reversal is not predicted by grooming severity or task acquisition

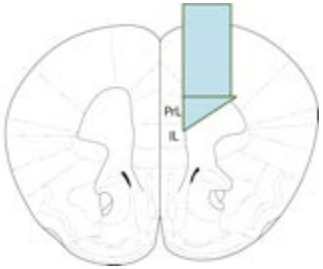


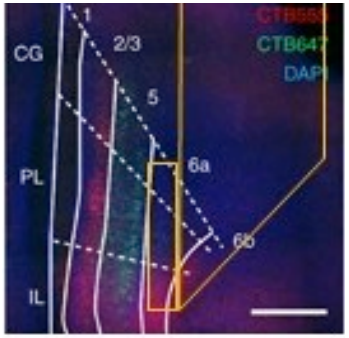
- Striking but variable deficit in reversal learning
- Underlying circuit mechanisms are unclear

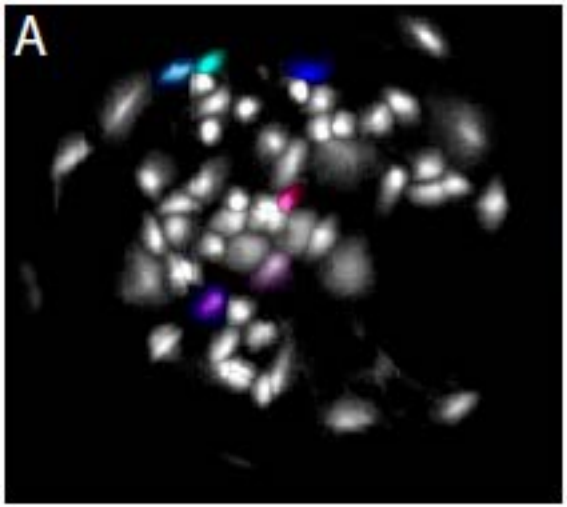
Manning et al., 2018, *Neuropsychopharmacology*

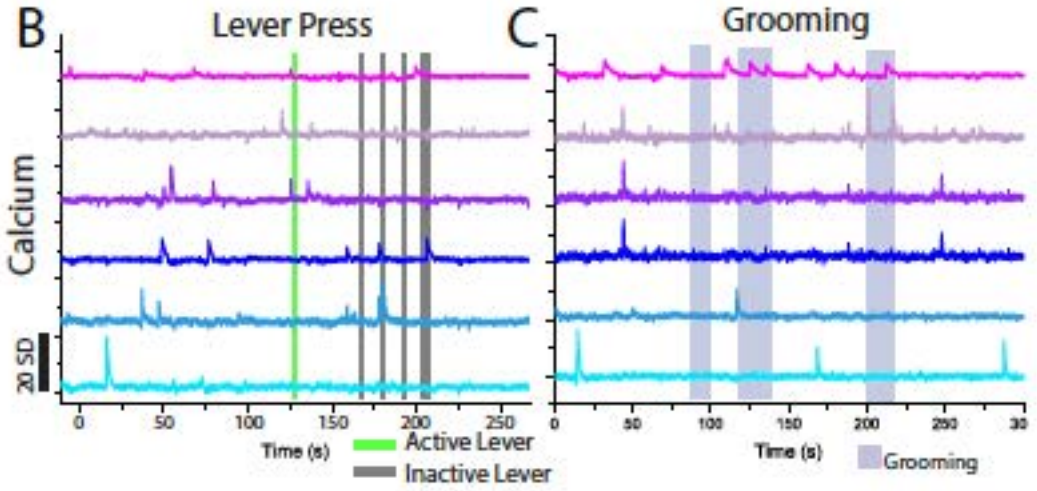
Longitudinal imaging allows tracking of neurons during different OCD-relevant behaviors



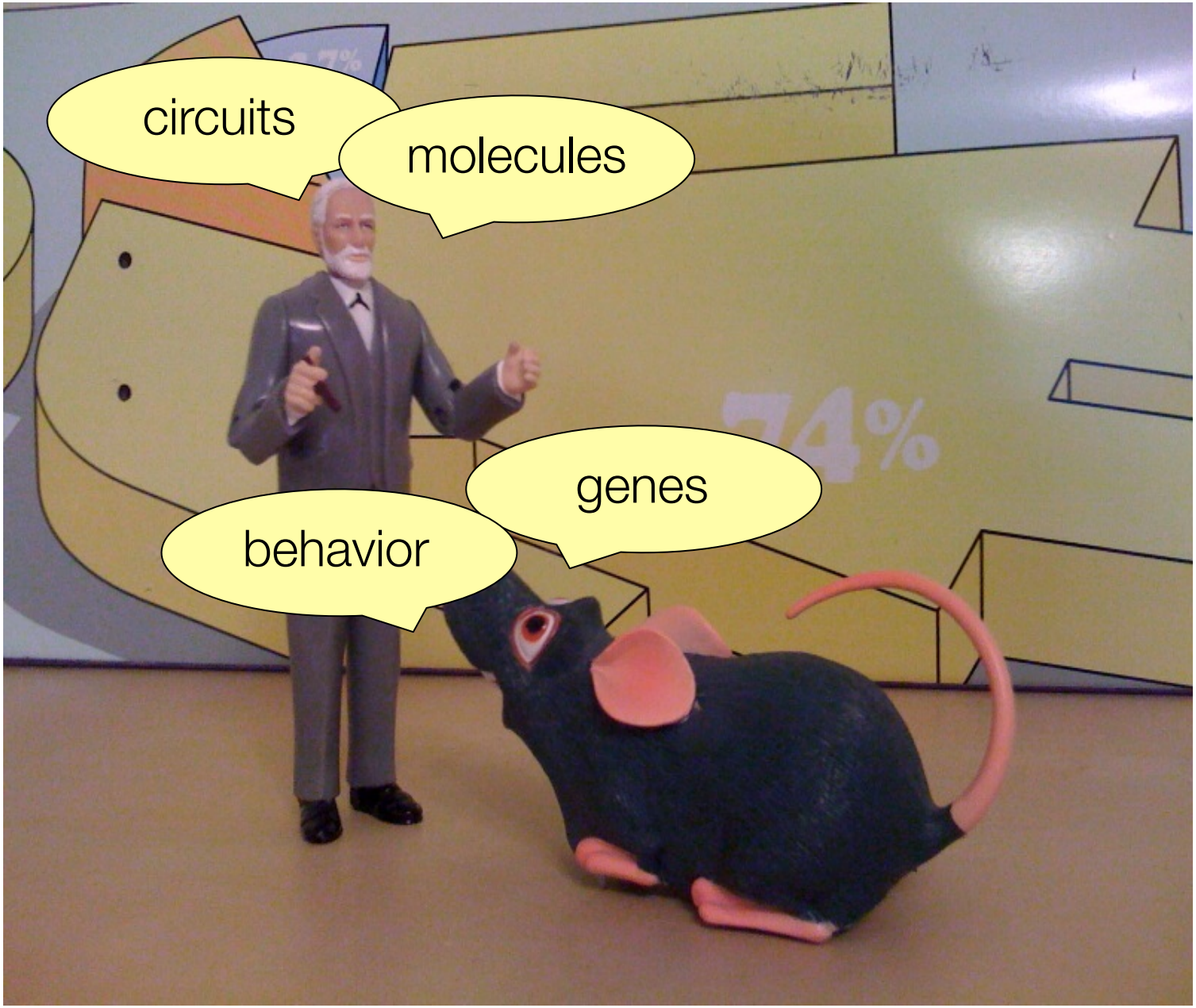




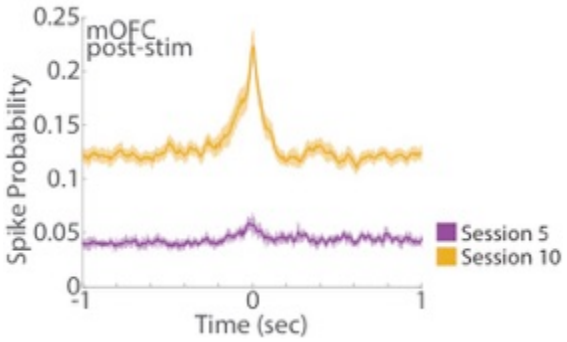


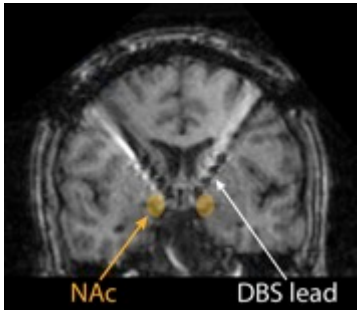


Translational strategies to develop new treatments

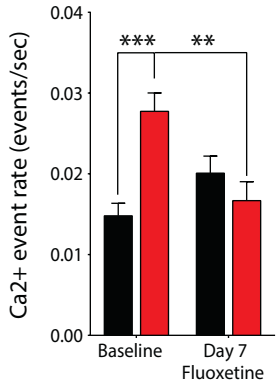


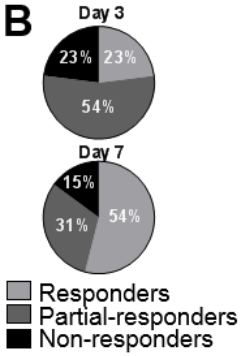
Overall goal: develop improved, neuroscience-based treatments for OCD





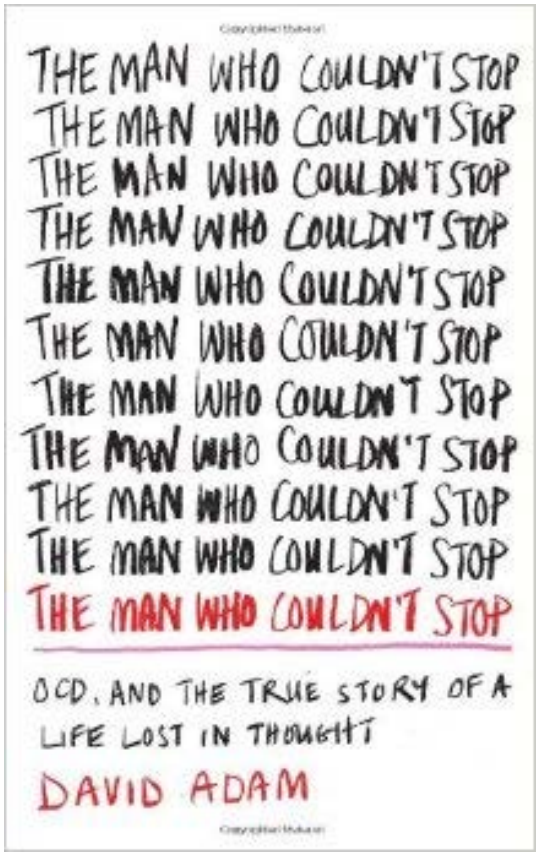
New stimulation programs?





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

International OCD Foundation

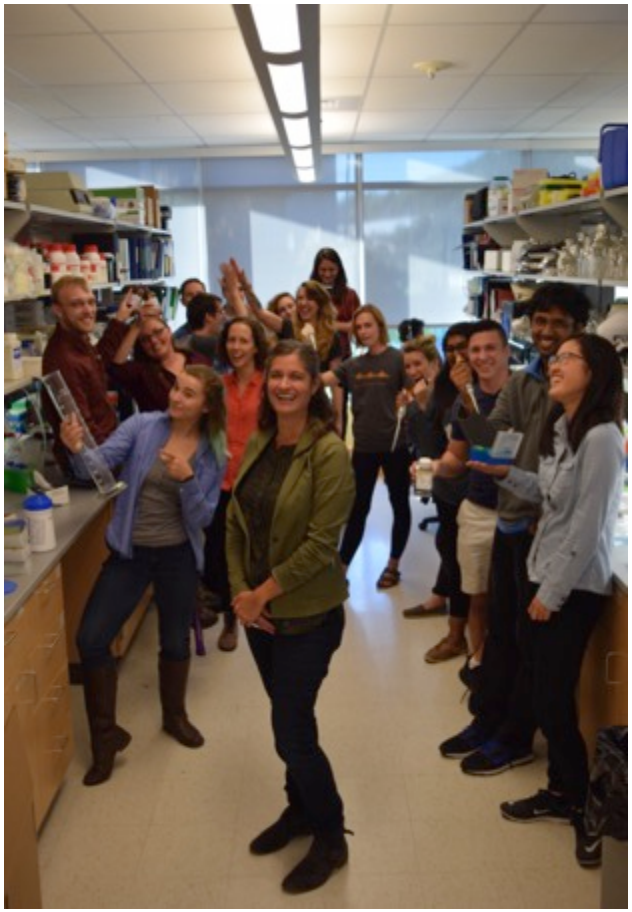
www.iocdf.org

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

Please consider brain donation!!!

www.braindonorproject.org

Ahmari Lab



- Lizzie Manning, Ph.D
- Jesse Wood, Ph.D.
- James Hyde, Ph.D.
- Jamie Pierson, Ph.D.
- Britny Hildebrandt, Ph.D.
- Victoria Corbit
- Sean Piantadosi
- Jared Kopelman
- Zoe LaPalombara
- Jay Wang
- Ruth Snyder
- Brittany Chamberlain

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