

Hydrogen Peroxide, Dopamine, and Serotonin: Overlapping Chemical Systems Contribute to the Control of Dyskinetic Movements in the Rat During Chronic L-DOPA Treatment for Parkinson's Disease

Sambit Panda

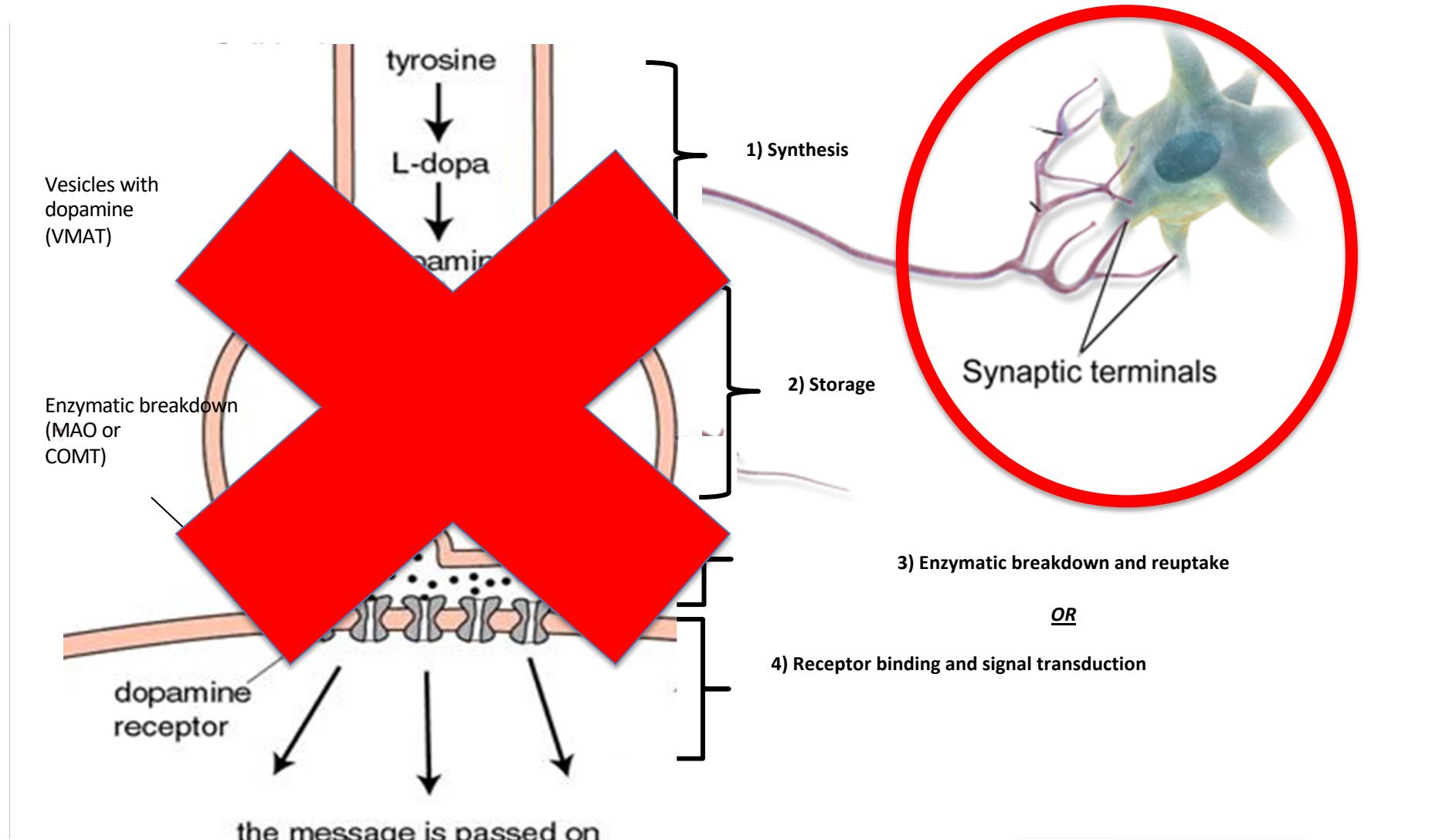
Leslie R. Wilson, Catherine F. Mason, Karen E. Butler, Christie A. Lee, Leslie A. Sombers

North Carolina State University
Department of Chemistry

SOMBERS LAB

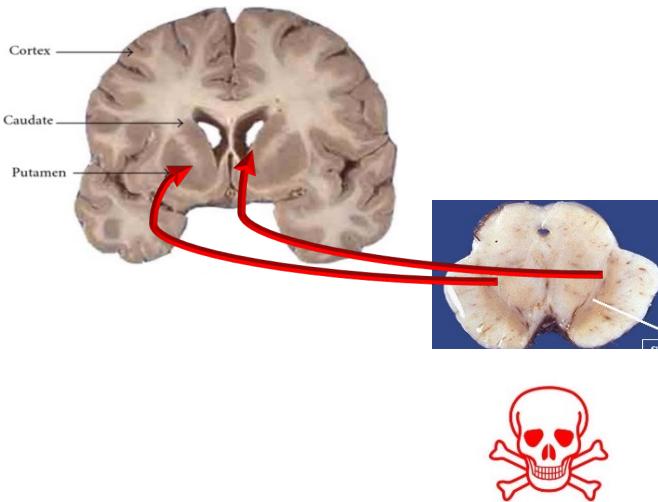


The Complex Environment of the Brain



Parkinson's Disease: A Neurodegenerative Disorder

- Estimated 10 million people worldwide suffer from PD.
- Results in the loss of dopaminergic neurons.
- Dopaminergic replacement therapy with L-DOPA is the standard treatment



- Slowness to initiative movement
- Rigidity
- Resting tremor

Negative Side Effects with Prolonged L-DOPA Treatment



After five years of
levodopa treatment,
about 50% of PD



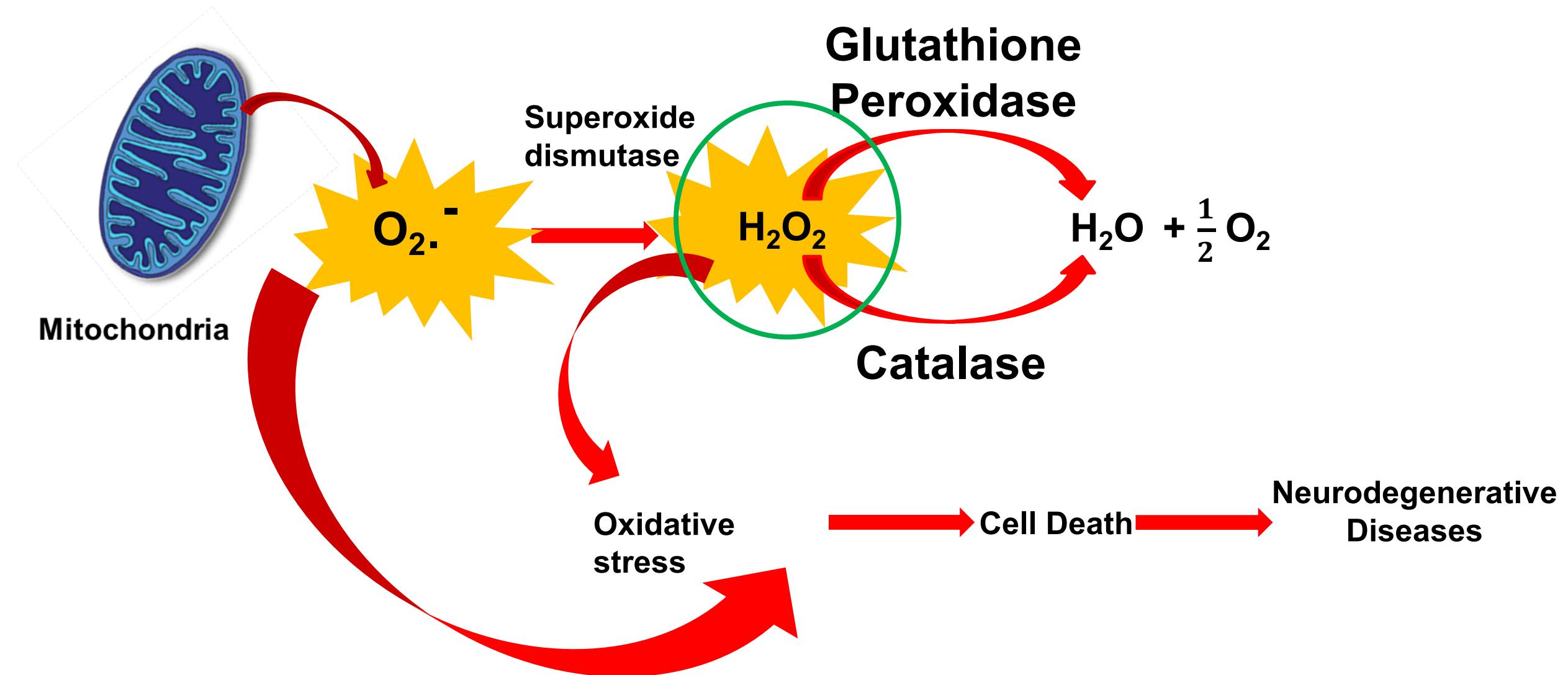
What are the underlying causes of
these abnormal involuntary
movements?

“FOR PATIENTS, PARKINSON'S DISEASE
IS NOT A TIME-NEUTRAL SITUATION.
IT'S A TICKING CLOCK.”

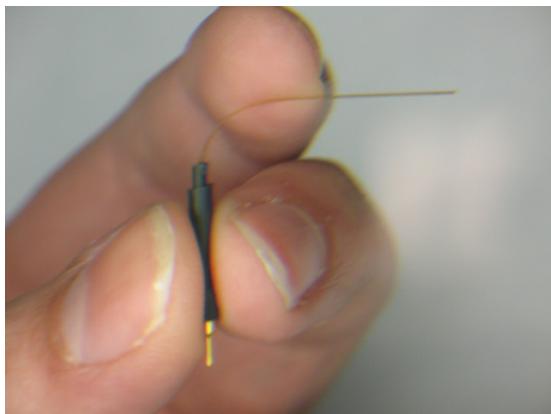
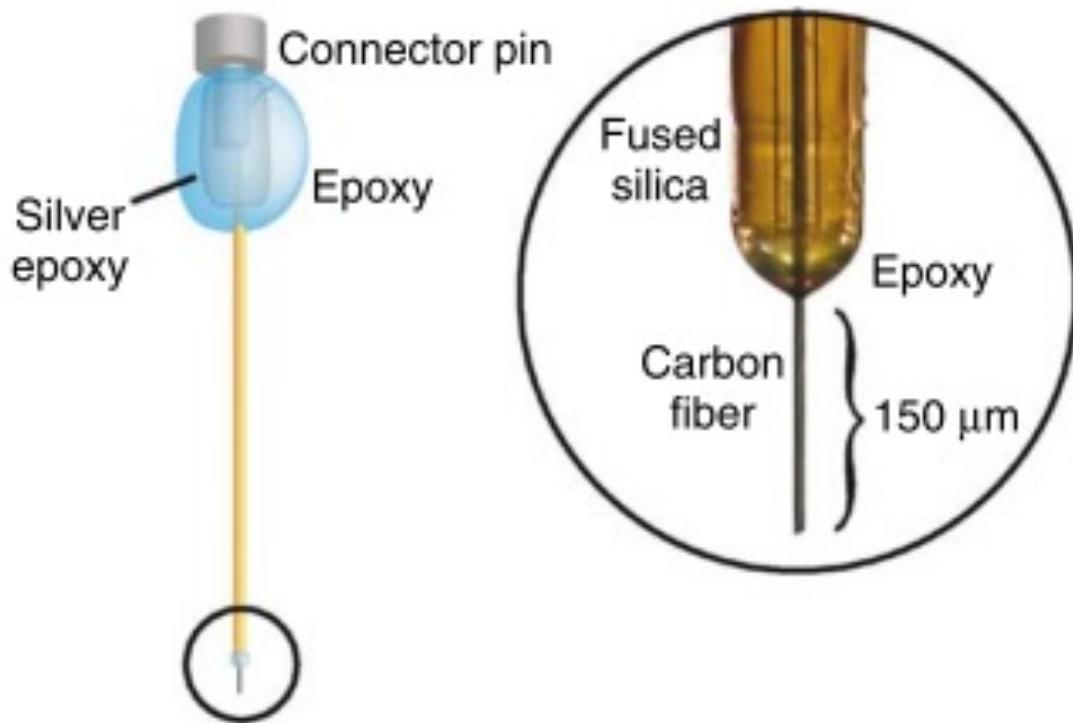
— MICHAEL J. FOX



Oxidative Stress and Neurodegenerative Diseases

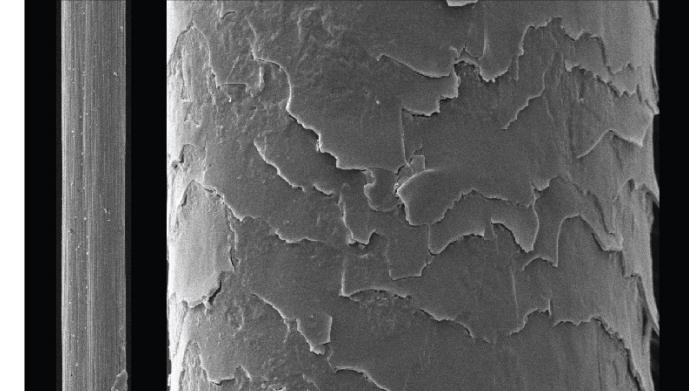


Microelectrodes for *In-Vivo* Neurochemical Monitoring

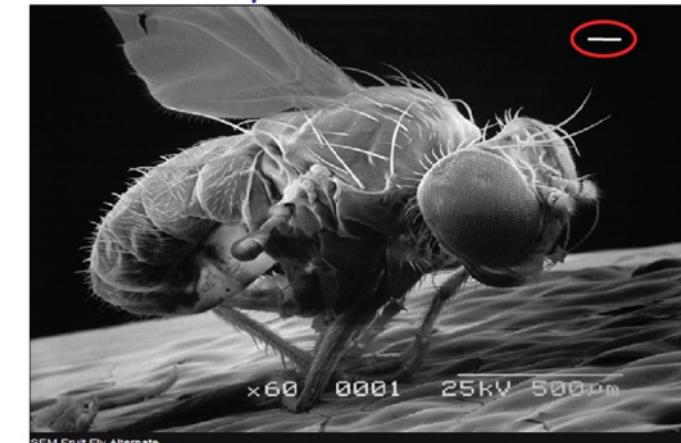


**Great stability
Great biocompatibility**

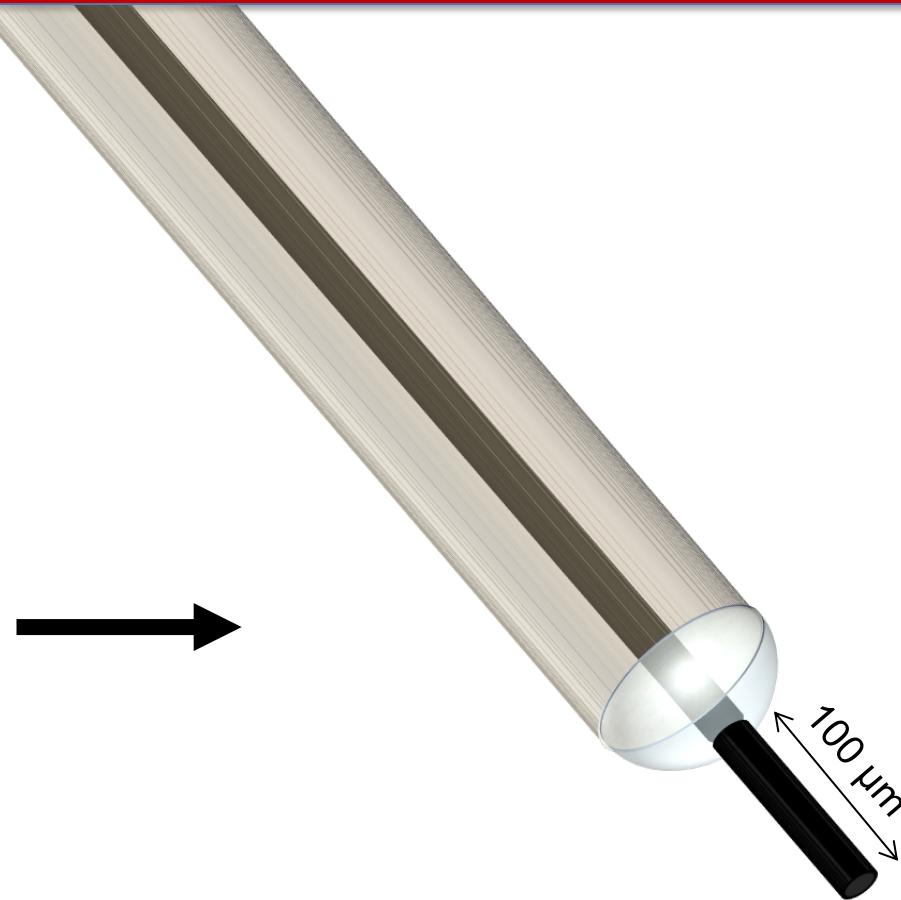
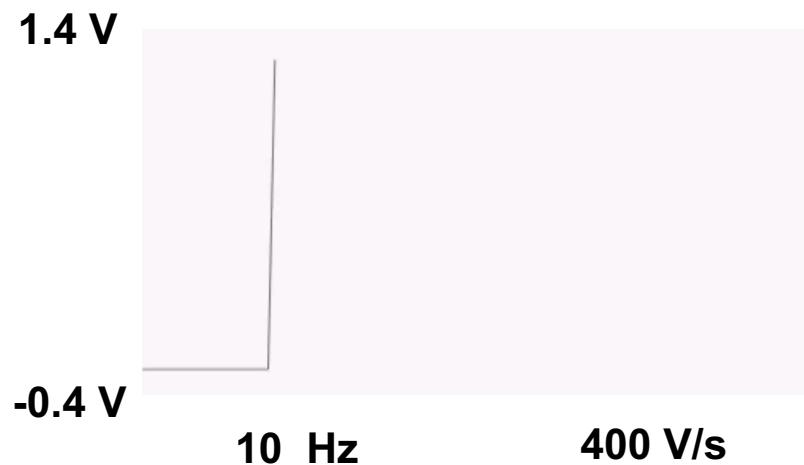
Carbon Fiber vs. Hair



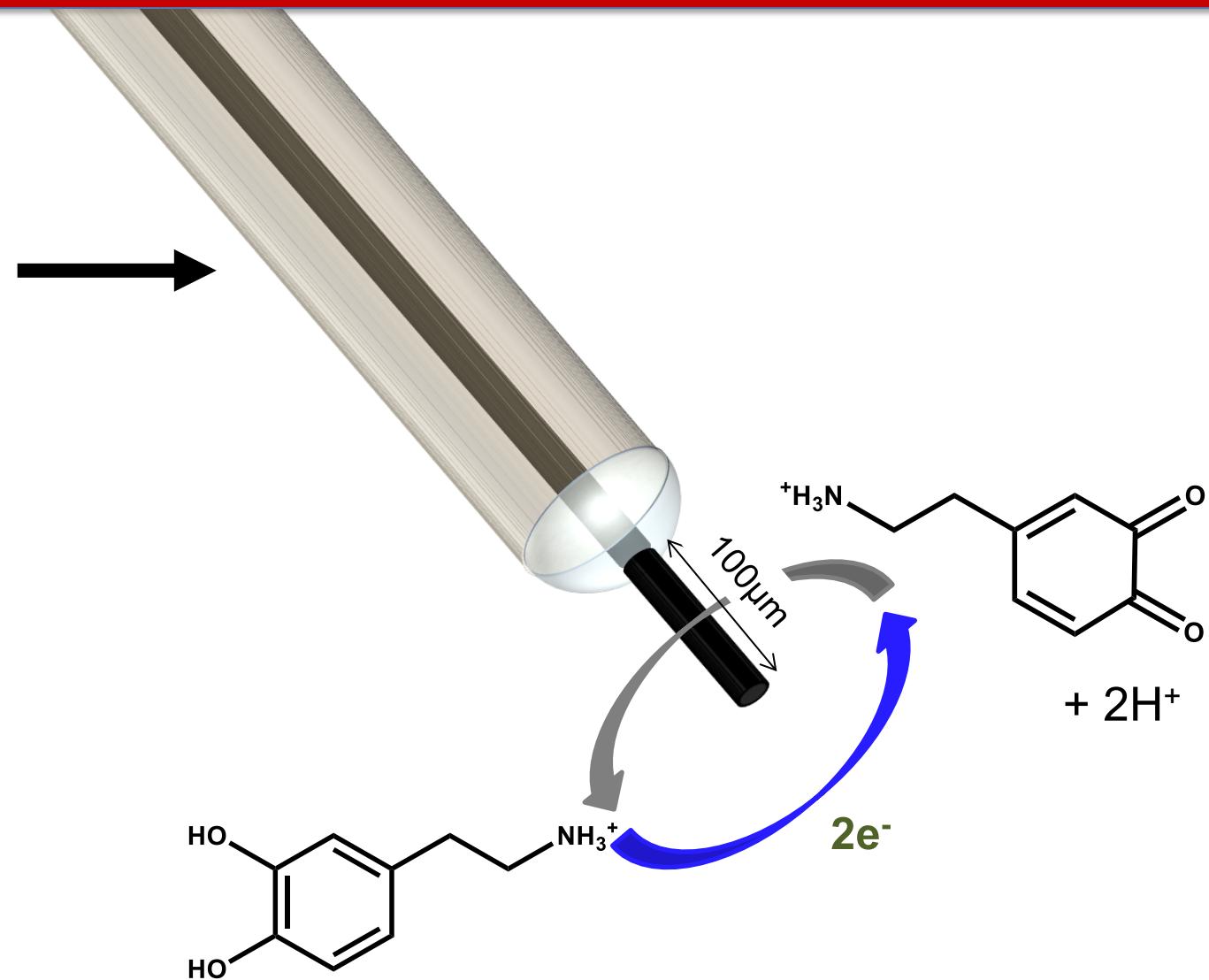
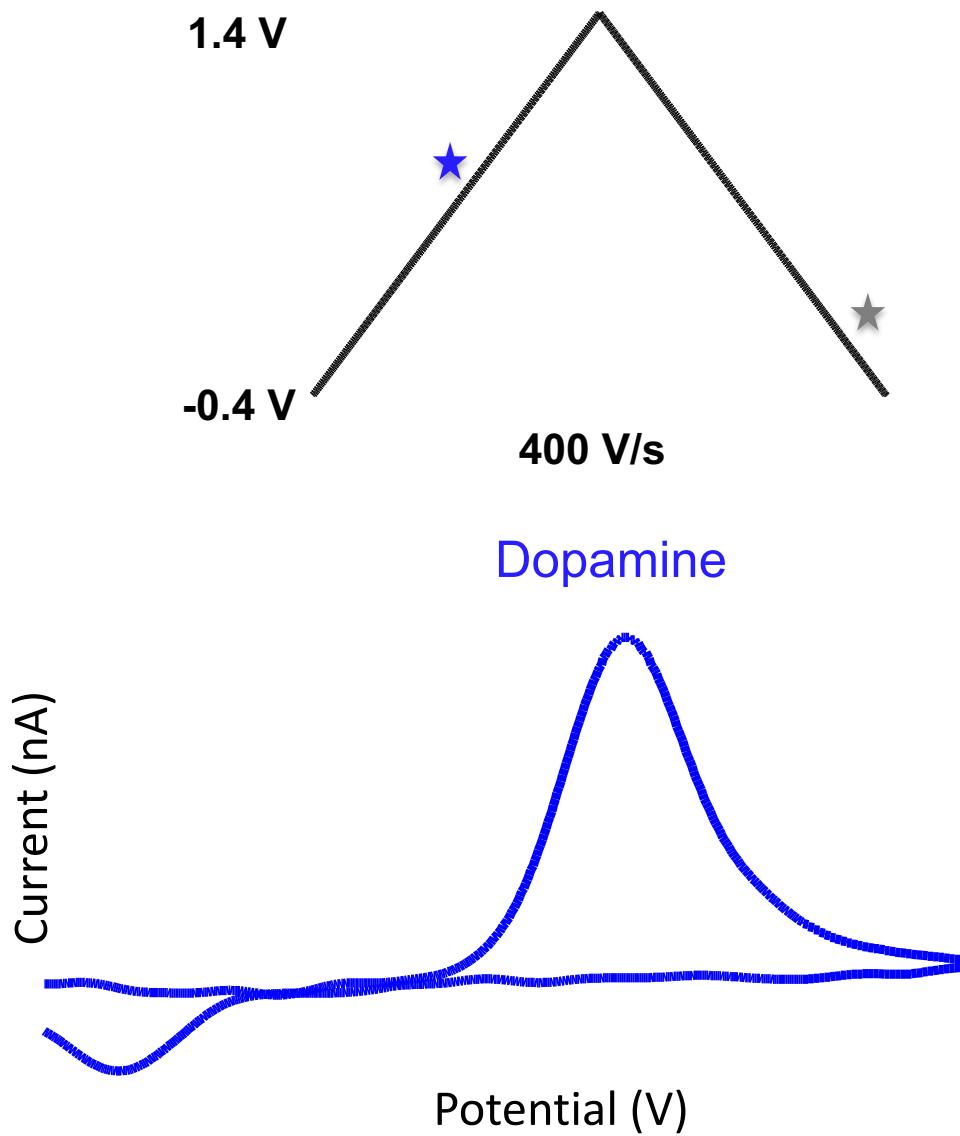
Fruit Fly vs. Carbon Fiber



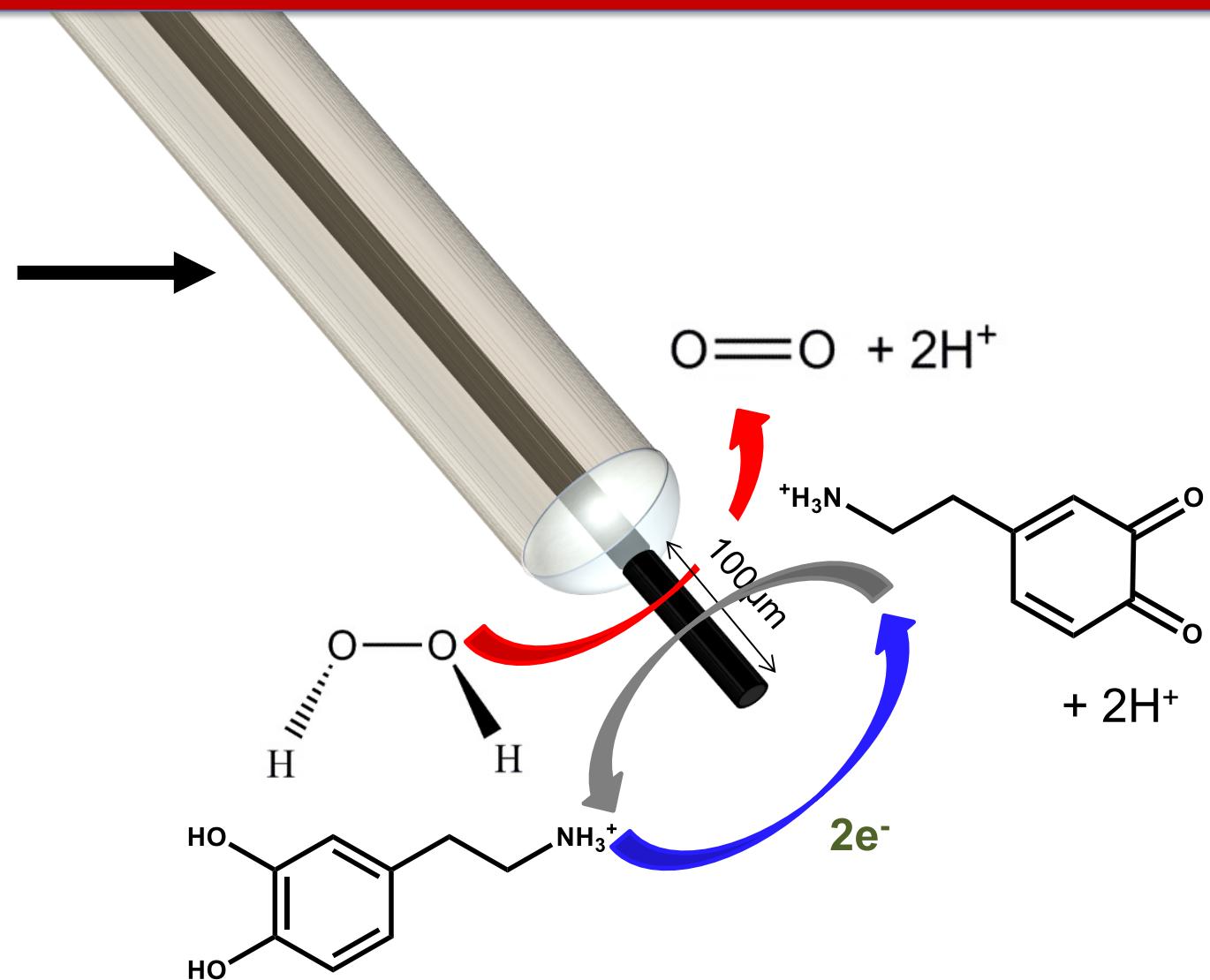
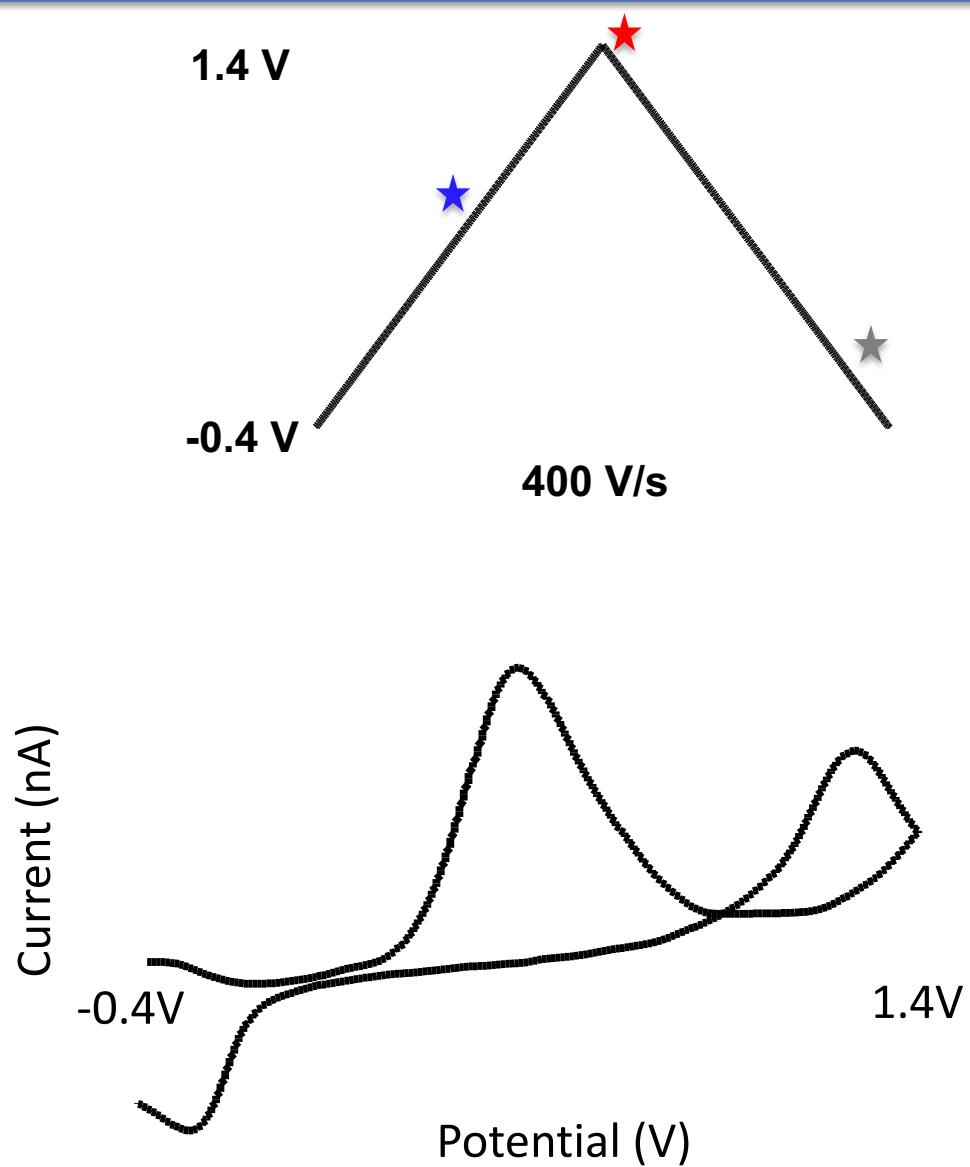
Background-Subtracted Fast Scan Cyclic Voltammetry



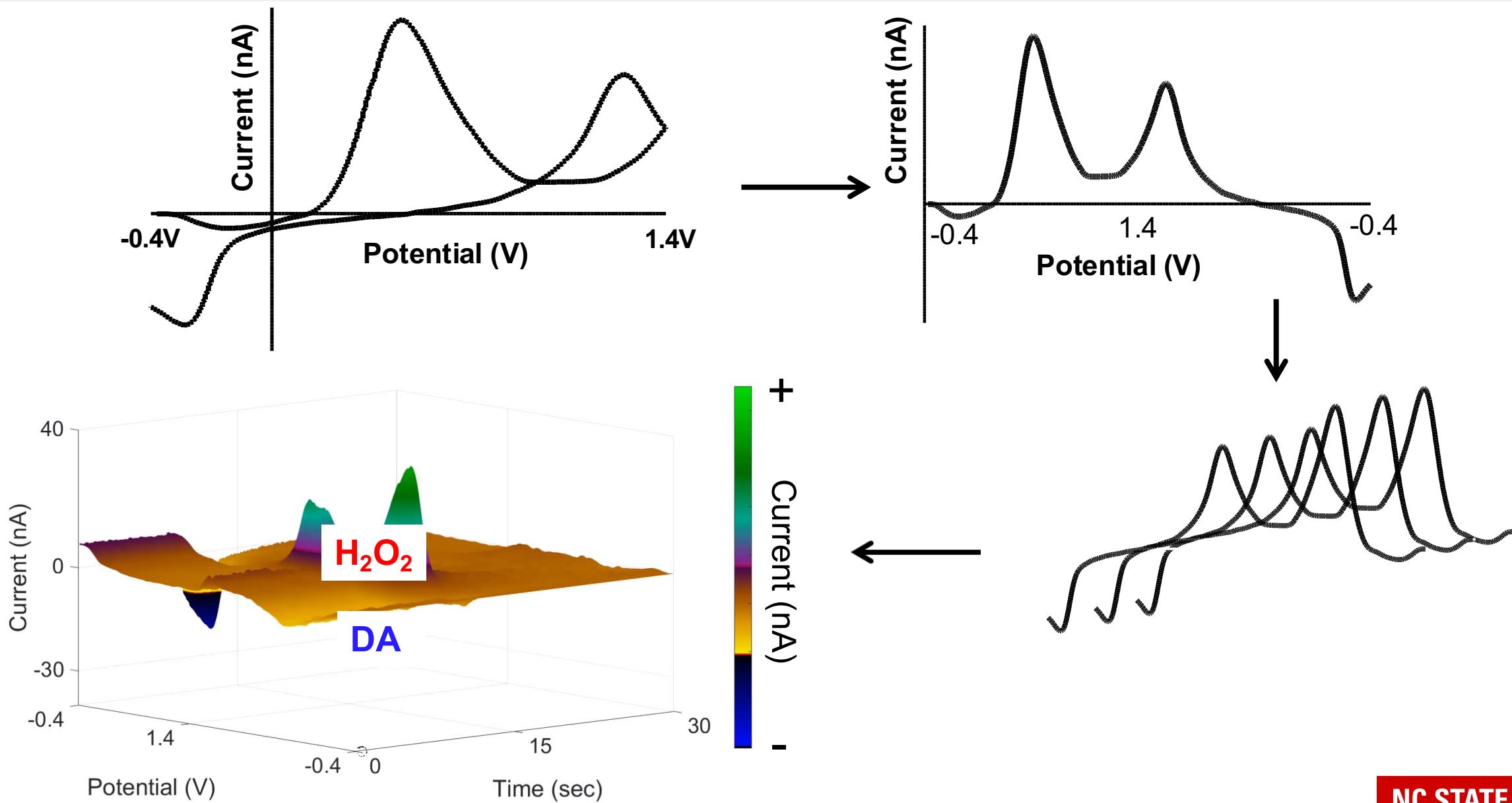
Background-Subtracted Fast Scan Cyclic Voltammetry



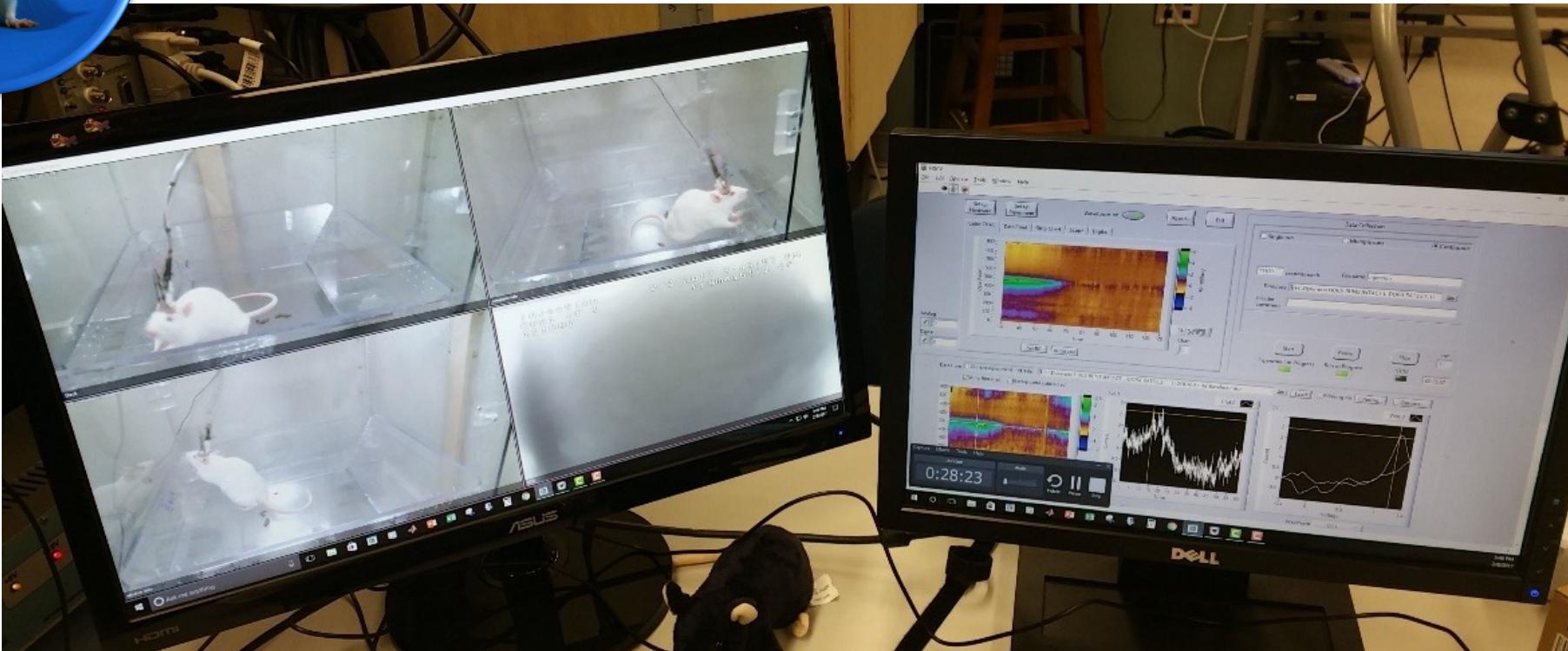
Background-Subtracted Fast Scan Cyclic Voltammetry



Color Plots: Visualizing the Data

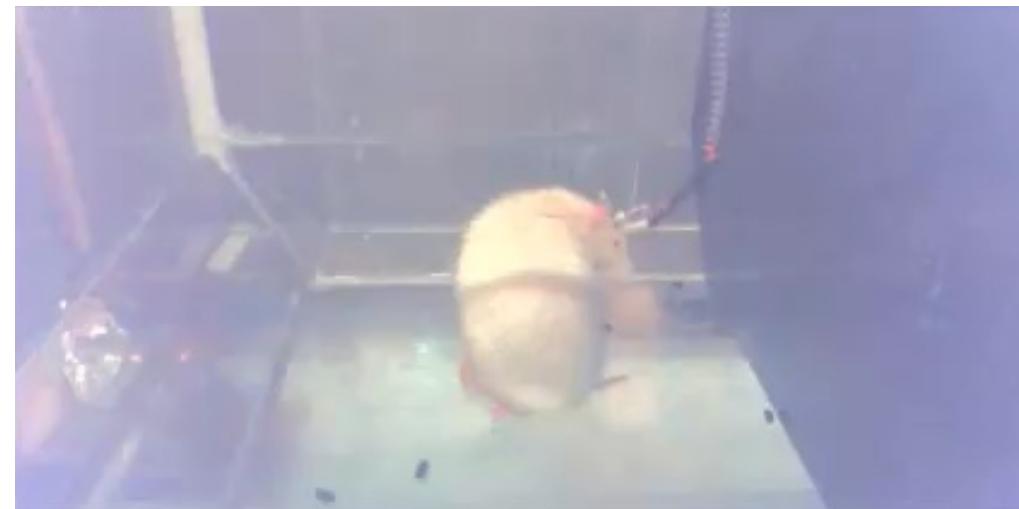
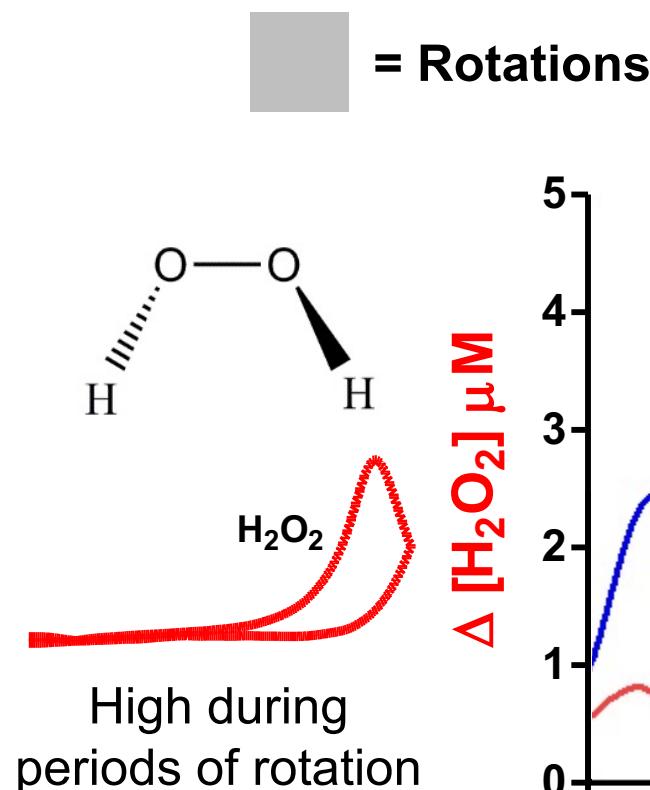


Simultaneously Recording Neurochemistry and Behavior

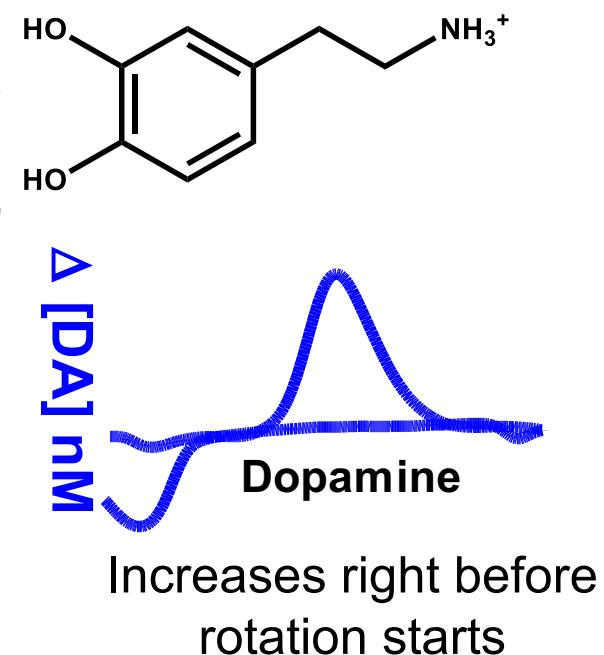


Neurochemical Dynamics in Striatum Correlate with Rotational Behavior

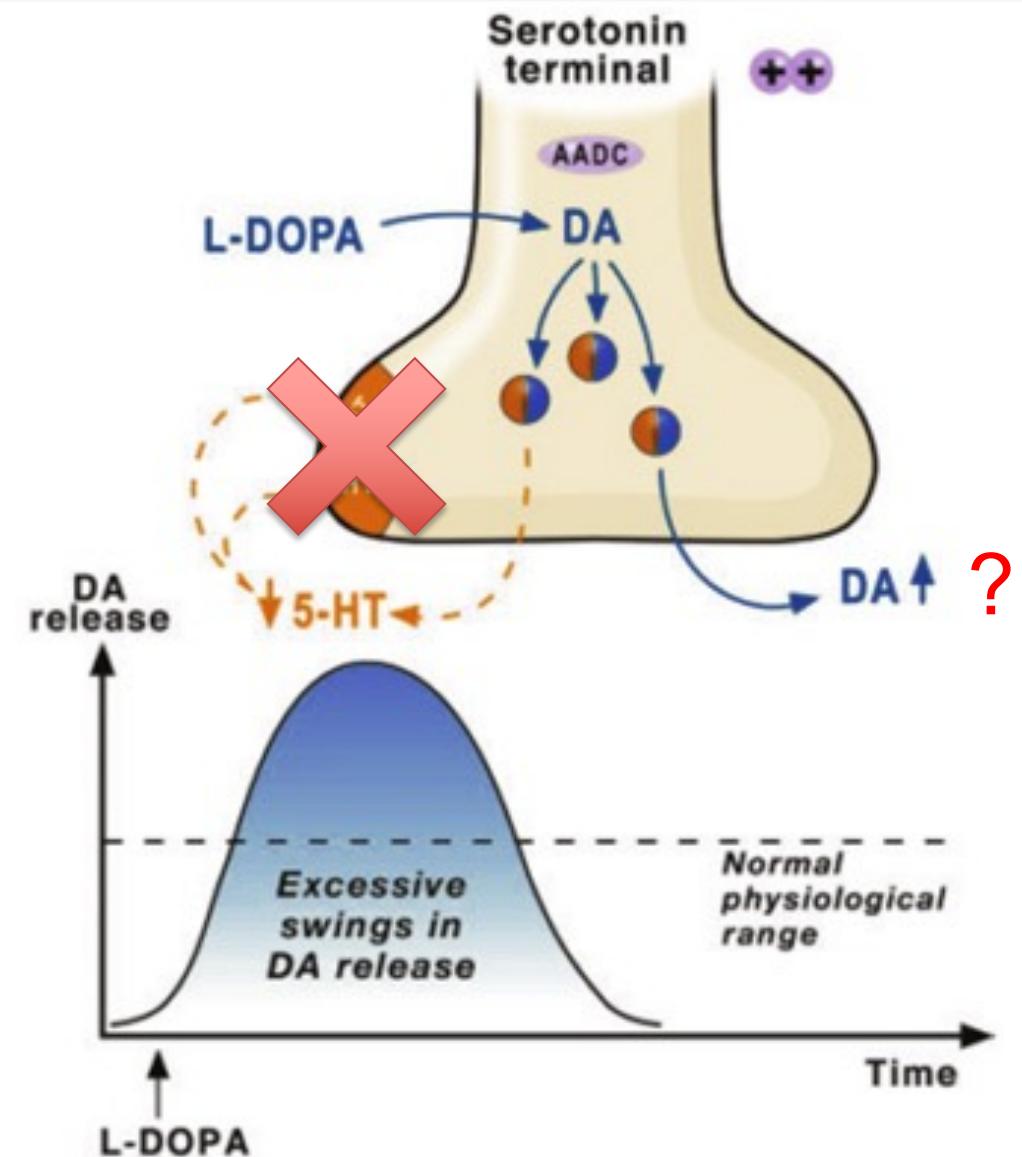
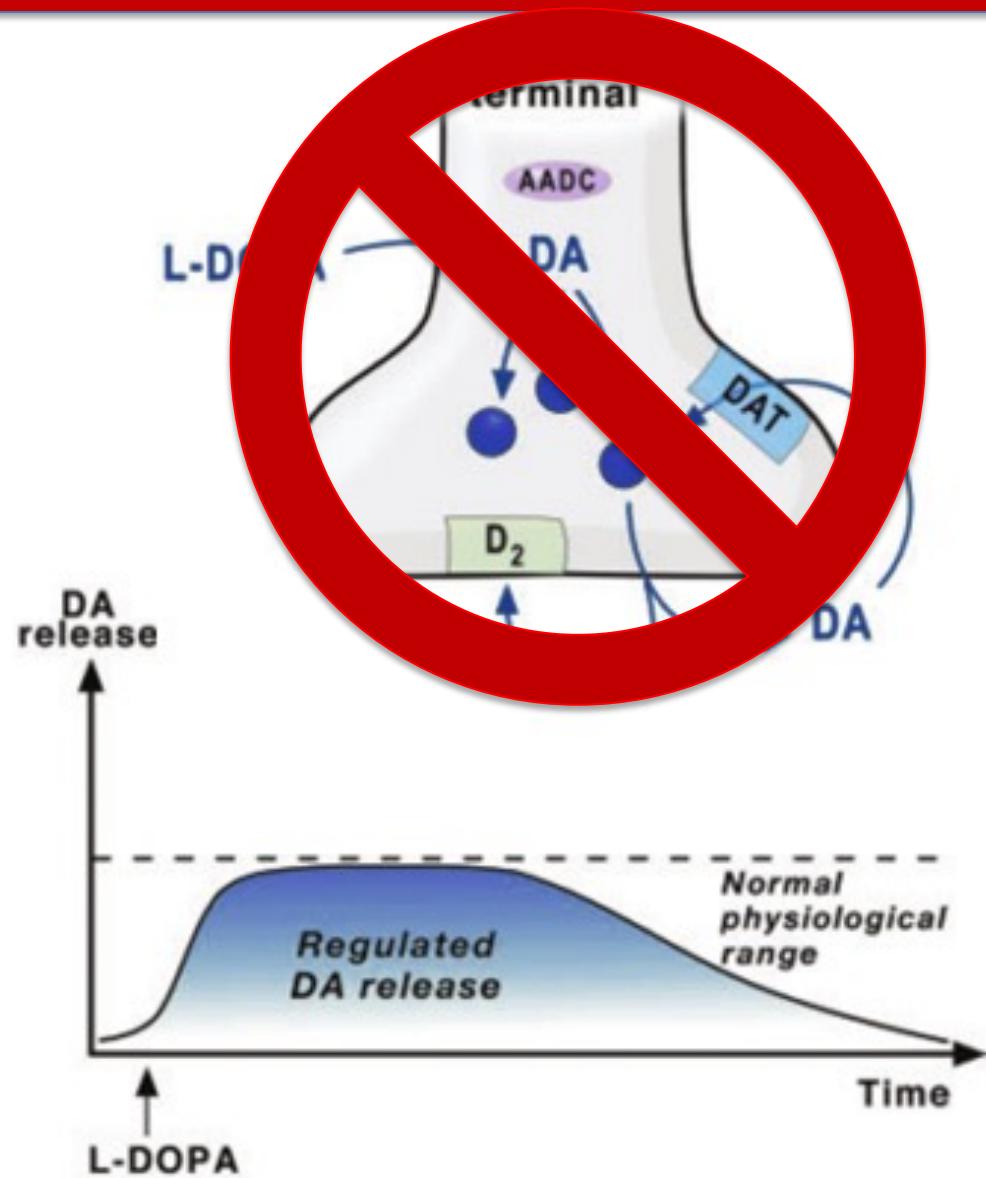
~90 minutes after L-DOPA administration



Week 3 of L-DOPA Administration



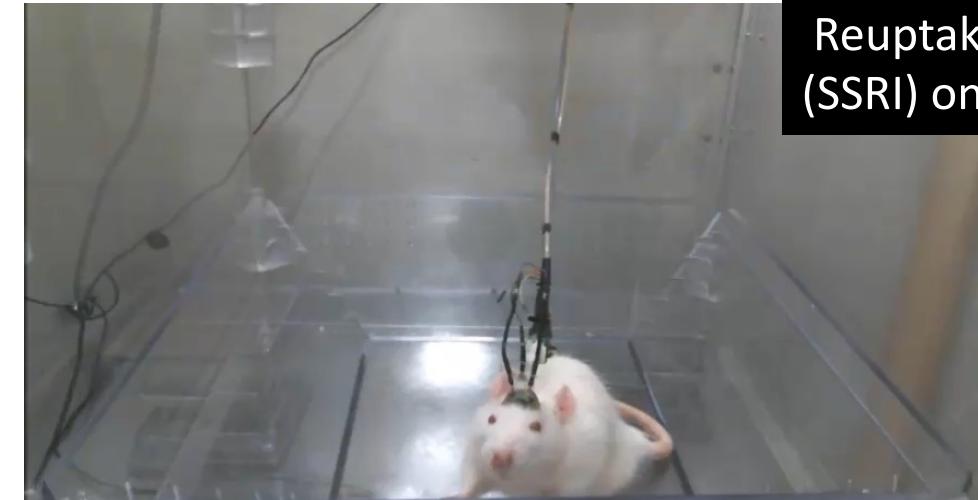
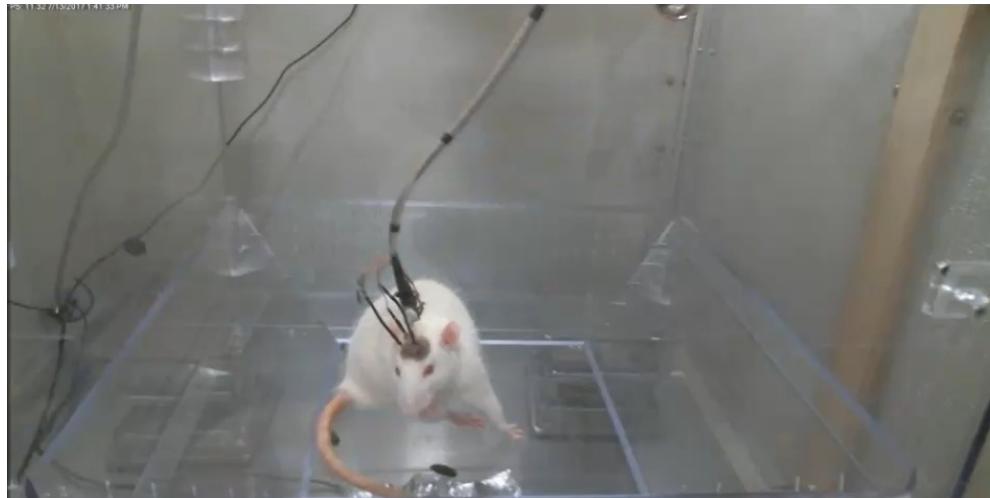
The Role of Serotonin Terminals



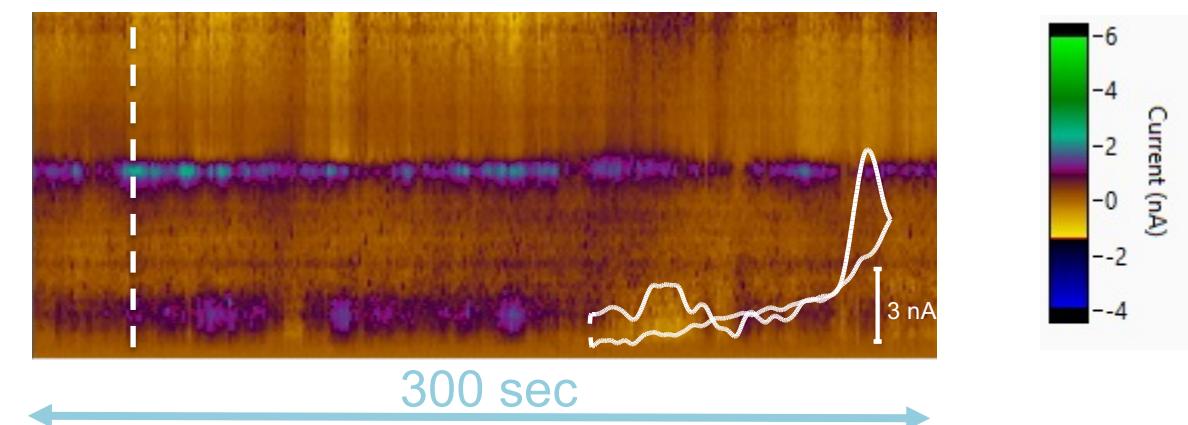
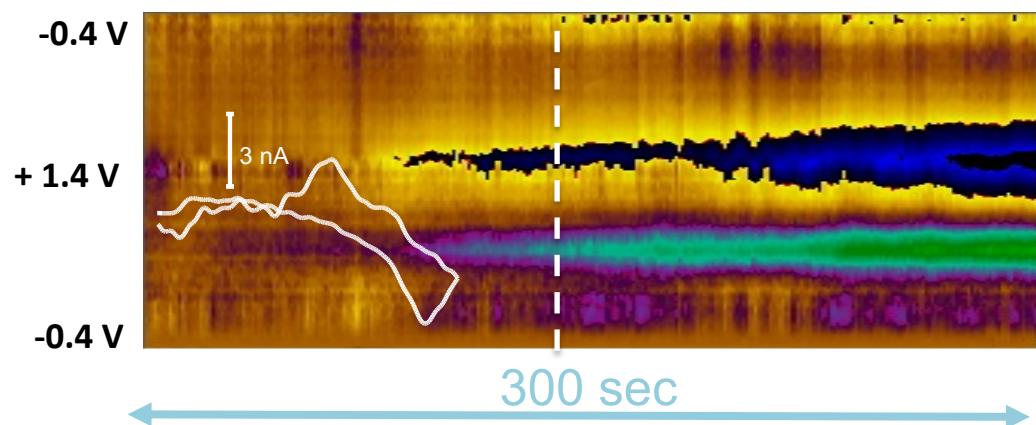
M. Carta et al., 2007

Saline and L-DOPA (10mg/kg)
40 min after L-DOPA treatment

Citalopram (10mg/kg) and L-DOPA (10mg/kg)
40 min after L-DOPA treatment



Selective Serotonin
Reuptake Inhibitor
(SSRI) on board



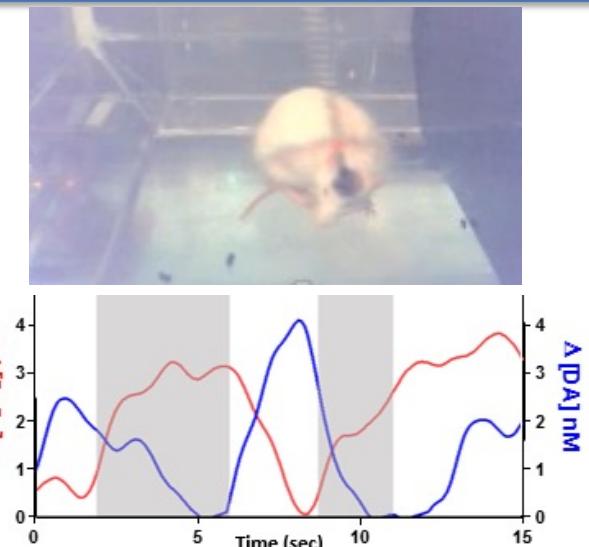
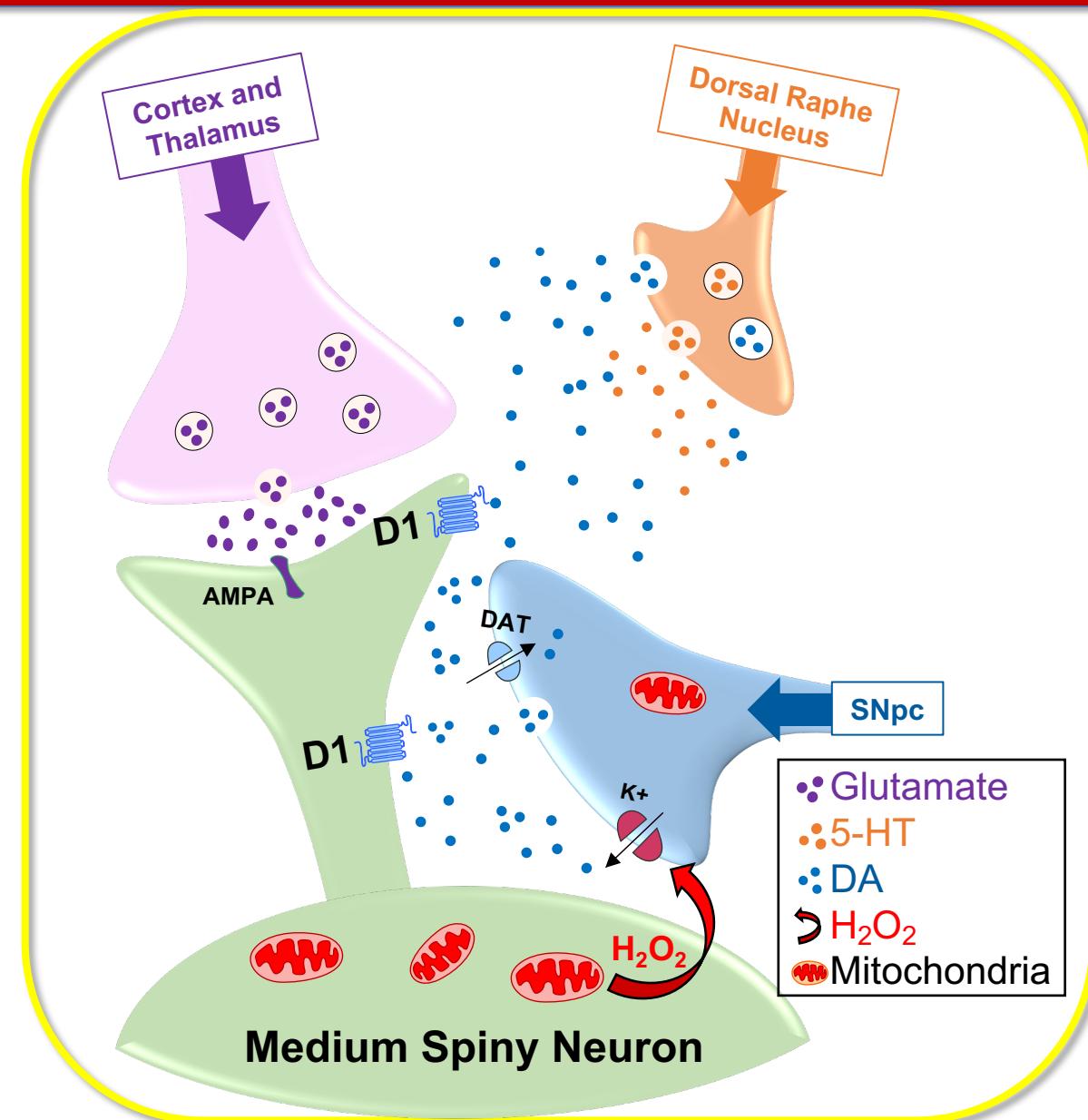
Hypothesis: H₂O₂ Negatively Modulates DA Release

DA encodes the 'Go' signals that contributes to the robust rotation.

Activation of medium spiny neurons causes an increase in cellular respiration, resulting in the generation of H₂O₂. H₂O₂ is also be generated in DA metabolism.

H₂O₂ negatively modulates DA release by way of K_{ATP} channels (Rice et al, 2003, 2008, 2012).

L-DOPA increases vesicular DA content in striatal terminals. DA released from serotonin terminals is relatively unchecked, due to lack of autoreceptors



Acknowledgements

Somers Lab Group Members:

Senior Researchers:

Greg McCarty

Lab Manager:

Christie Lee

Post Doctoral Researchers:

James Roberts

Graduate Students:

Leslie Wilson

Samantha Smith

Sarah Calhoun

Carl Meunier

Karen Butler

Undergraduate Students:

Catherine Mason

Sambit Panda

Matt Dausch

Saahj Gosrani

Tooba Rashid

Tarik Dahnoun

Hannah Styers



Collaborators:

Yuntian Zhu – NCSU Materials Science and Eng

Philip Bradford – NCSU Textile Eng, Chem and Sci

Saad Khan – NCSU Chem and Biochem Eng

Owen Duckworth – NCSU Soil Science

Heather Patisaul – NCSU Biological Sciences

Chuck Mooney – NCSU Analytical Instrumental Facility

Elyssa Margolis and Howard Fields – UCSF Neurology

Olaf Paulson – University of Copenhagen Neurology

Jonathan Sweedler and Elena Romanova – Univ of Illinois Chemistry

W. M. Keck Center
for Behavioral Biology

NIDA
NATIONAL INSTITUTE

ON DRUG ABUSE

R03DA027969

R01 DA043007



National Science Foundation
WHERE DISCOVERIES BEGIN

CAREER CHE7151264

CHE 1407180

DGE-1252376 to LED

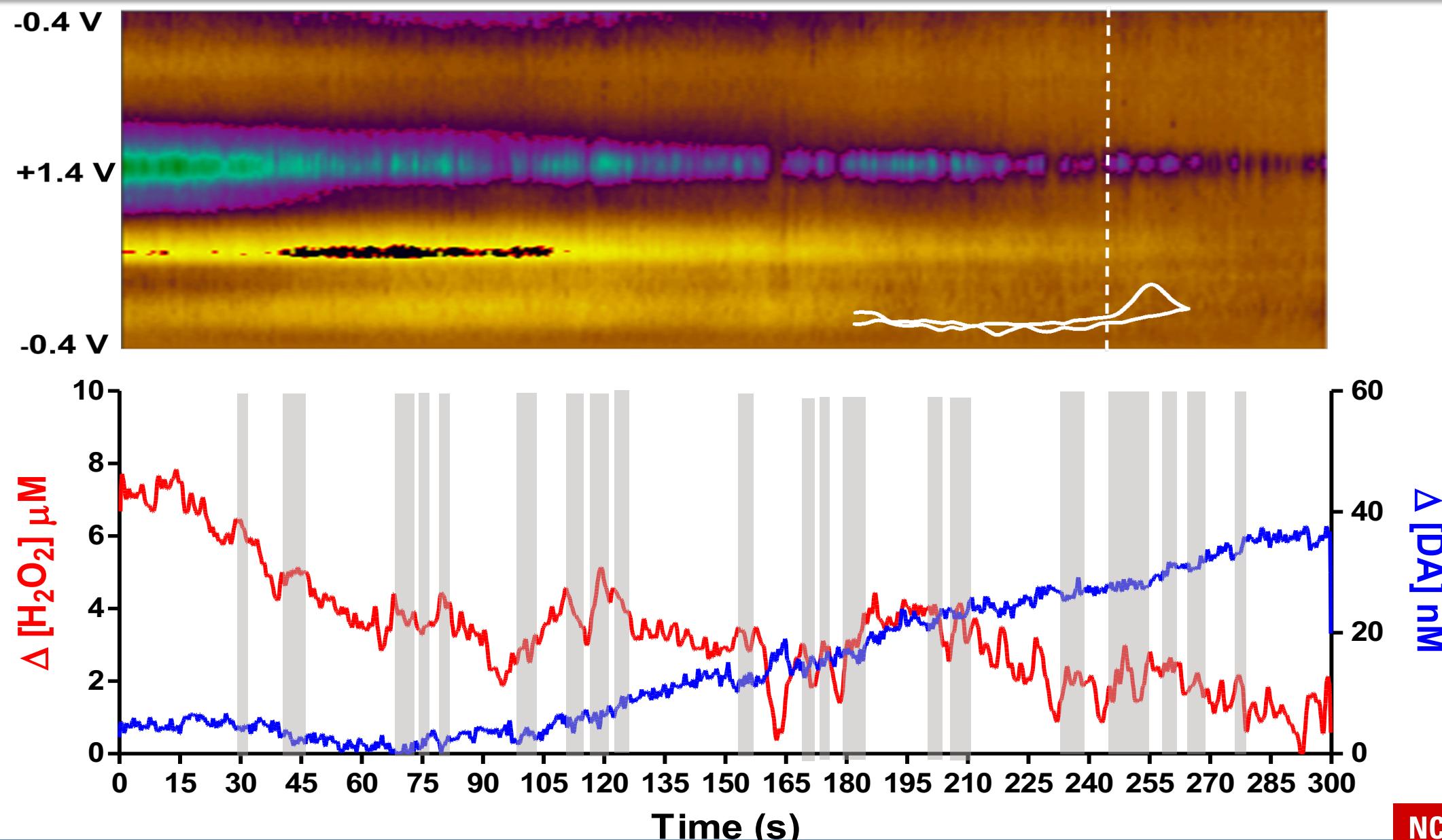
DGE-1252376 to CJM

National Institute of
Neurological Disorders and Stroke
National Institutes of Health

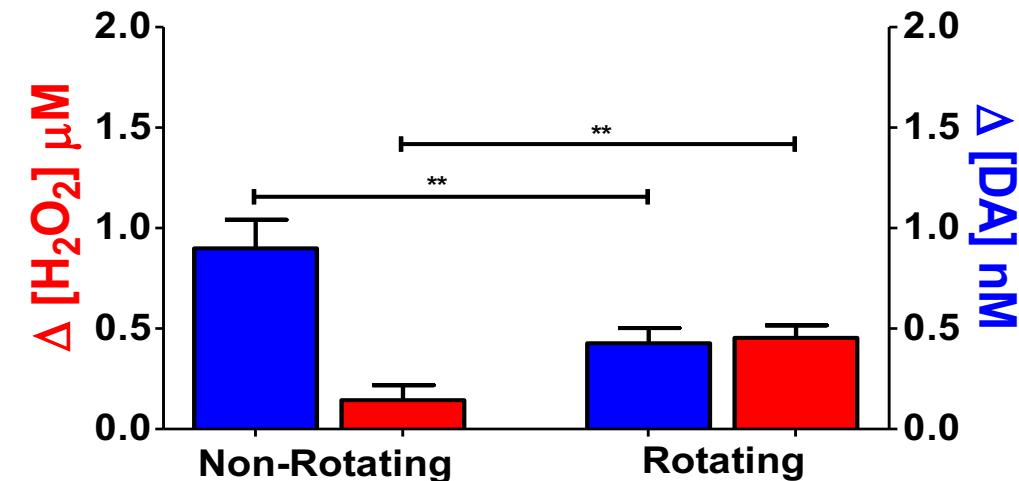
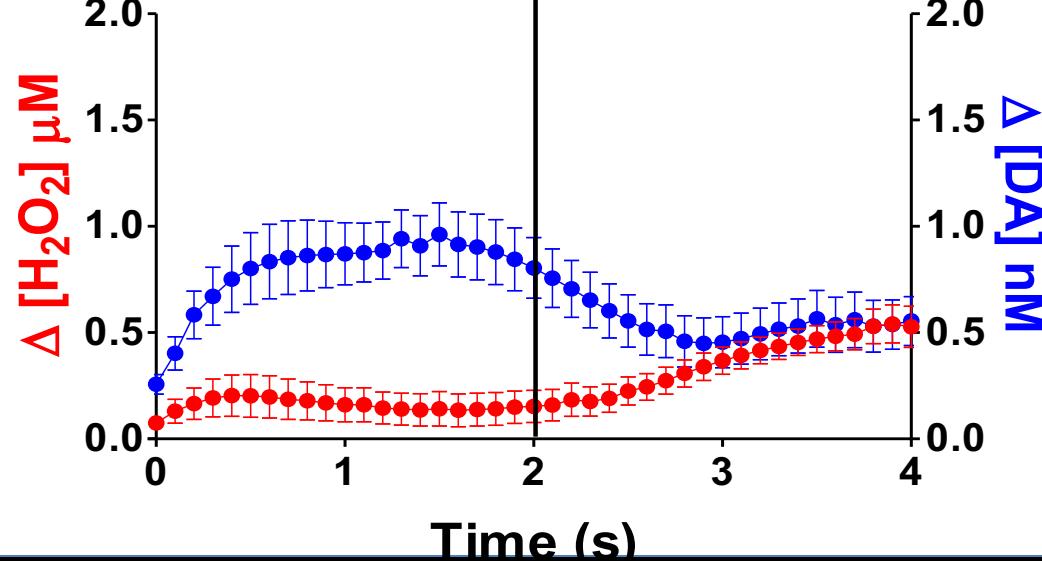
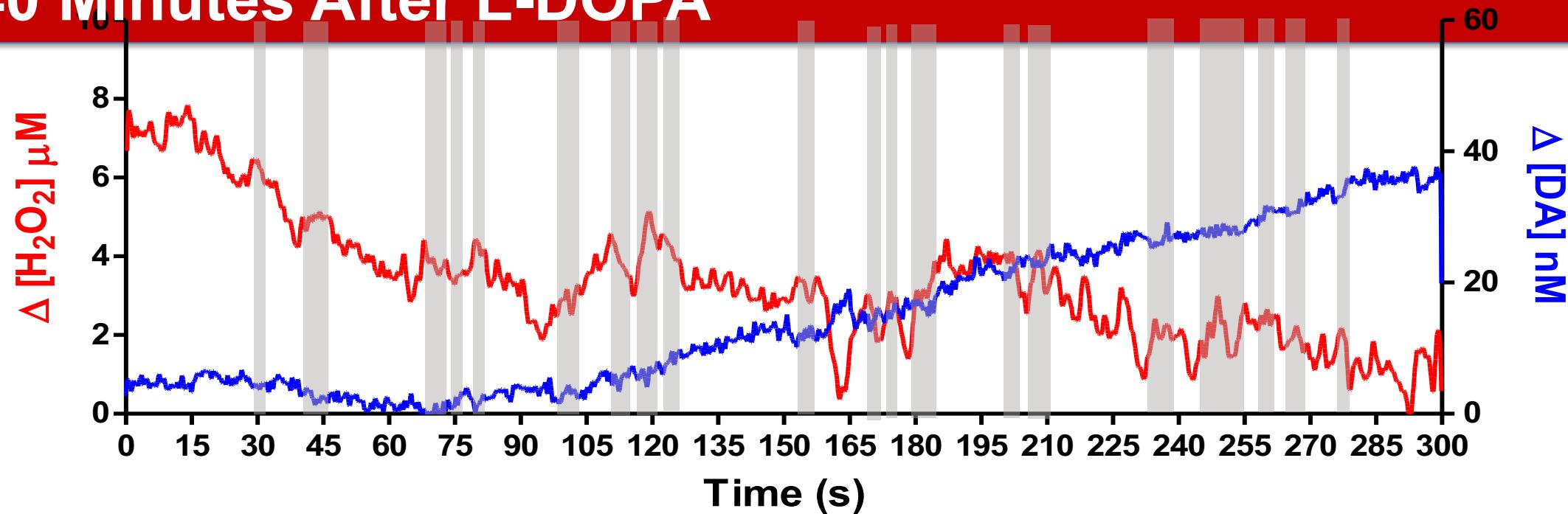
5R01NS076772

NC STATE
UNIVERSITY

35-40 Minutes After L-DOPA

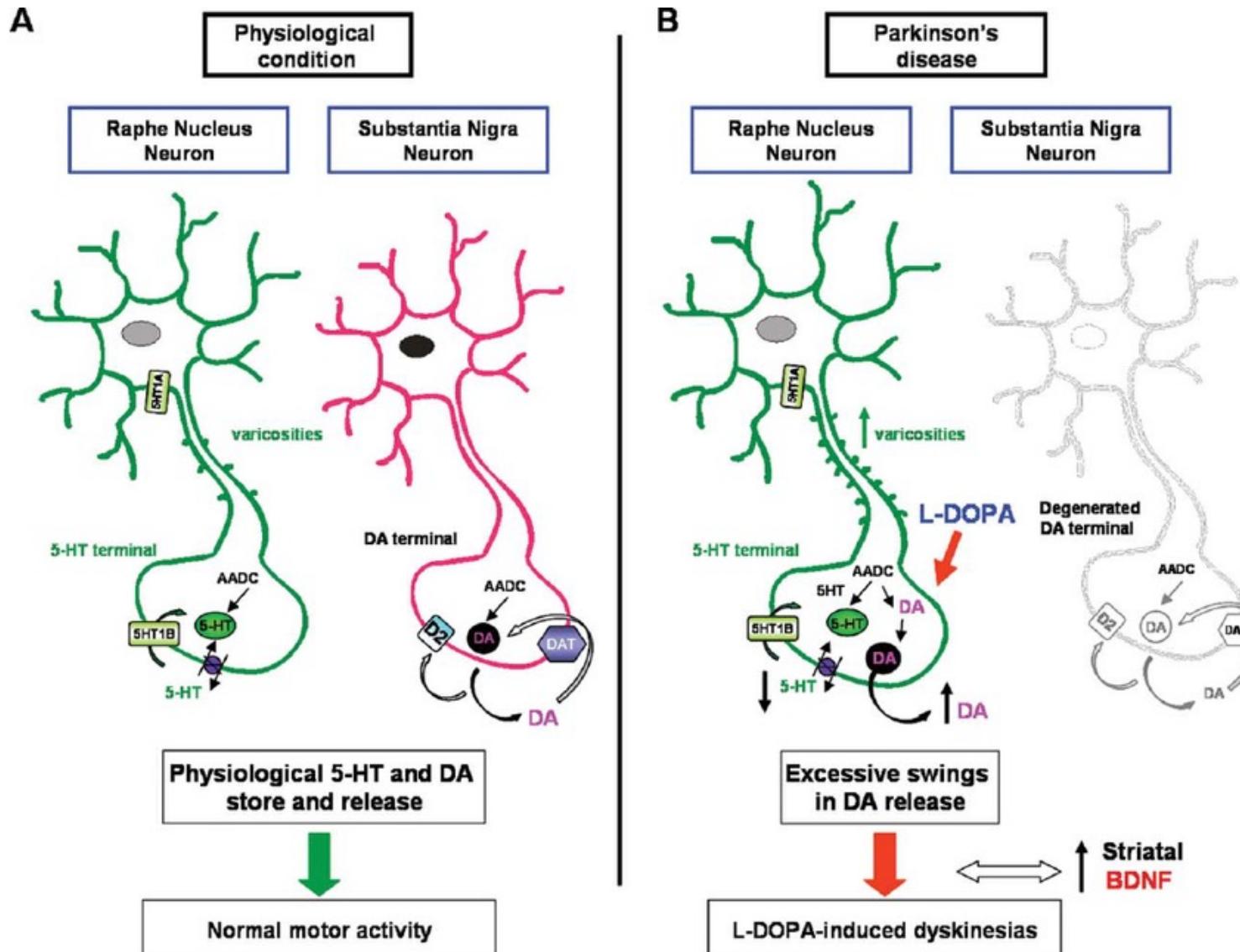


35-40 Minutes After L-DOPA

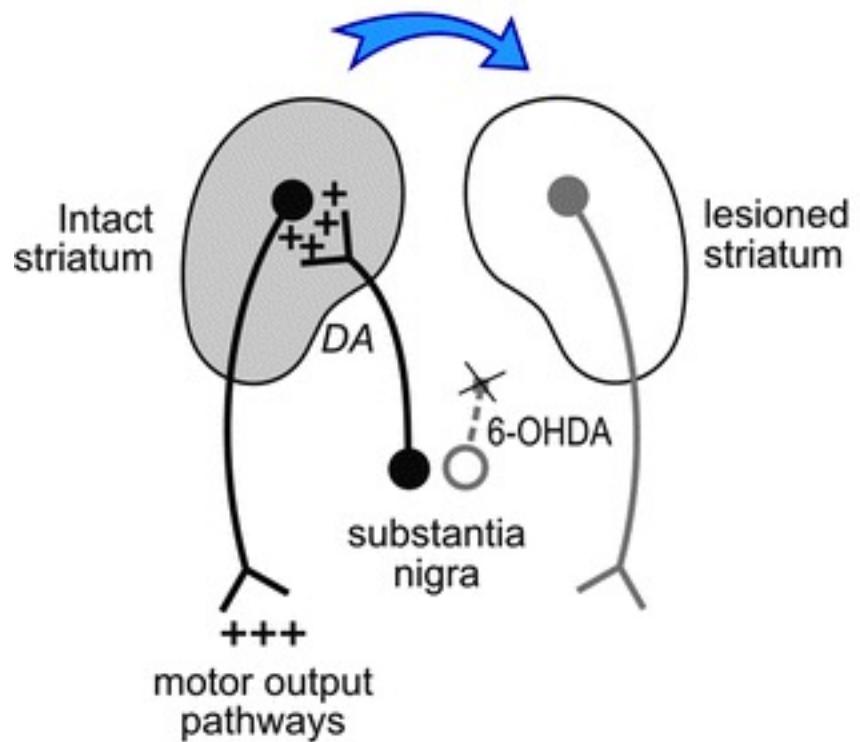


DA: two tailed t-test; $t(19)= 2.879$, ** $p=0.0097$
 H_2O_2 : two tailed t-test; $t(19)= 3.574$, ** $p=0.0020$

Serotonin



a Amphetamine



b Apomorphine

