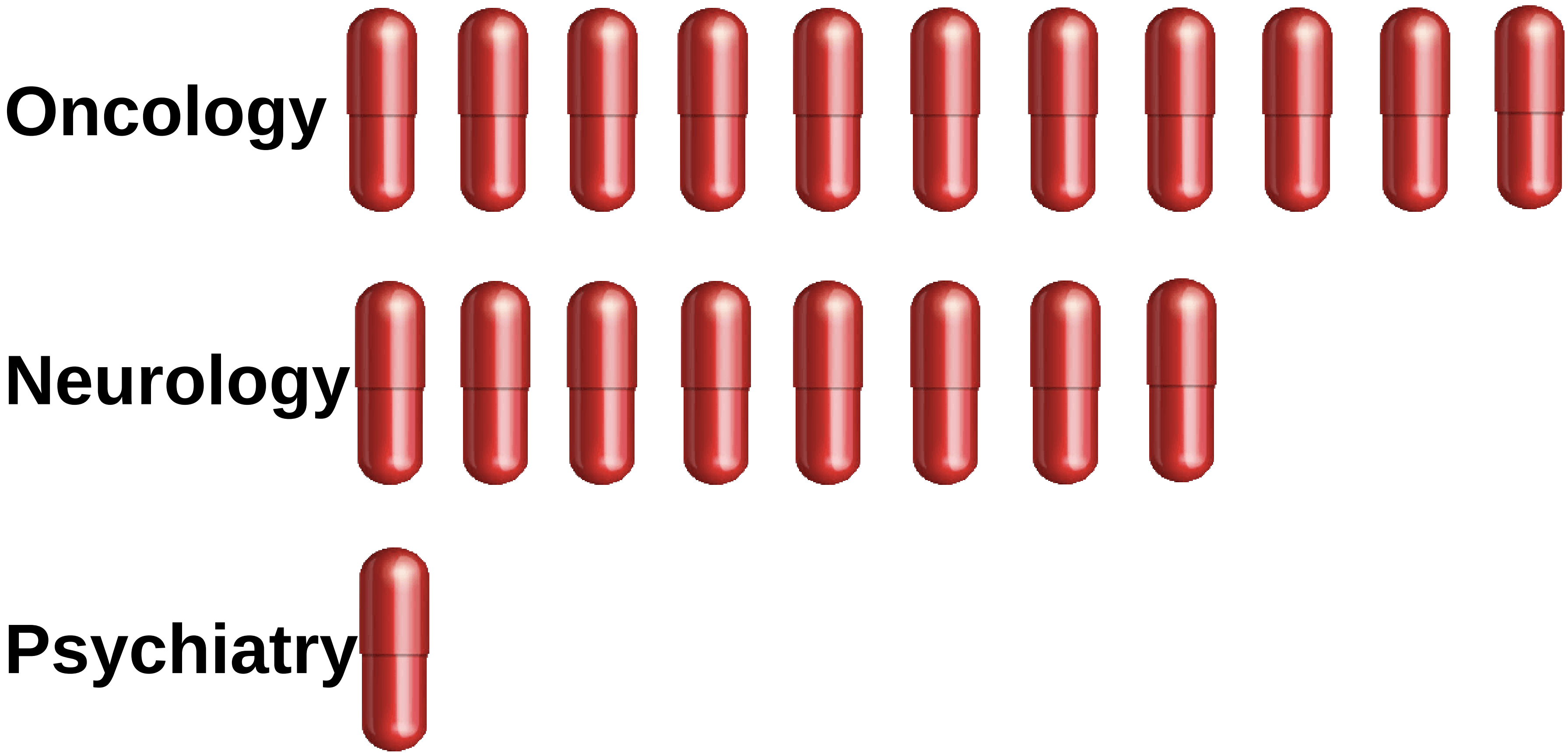
Stanford MEDICINE | Department of Psychiatry and Behavioral Sciences

Rodriguez | LAB
Translational Therapeutics

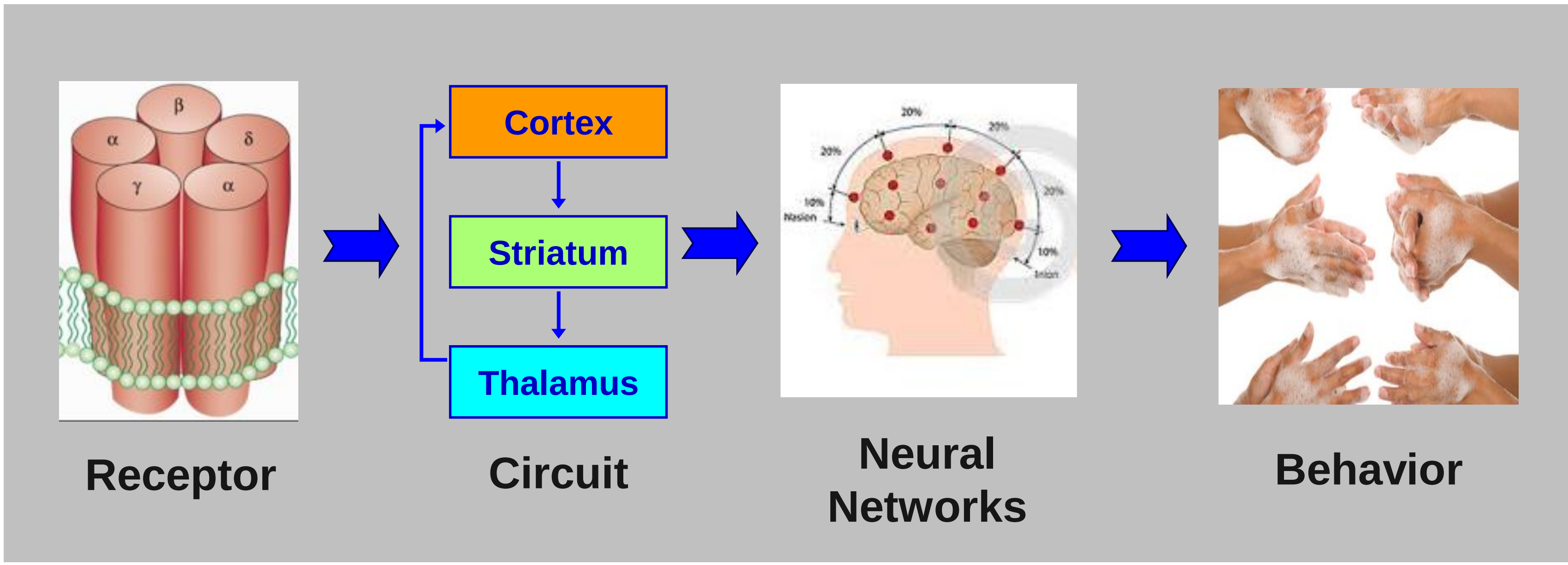
Building Precision into Translational Therapeutics:

MECHANISMS AND MODULATION OF COMPULSIVE BEHAVIORS

Carolyn Rodriguez, MD, PhD


Oncology
Neurology
Psychiatry

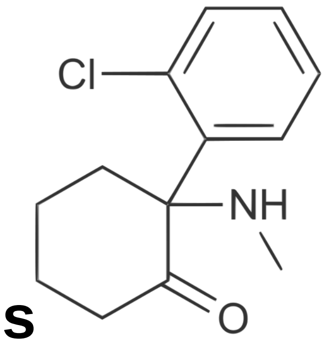
Multimodal/Multilevel Approach

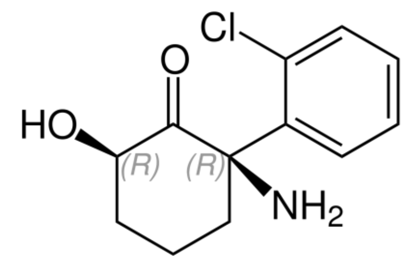


Molecular: Translational Therapeutics

Compulsive Behaviors

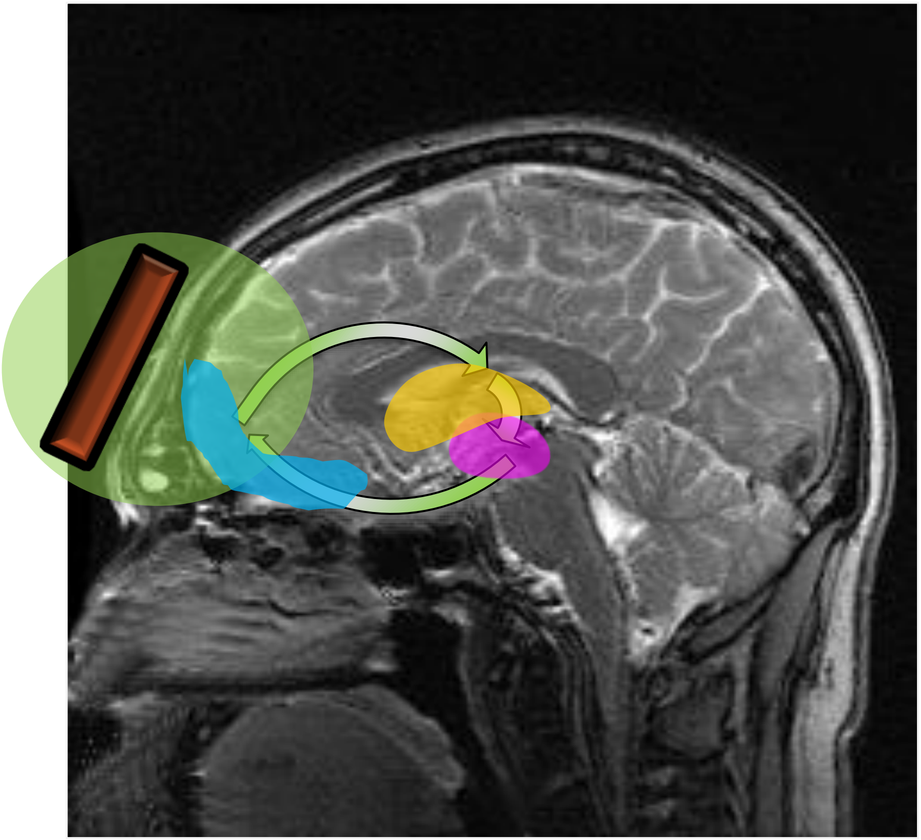
Novel Compounds



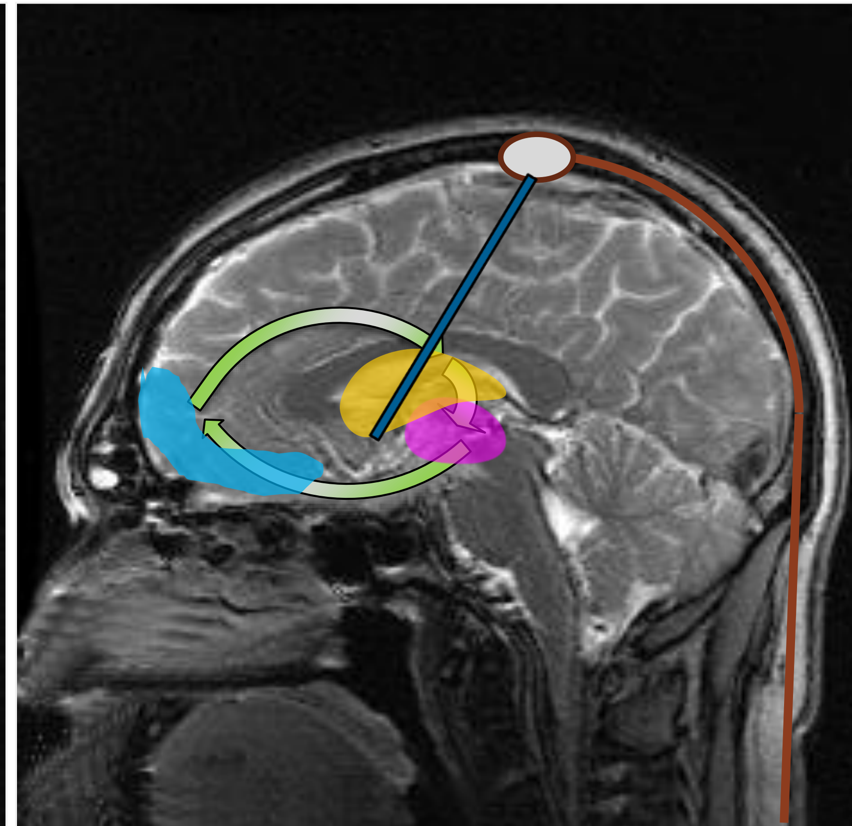


Compulsive Behaviors

Circuit: Neuromodulation

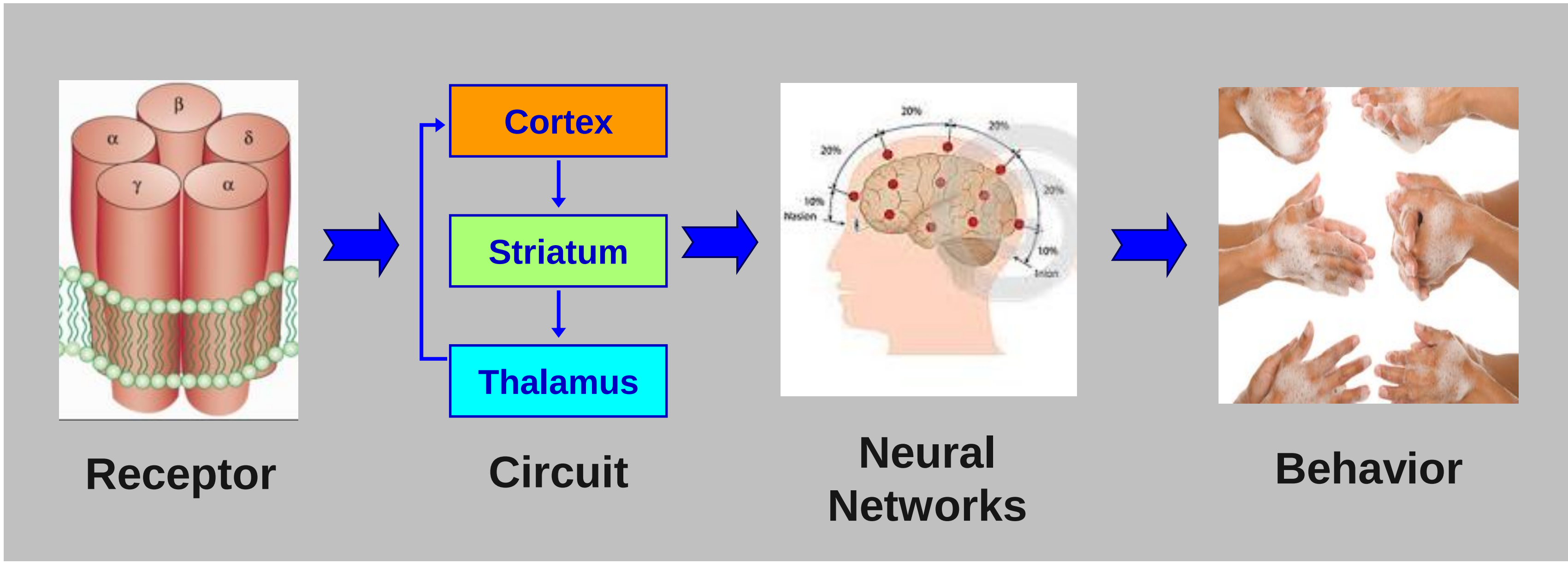


Cortical Stimulation

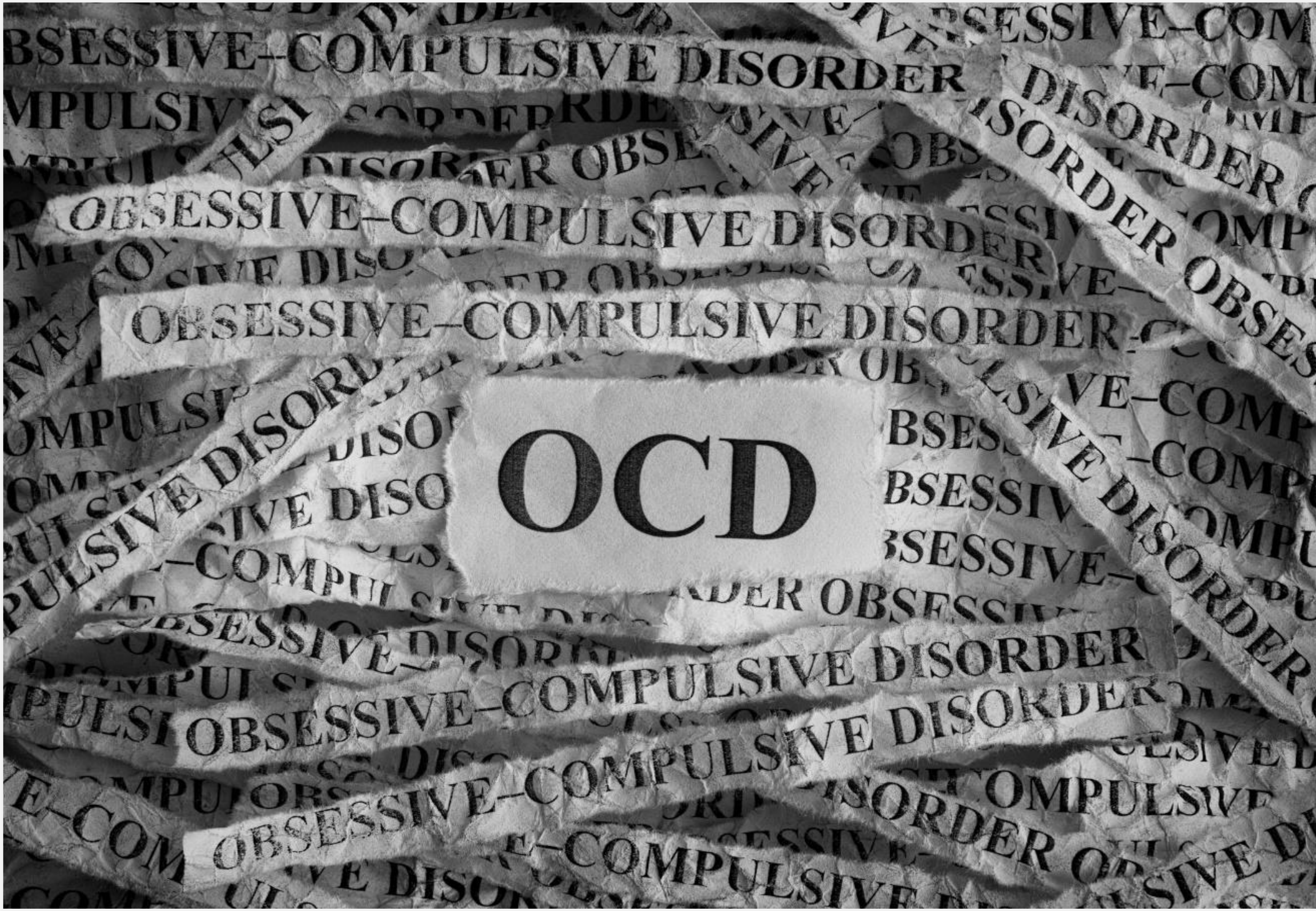


Deep Stimulation

Multimodal/Multilevel Approach



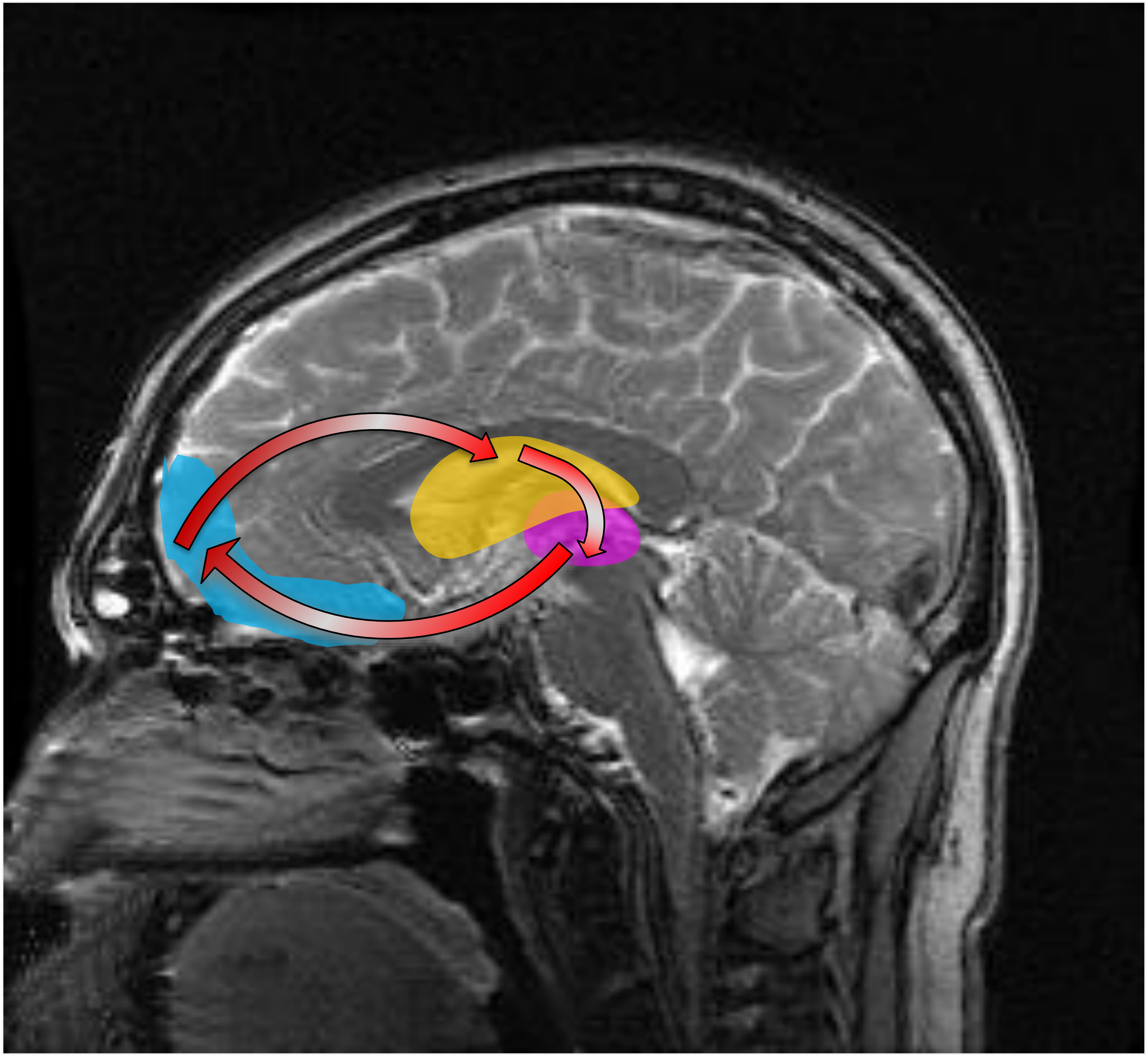
"John"

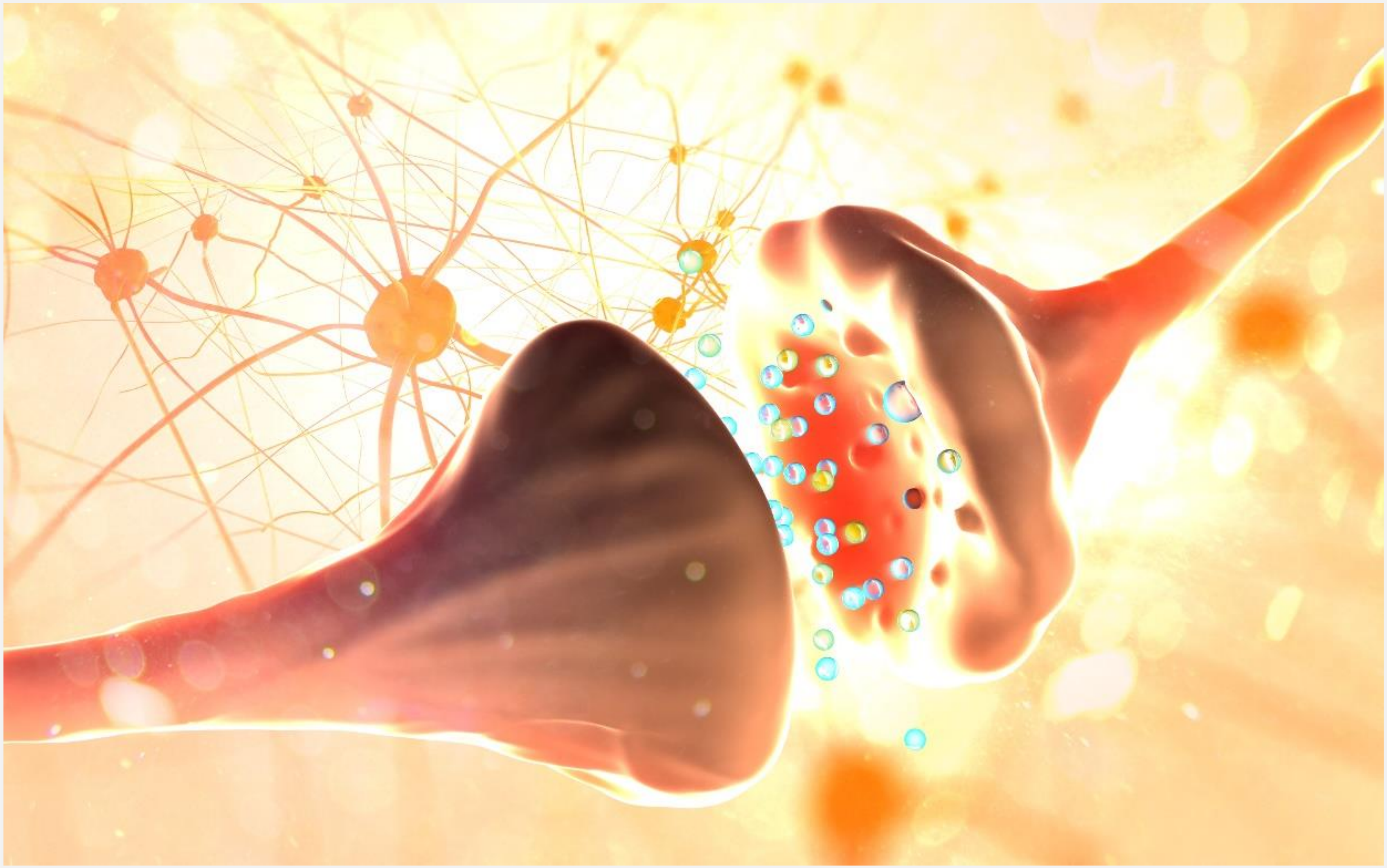

OCD
OBSESSIVE-COMPULSIVE DISORDER

Standard OCD Treatments

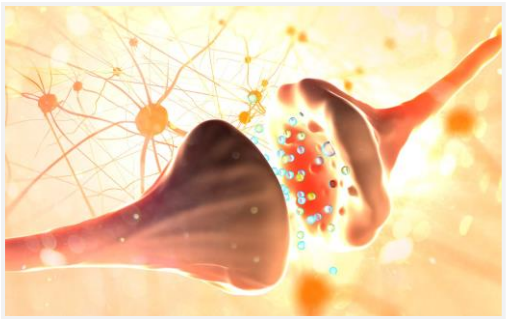
Medications

CBT





Model for Compulsive Behaviors



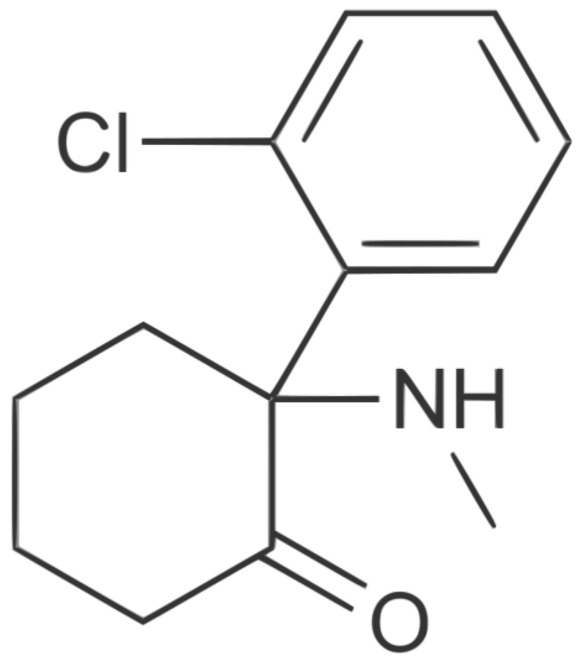
<u>SAPAP family proteins</u>
form a key scaffolding complex at excitatory (**glutamatergic**) synapses

<u>SAPAP3 -/-</u>
Excessive grooming
Anxiety-like behaviors
Cortico-striatal synaptic defects

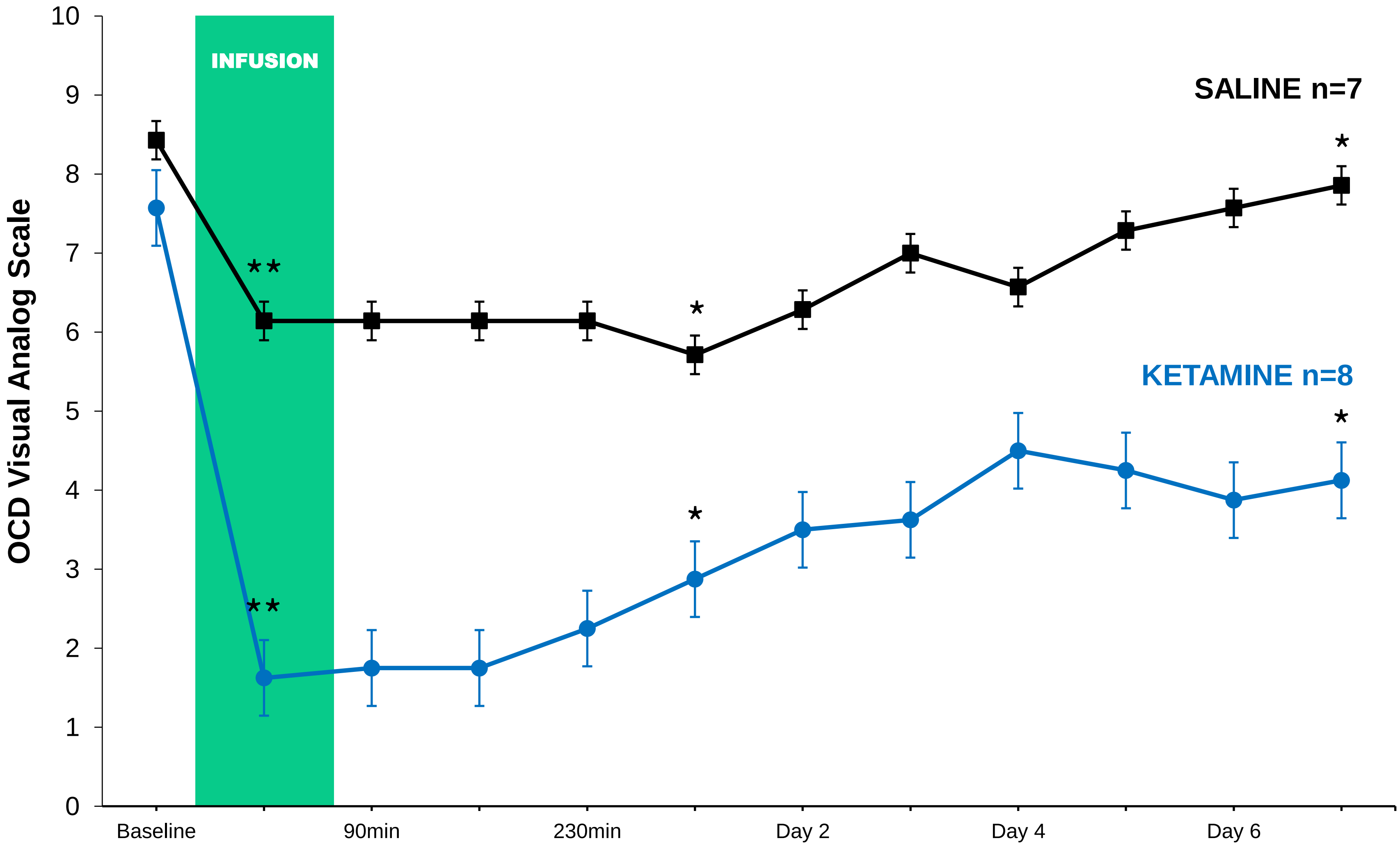
Rescued by **SAPAP3** expression in striatum

Welch et al., 2007

Ketamine



Ketamine Rapidly Reduces OCD



Rodriguez et al., *Neuropsychopharmacology*, 2013

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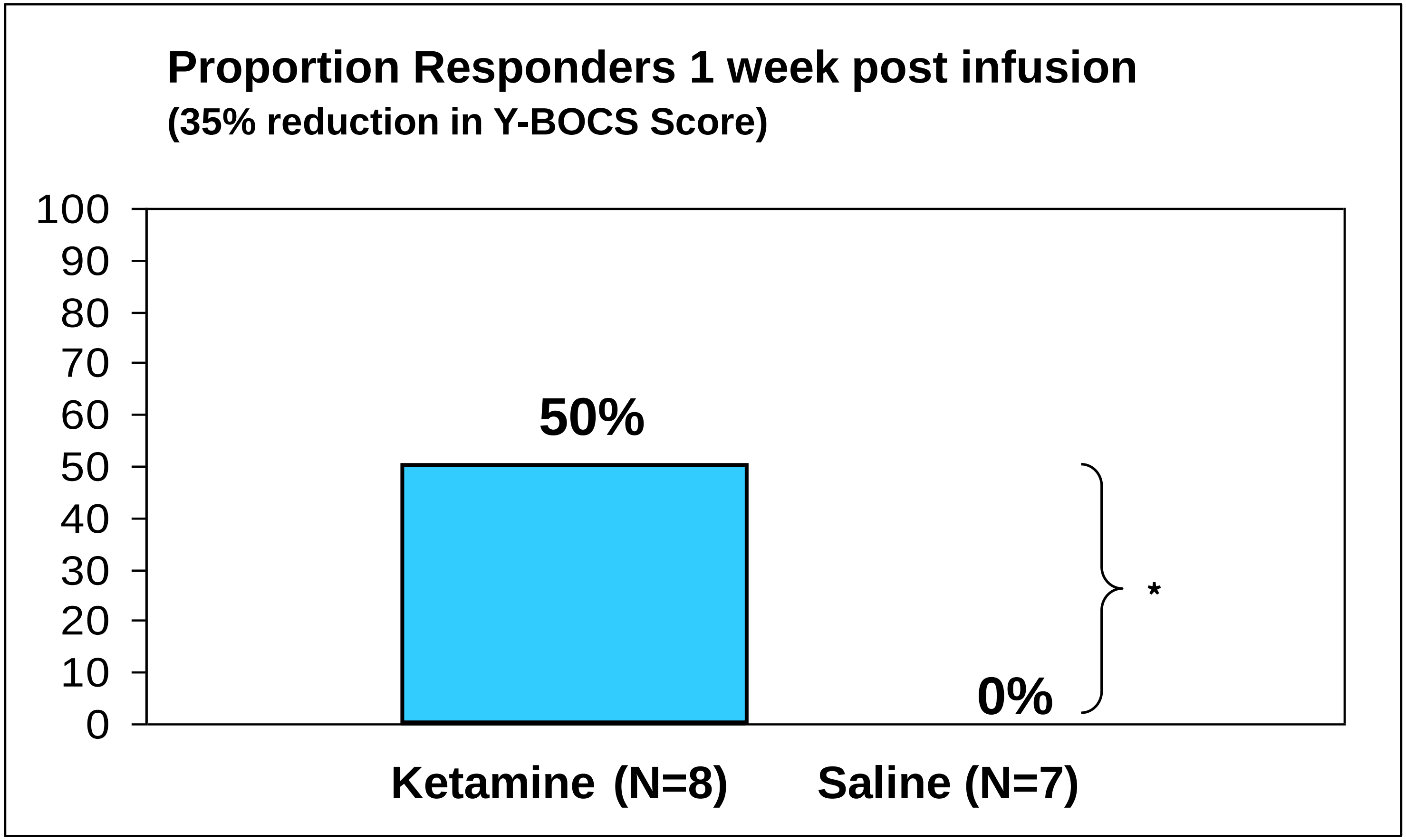
First Phase



* $p < 0.05$

Rodriguez et al., *Neuropsychopharmacology*, 2013

Quotes From Responders After Ketamine

Responders (4 out of 8):

1. "I feel as if the weight of OCD has been lifted…I want to feel this way forever."
2. "I feel like someone is giving me an explanation [for my OCD]."
3. "I don't have any intrusive thoughts. I was laughing when you couldn't find the key, which normally is a trigger for me. This is amazing; unbelievable. This is right out of a movie."
4. "I tried to have OCD thoughts, but I couldn't."

Rodriguez et al., *Neuropsychopharmacology*, 2013

Side Effects

Side effects in order of frequency	TOTAL N=15 (8 Ketamine, 7 Saline) n Ketamine	n Saline	% Ketamine	% Saline
Feelings of Unreality/ Dissociation	8	1	100%	12.5%
Dizziness	2	0	25%	0%
Nausea	1	0	12.5%	0%
Vomiting	1	0	12.5%	0%
Headache	1	0	12.5%	0%

Mild transient changes in blood pressure and heart rate observed on infusion day consistent with MDD studies that show mean change pre/post IV ketamine of less than 20 mm Hg systolic and 10 mm Hg diastolic.

Rodriguez et al., *Neuropsychopharmacology*, 2013
Murrough, et al., 2013

Summary #1

First study showing ketamine can decrease intrusive thoughts in the absence of SRIs

Glutamate modulation may be a rapid-acting therapeutic target for OCD

Rodriguez et al., *Neuropsychopharmacology*, 2013

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Reason for Caution

Effects are transient (costly)

Side effects

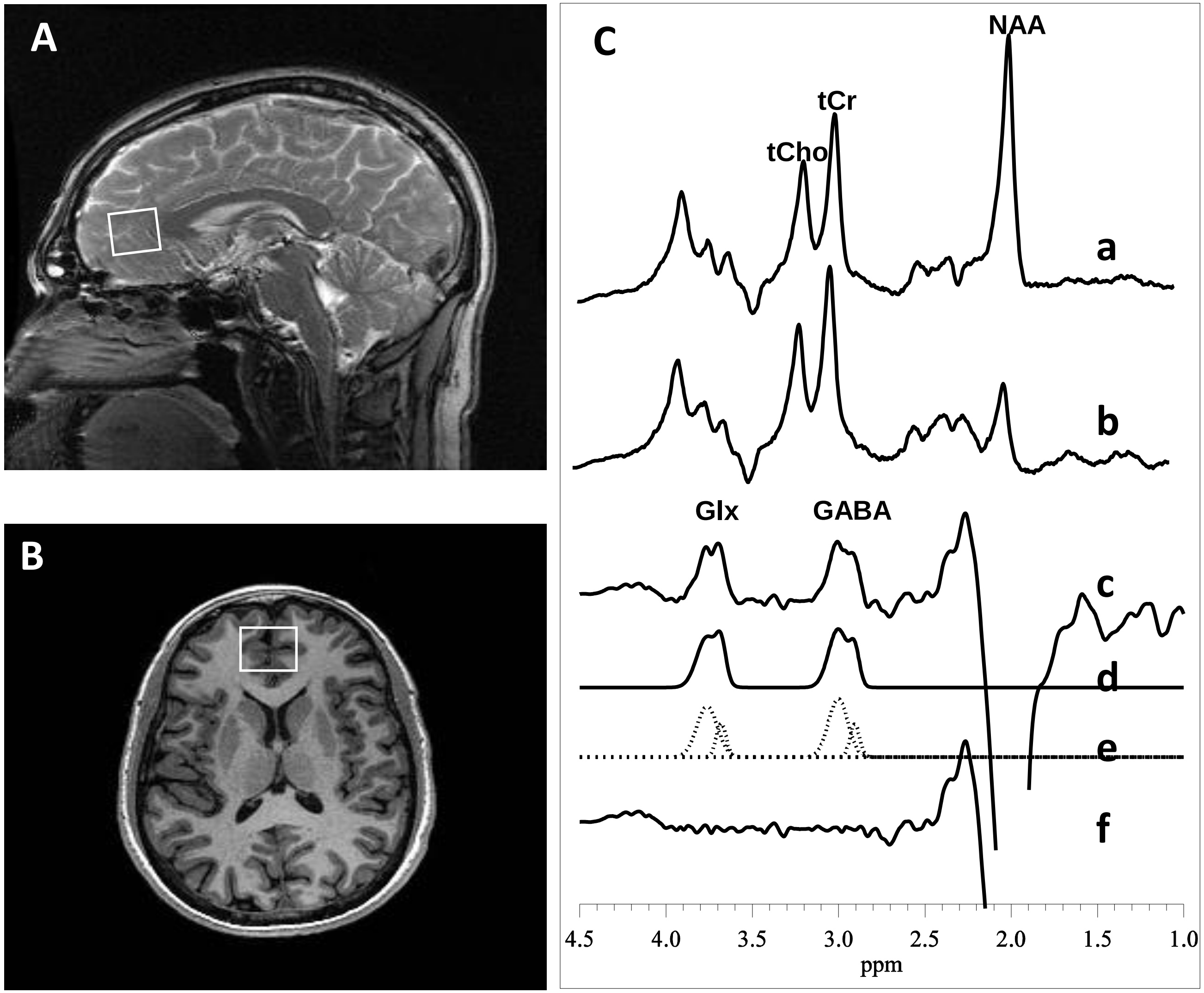
Drug of abuse

Newport et al.,, 2015
Sanacora, et al., 2017

Mechanisms

Does ketamine change levels of glutamate?

Ketamine Increases GABA in Prefrontal Cortex



Rodriguez et al., *Psychiatry Neuroimaging,* 2015

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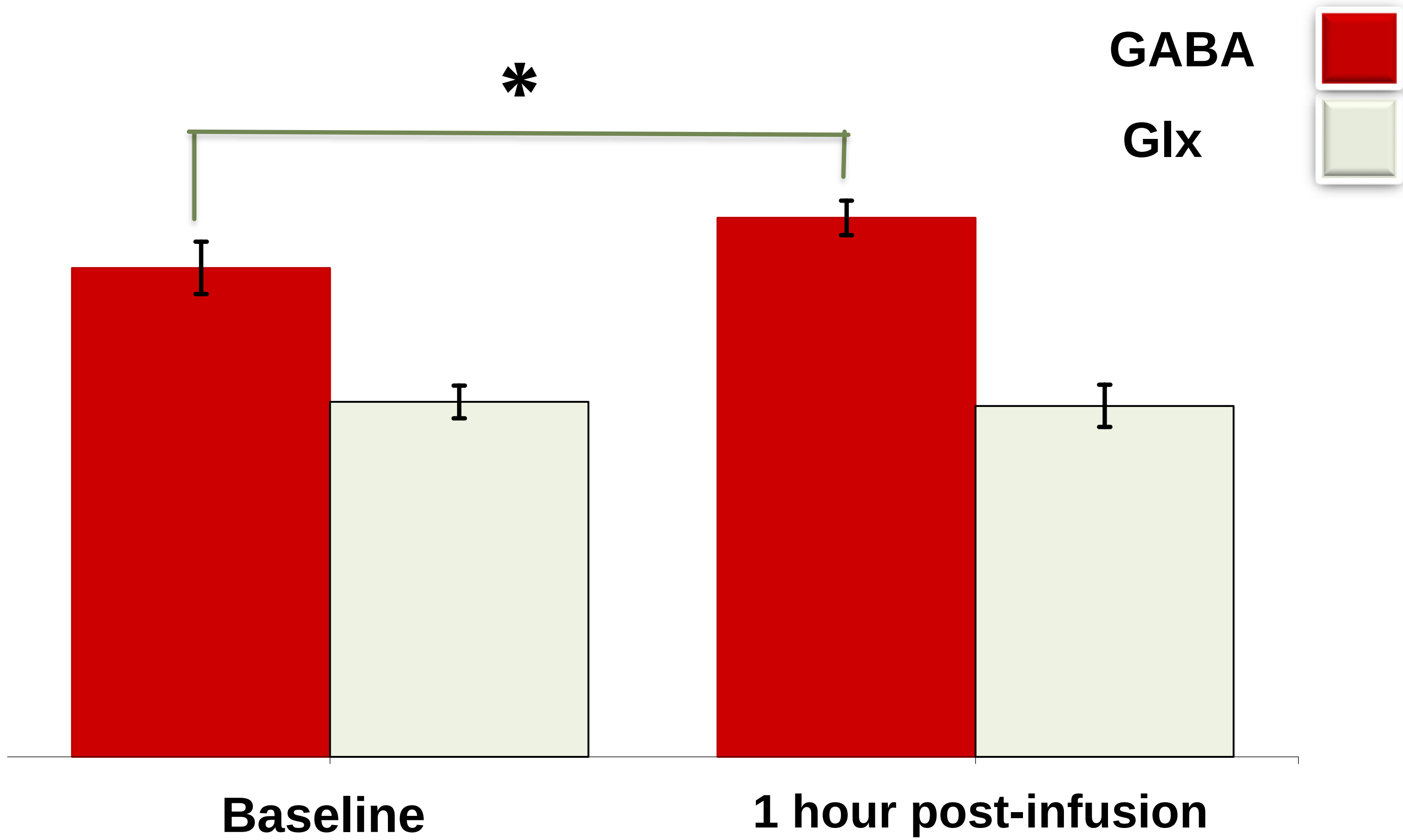
Ketamine Increases GABA 1 Hour Post-Infusion



Rodriguez et al., *Psychiatry Research: Neuroimaging,* 2015
Milak et al., *Molecular Psychiatry*, 2016

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Summary #2

First study of effects of ketamine on glutamate, glutamine, GABA in OCD in prefrontal cortex

Ketamine may have a unique neurochemical signature in OCD relative to depression

Needs replication in larger sample

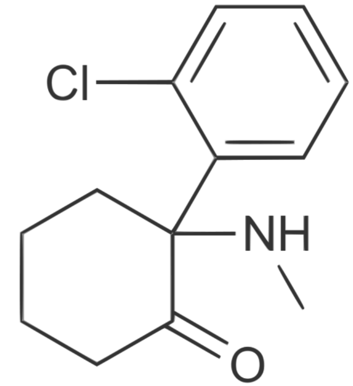
Rodriguez et al., *Psychiatry Research: Neuroimaging*, 2015
Milak et al., *Molecular Psychiatry*, 2016

Translational Therapeutics

Compulsive Behavior

SAPAP3

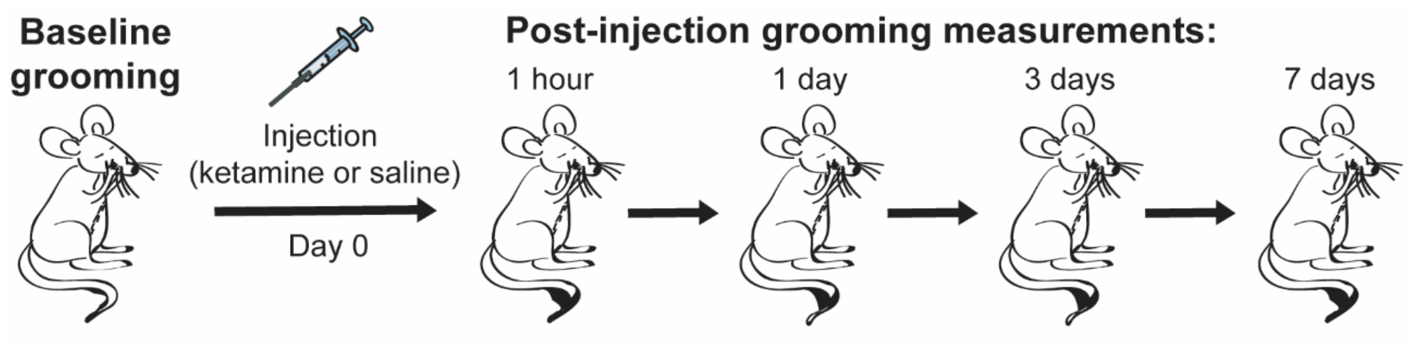
Ketamine



OCD

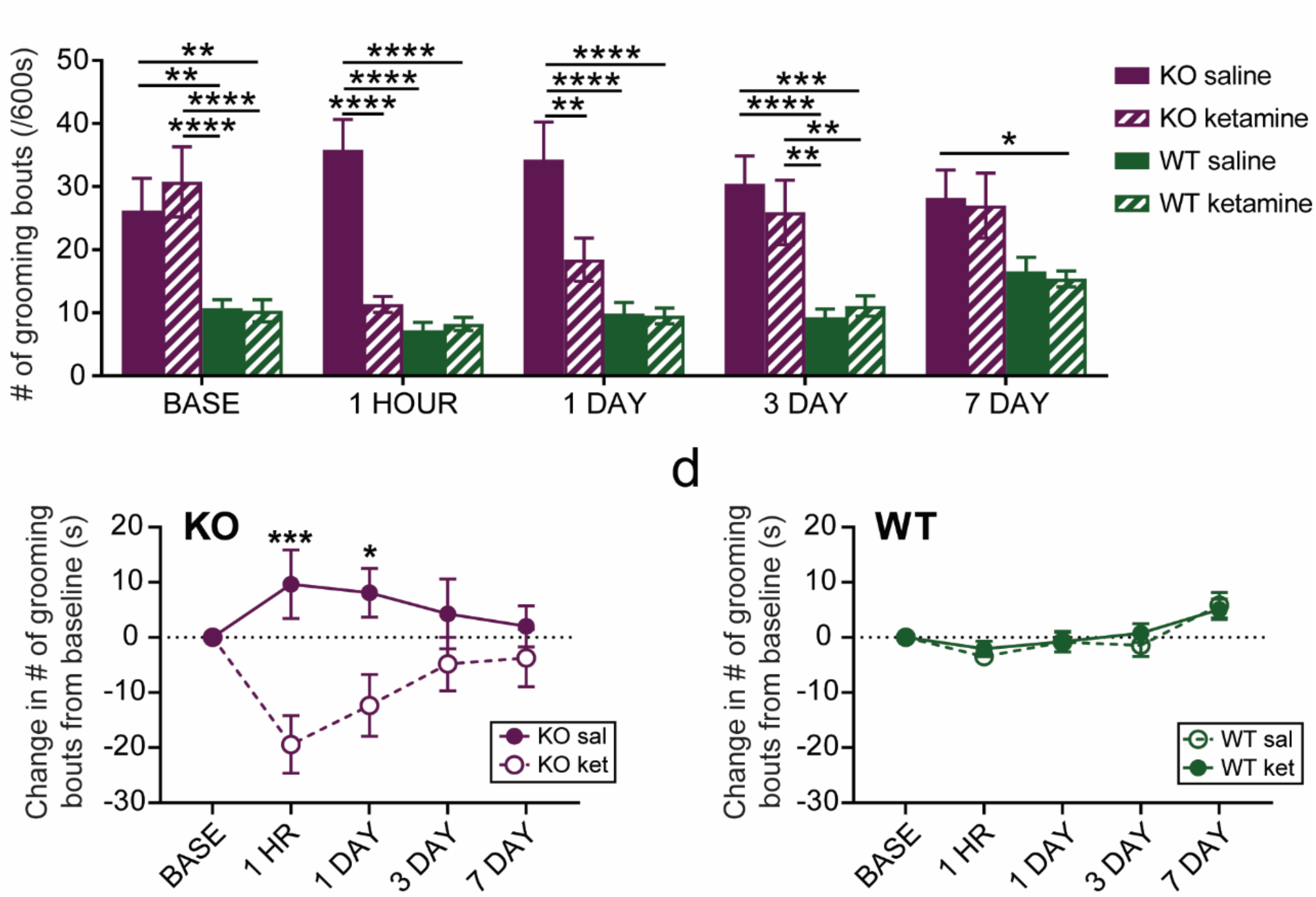
Ketamine increases activity of a fronto-striatal projection that regulates compulsive behavior in SAPAP3-knockout mice

Lisa Gunaydin, PhD **Gwynne Davis, PhD**



Davis et al., *Nature Communications*, in press

Ketamine reduces compulsive grooming SAPAP3-knockout mice



Davis et al., *Nature Communications*, in press

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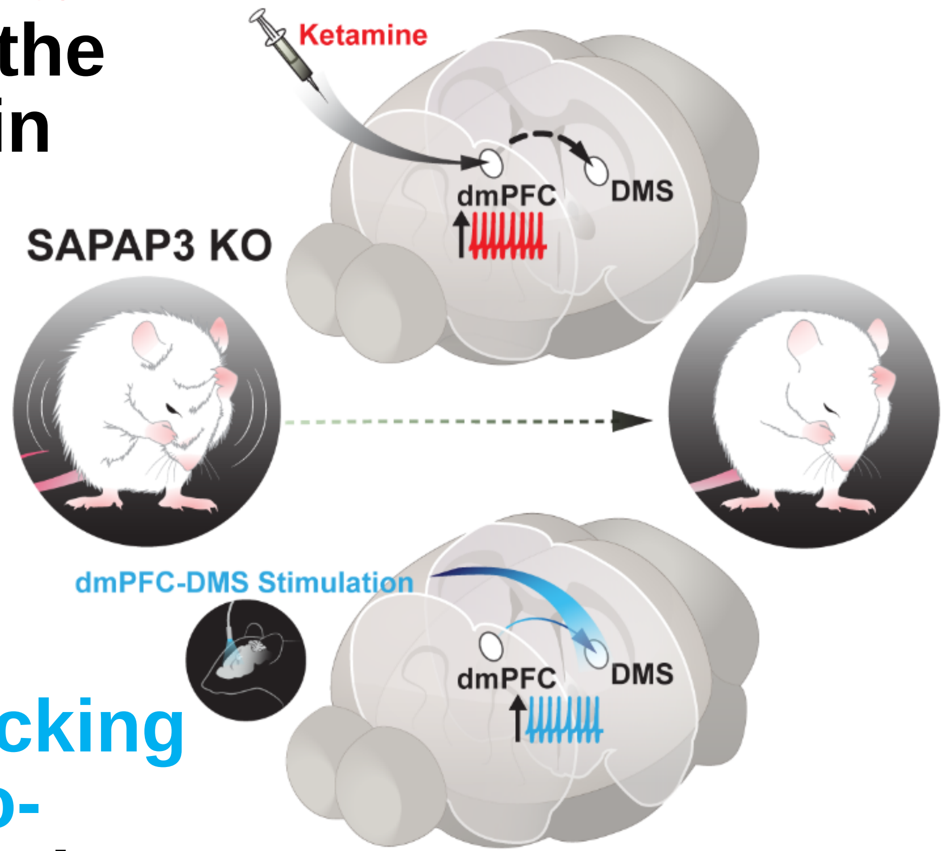
Ketamine increases activity of dorsomedial prefrontal neurons projecting to the dorsomedial striatum in knockout mice.



Optogenetically mimicking this increase in fronto-striatal activity reduced compulsive grooming behavior in knockout mice.

Davis et al., *Nature Communications*, in press

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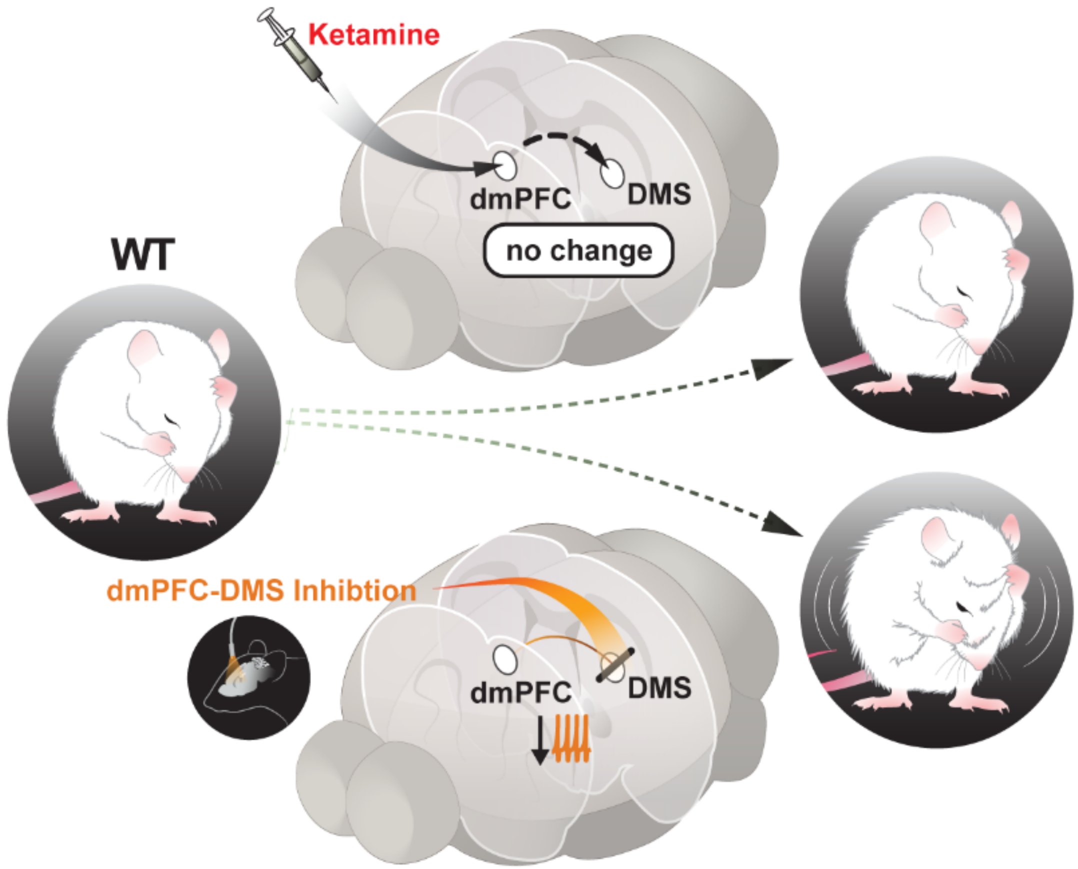
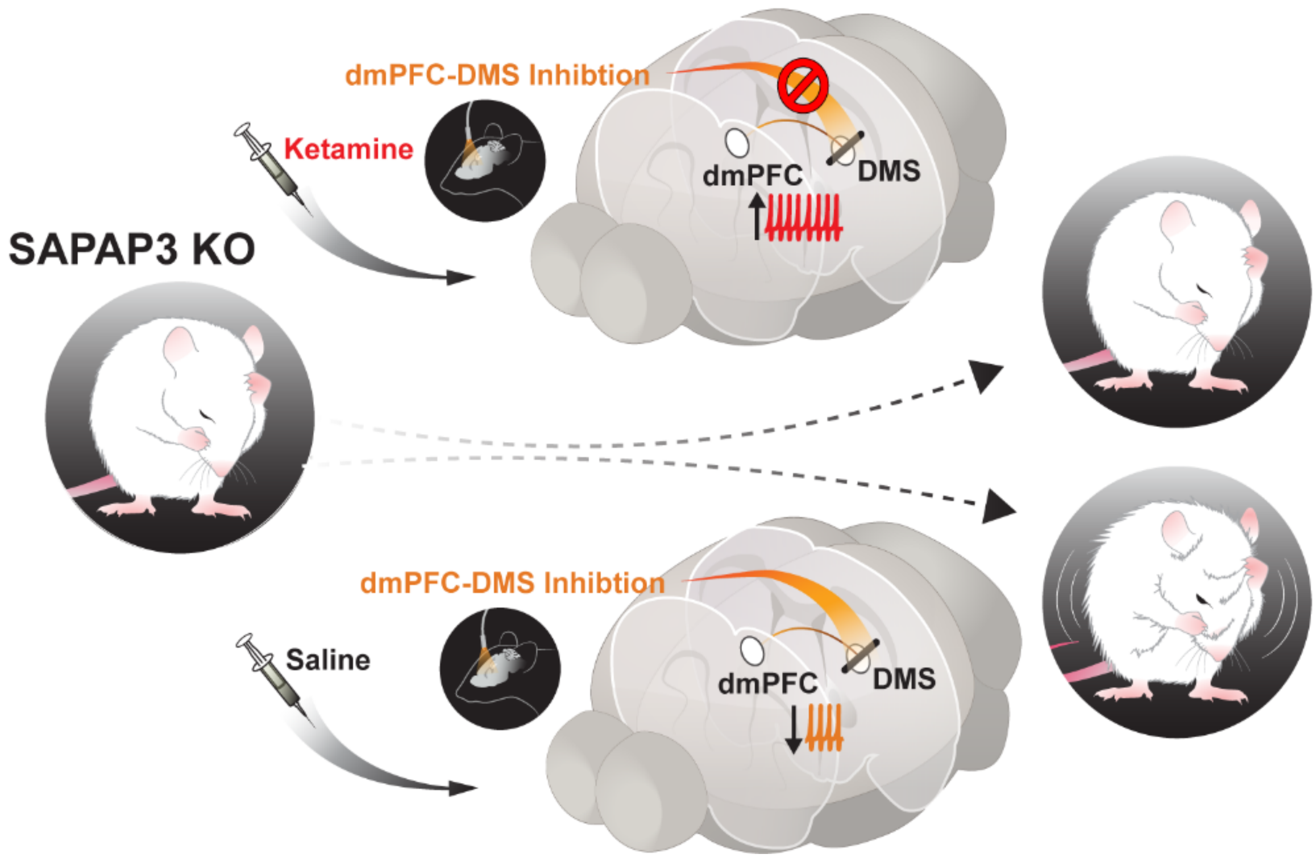
Conversely, inhibiting this circuit in wild-type mice increased grooming.



Davis et al., *Nature Communications*, in press

Ketamine blocks the exacerbation of grooming in KO mice caused by optogenetically inhibiting fronto-striatal activity.



Davis et al., *Nature Communications*, in press

Summary #3

Experiments demonstrate that ketamine increases activity in a fronto-striatal circuit that causally controls compulsive grooming behavior, suggesting this circuit may be important for ketamine's therapeutic effects in OCD

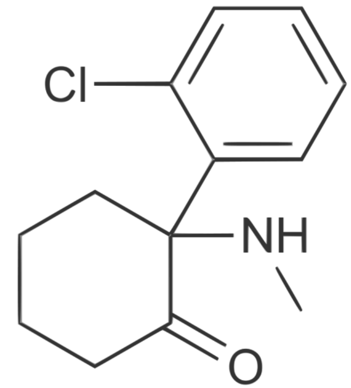
Davis et al., *Nature Communications*, in press

Future Directions: Therapeutics

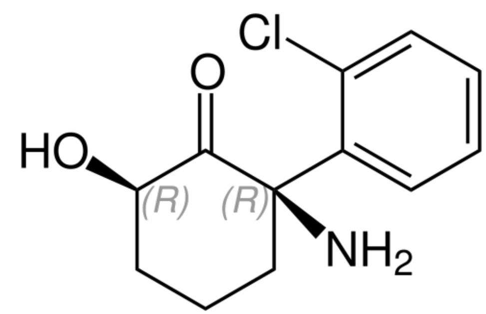
Compulsive Behavior

SAPAP3

Ketamine



RR-HNK



OCD

Biomarkers of Response

MRS/fMRI/EEG

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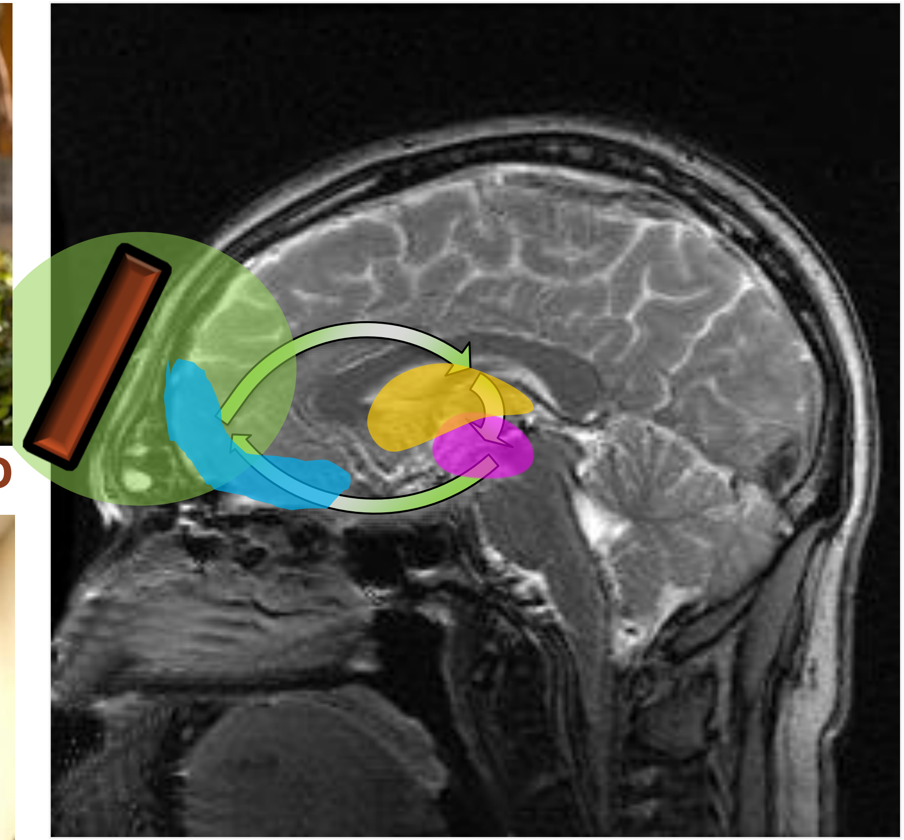
Circuit: Neuromodulation

Nolan Williams, MD

Keith Sudheimer, PhD



Cortical Stimulation

Leanne Williams, PhD

Lorrin Koran, MD

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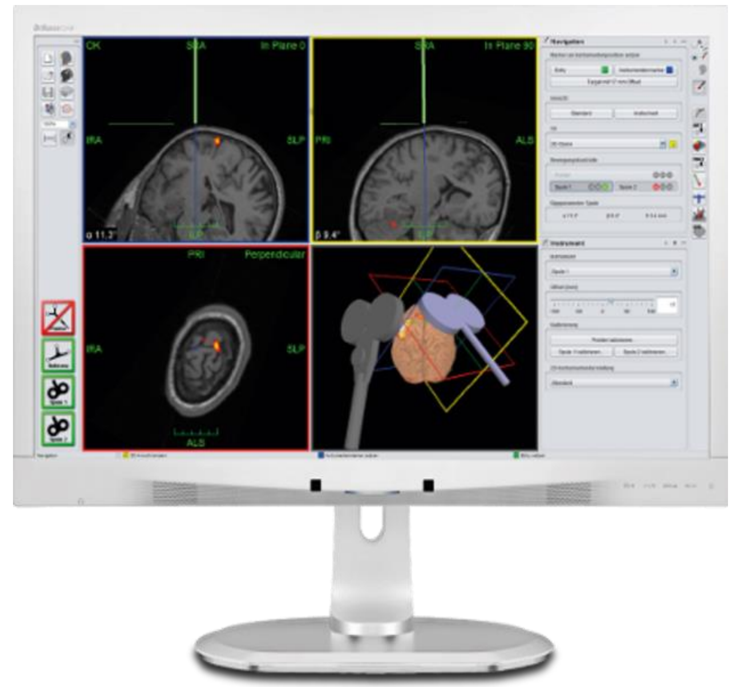
Personalized Target

Hierarchical clustering algorithm can be applied to each participant's resting state scan to identify personalized functional subregions.



Williams et al., 2018; Cole et al., 2020

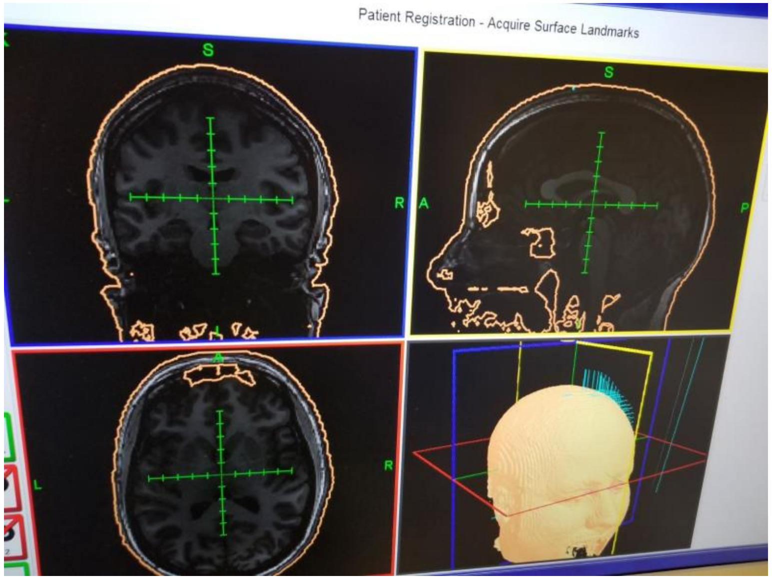
Phase 1: Mapping Resting-State Connectivity

8min resting-state sequence

The right frontal pole subunit showing greatest connectivity across all the ventral striatum subunits was selected as the stimulation target.

Williams, Sudheimer, Cole et al., 2021

Phase 2: Registration and Stimulation



The Localite Neuronavigation System was used to position the TMS coil over this individualized right frontal pole functional target for each participant.

Williams, Sudheimer, Cole et al., 2021

Method

Open-label OCD (n=7)

5 consecutive days of accelerated course of modified continuous theta-bust stimulation (cTBSmod) to right frontal pole

Ten sessions per day (18,000 pulses/day, hourly)

90,000 total pulses

Using single pulse TMS Magventure Magpro X100

OCD Symptom Severity Change Over Time

Age/ Sex	YBOCS Day 0	YBOCS Day 7	% Change from Day 0	YBOCS Day 14	% Change from Day 0	YBOCS Day 21	% Change from Day 0	YBOCS Day 28	% Change from Day 0
28/F	28	7	-75%	6	-79%	6	-79%	5	-82%
39/M	30	27	-10%	15	-50%	22	-27%	26	-13%
70/M	26	27	4%	23	-12%	31	19%	26	0%
48/M	19	7	-63%	6	-68%	6	-68%	8	-58%
31/M	26	12	-54%	21	-19%	22	-15%	21	-19%
31/F	36	30	-17%	33	-8%	35	-3%	33	-8%
31/M	24	12	-50%	6	-75%	3	-88%	3	-88%

Williams, Sudheimer, Cole et al., 2021

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Side Effects

Headache: **resolved 1-3 days post stimulation start (n=4)**

Fatigue: **resolved 1-3 days post stimulation end (n=3)**

Serious Adverse Events: **None reported**

Williams, Sudheimer, Cole et al., 2021

Summary #4:

Robust and rapid in 5 of 7 (71%)
- at least 50% reduction within 7-14 days

Sustained in a subset
- 3 of 5 sustained effects up to 4 weeks

Non-invasive

Minimal, transient side effects

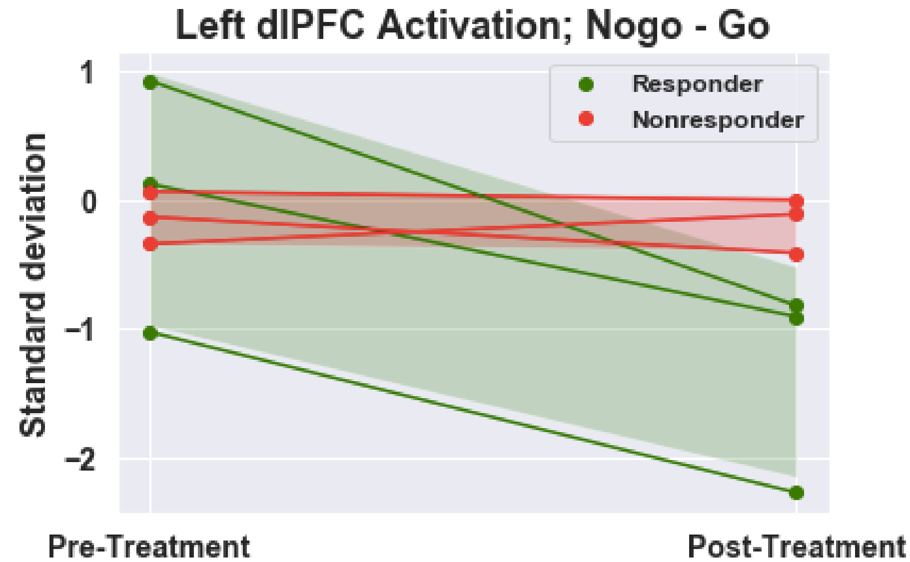
Questions to Explore:

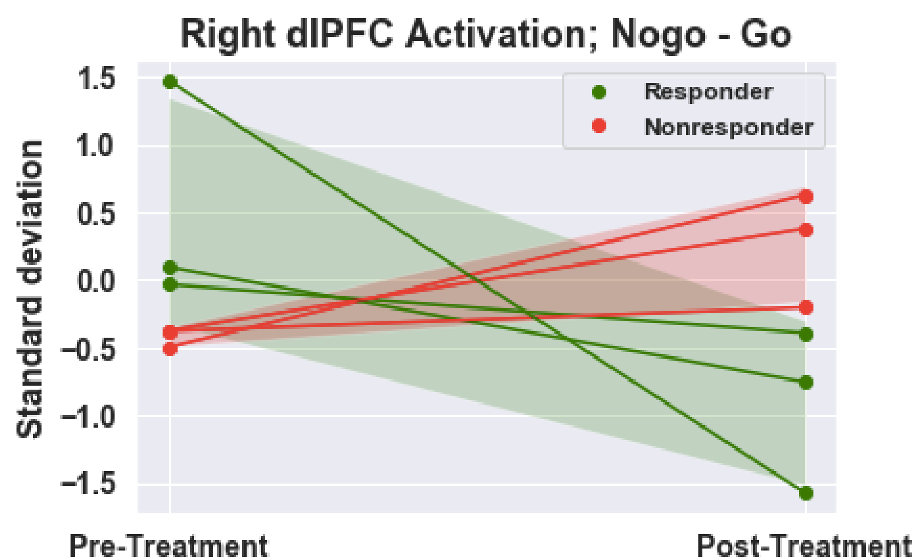
Why do most, but not all patients respond?

Why do some have peak response at different times and other have more durable response?

Exploring Biomarkers of Cognitive Control

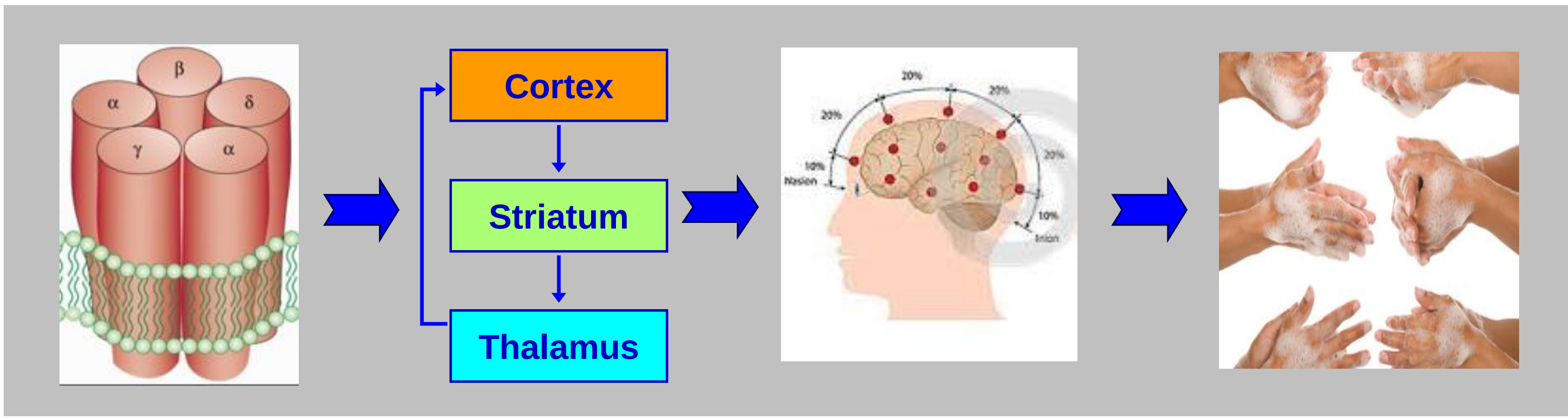
Responders showed greater decrease in dorsolateral prefrontal cortex activation during the cognitive control task following cTBSmod





Future Directions

Ketamine's Mechanism of Action (NIMH R01)



Phase II: RR-HNK (IOCDF Breakthrough Award)

Neural Dynamics of Drug Action (NIDA P50 Center)

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Contact us about:

Research Studies (Study Participants)
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Research Collaborations
Translate discoveries into treatments

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Funding and Disclosures (past 3 years)

Funding

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- Veterans Affairs

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- Biohaven Pharmaceuticals (Research Grant)

Deputy Editor

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