SIRT1 ACTIVITY IN THE DENTATE GYRUS MEDIATES STRESS-INDUCED BEHAVIORAL AND MOLECULAR CHANGES

NSF EPSCoR 2012 Symposium
Laura Schrader
Tulane University
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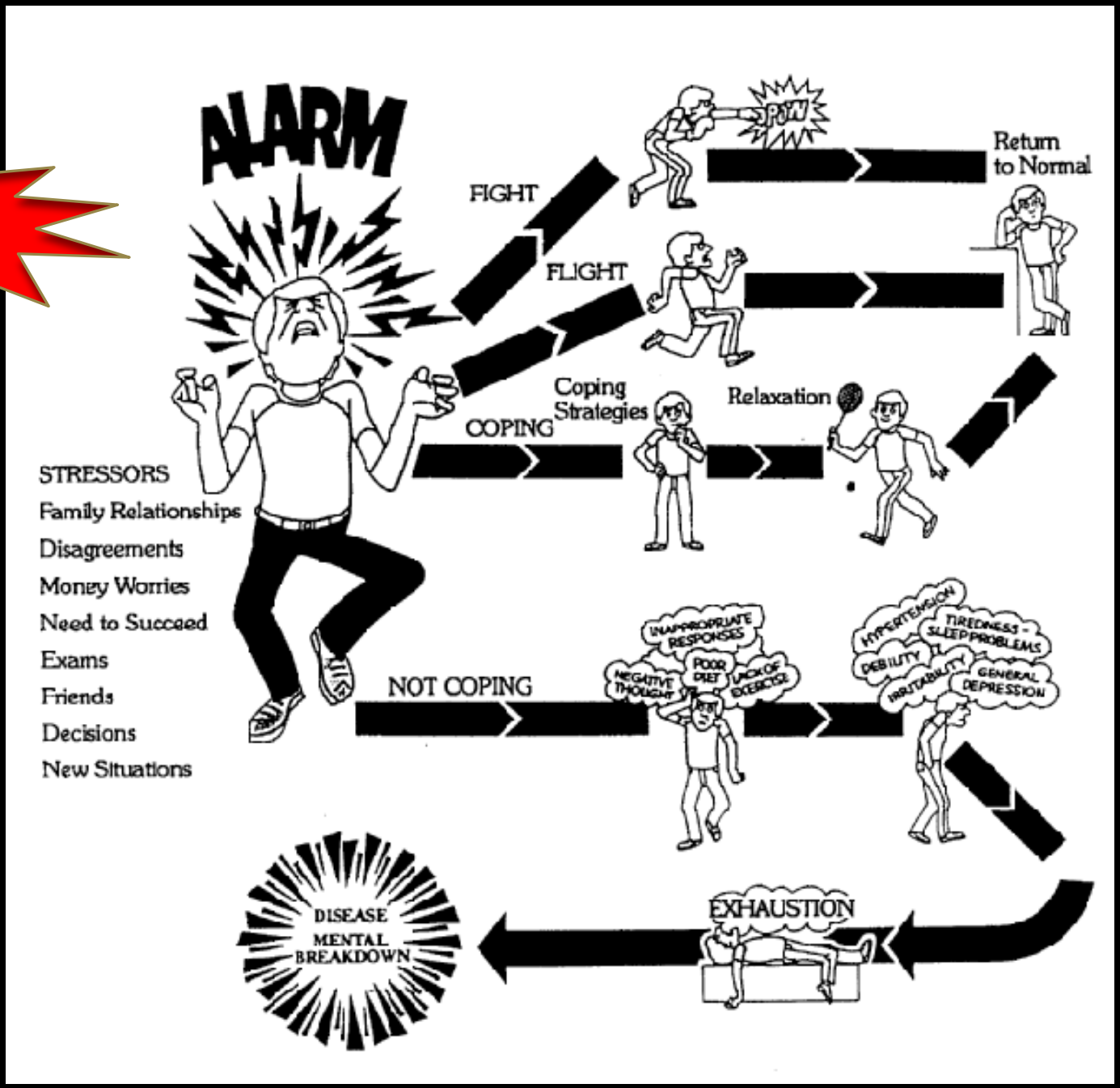
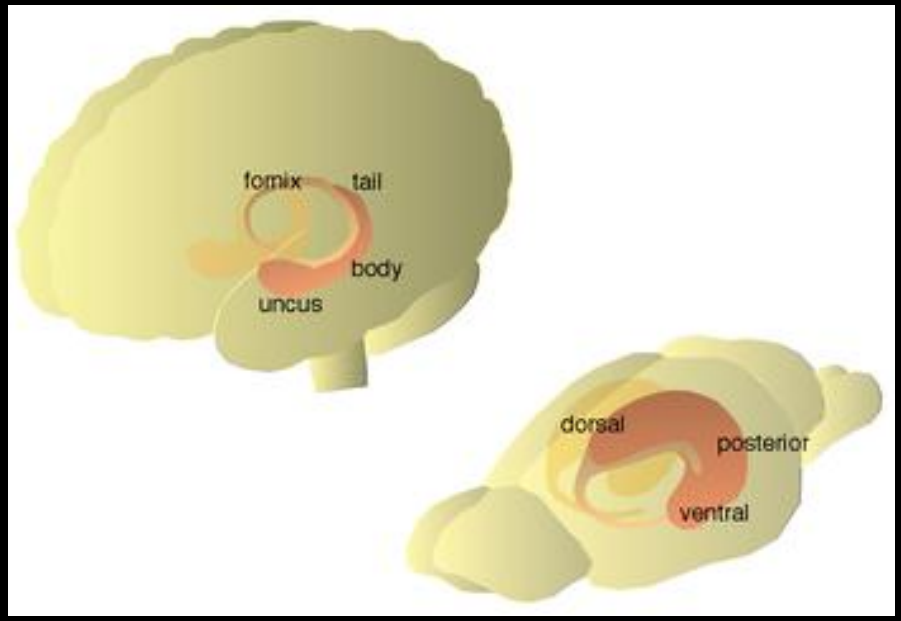
STRESS

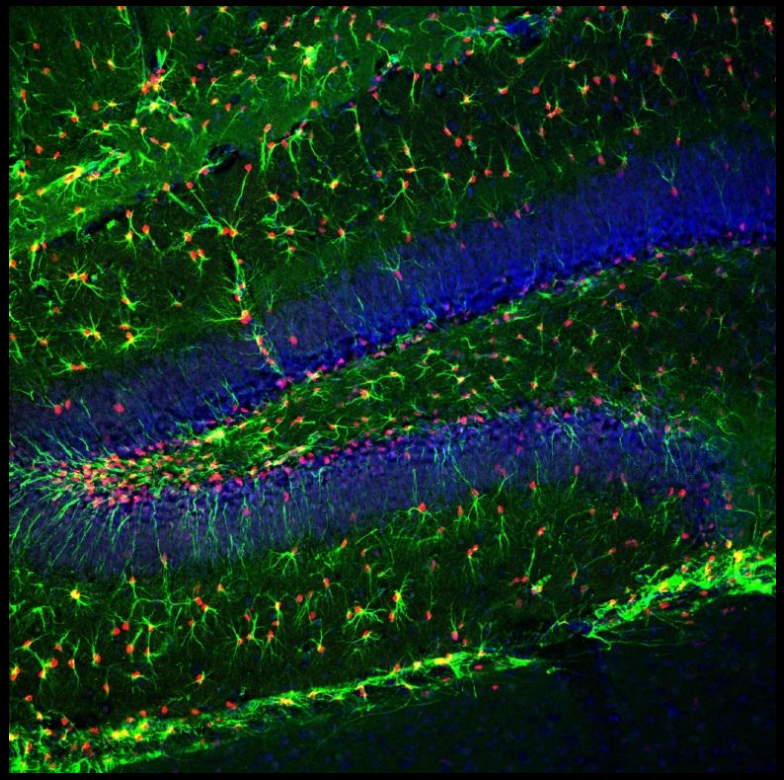

ALARM
FIGHT
POW
Return to Normal
FLIGHT
COPING
Coping Strategies
Relaxation
STRESSORS
Family Relationships
Disagreements
Money Worries
Need to Succeed
Exams
Friends
Decisions
New Situations
NOT COPING
INAPPROPRIATE RESPONSES
NEGATIVE THOUGHT
POOR DIET
LACK OF EXERCISE
HYPERTENSION
TIREDNESS - SLEEP PROBLEMS
DEBILITY
IRRITABILITY
GENERAL DEPRESSION
EXHAUSTION
DISEASE
MENTAL BREAKDOWN

Function of the hippocampus



- Hippocampus-dependent Memory
- Inhibition of HPA axis
  - Circadian control of corticosterone
  - Stress-inhibitory control of HPA axis
- Mood Regulation

Effects of stress on the hippocampus

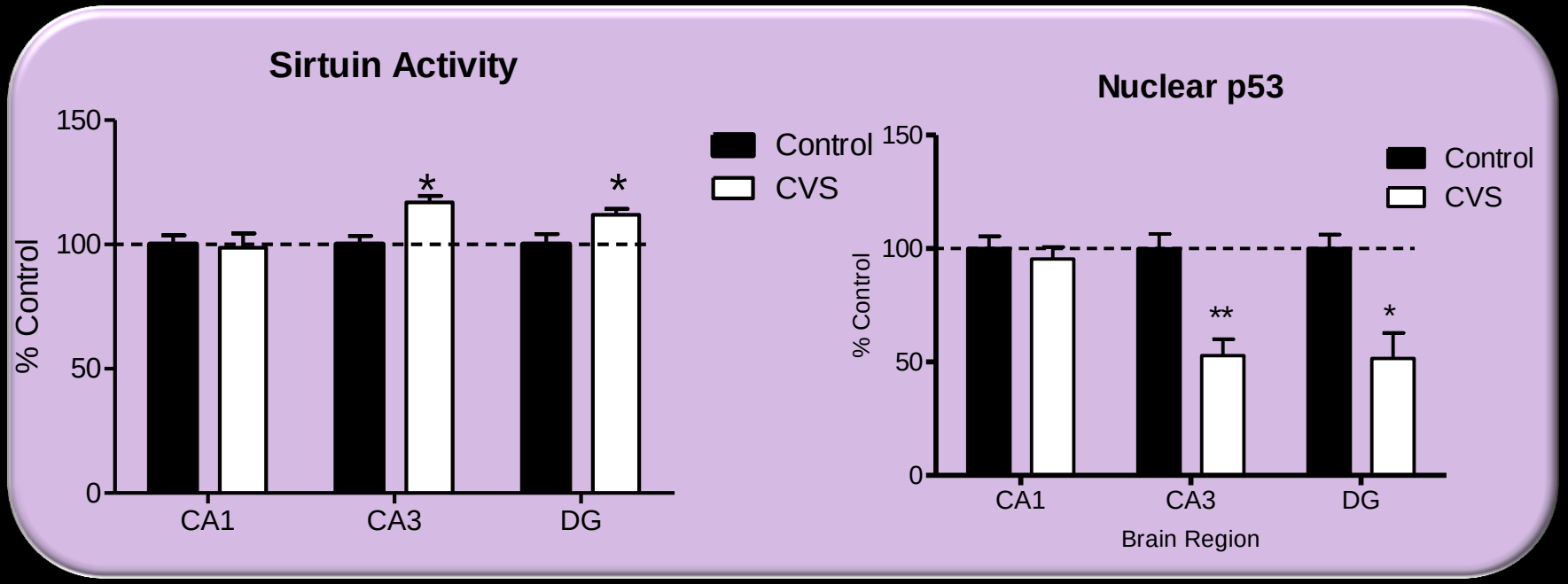


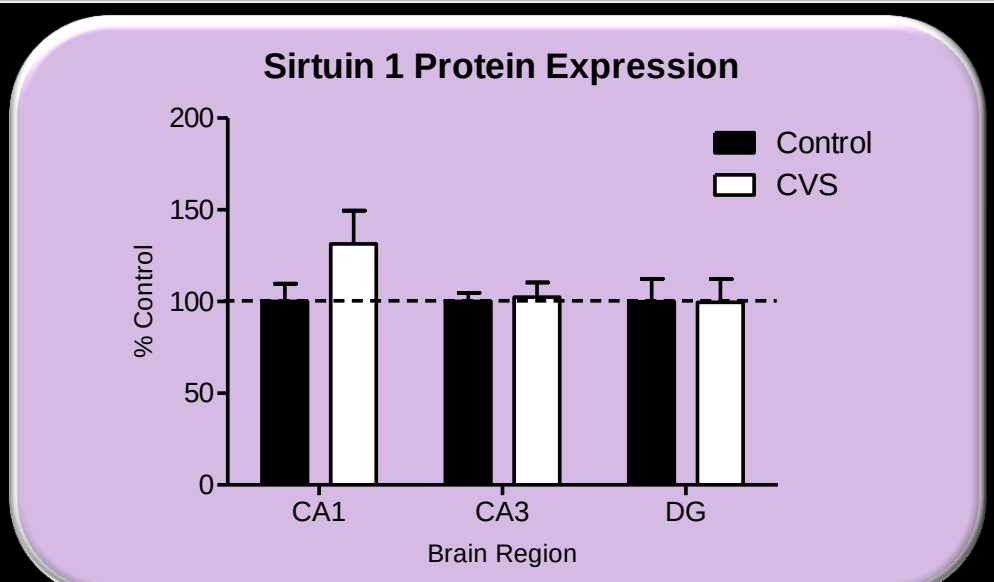
- Structural Abnormalities
  - Dendritic Retraction
  - Decreased Neurogenesis
  - Hippocampal Volume Loss
- Functional Deficits
  - Memory Impairment
  - Inhibition LTP Induction
  - Facilitation LTD Induction

Epigenetic Mechanisms
HATs and HDACs

- Histone acetyltransferases (HATs) and Histone deacetylases (HDACs)
- Classical HDAC's
  - Class I: HDAC 1-3, 8
  - Class II: HDAC 4-10
  - Class IV: HDAC 11
- **Sirtuins (or Class III HDACs)**
  - **Function via a NAD^+ (nicotinamide adenine dinucleotide) dependent mechanism**
  - **Deacetylates histones and transcription factors, including p53**
  - **Distributed in hippocampus**
  - **Role in aging and metabolic functions**
  - **Role in cognition and anxiety disorders**

Sirt1 activity is increased in the DG and CA3 of CVS animals



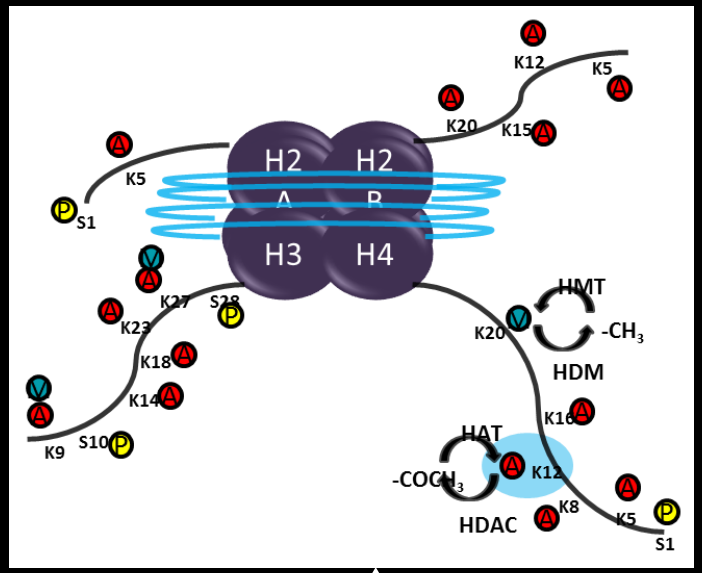


Ferland and Schrader 2011

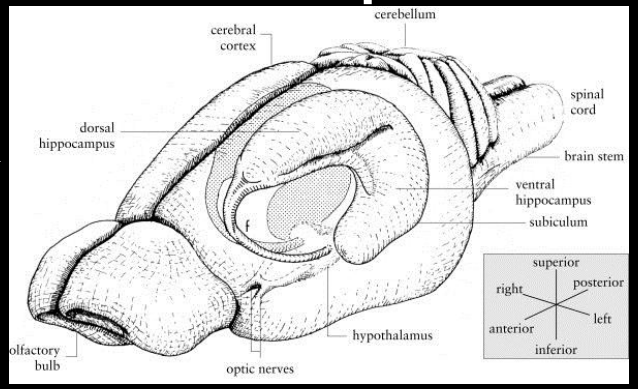
What are the Molecular and Behavioral Effects of Sirt1 Activation during Chronic Variable Stress in the Hippocampus?

STUDY DESIGN

Sucrose preference
Object location
anxiety



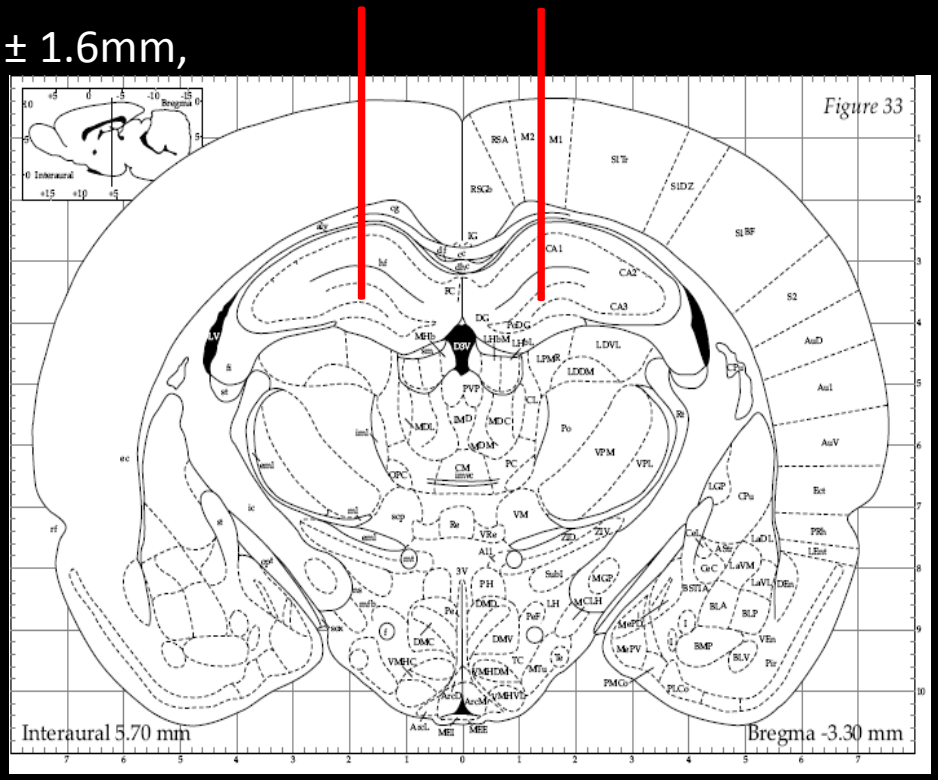
CVS Paradigm:
- Cold Swim (10min at 16-18°C)
- Warm Swim (20min at 31-33°C)
- Cold Room (1hr at 4°C)
- Rotation (1hr at 100 rpm)
- Social Isolation (overnight, one rat per cage)
- Crowding (overnight, 6 rats per cage)



(Cheung and Cardinal, 2005)

50 μM sirtinol into DG at 0.25μl/ hour or vehicle (5% hydroxylpropyl βcyclodextrin)

bregma AP -3.2mm; ML ± 1.6mm,
DV -5.0mm



AP -3.2, ML +-1.6

Cannula and Pump Placement

Group Housed

Start Chronic Stress

Start Behavioral Testing

Test 1

Sacrifice

Surgery and Recovery

CVS

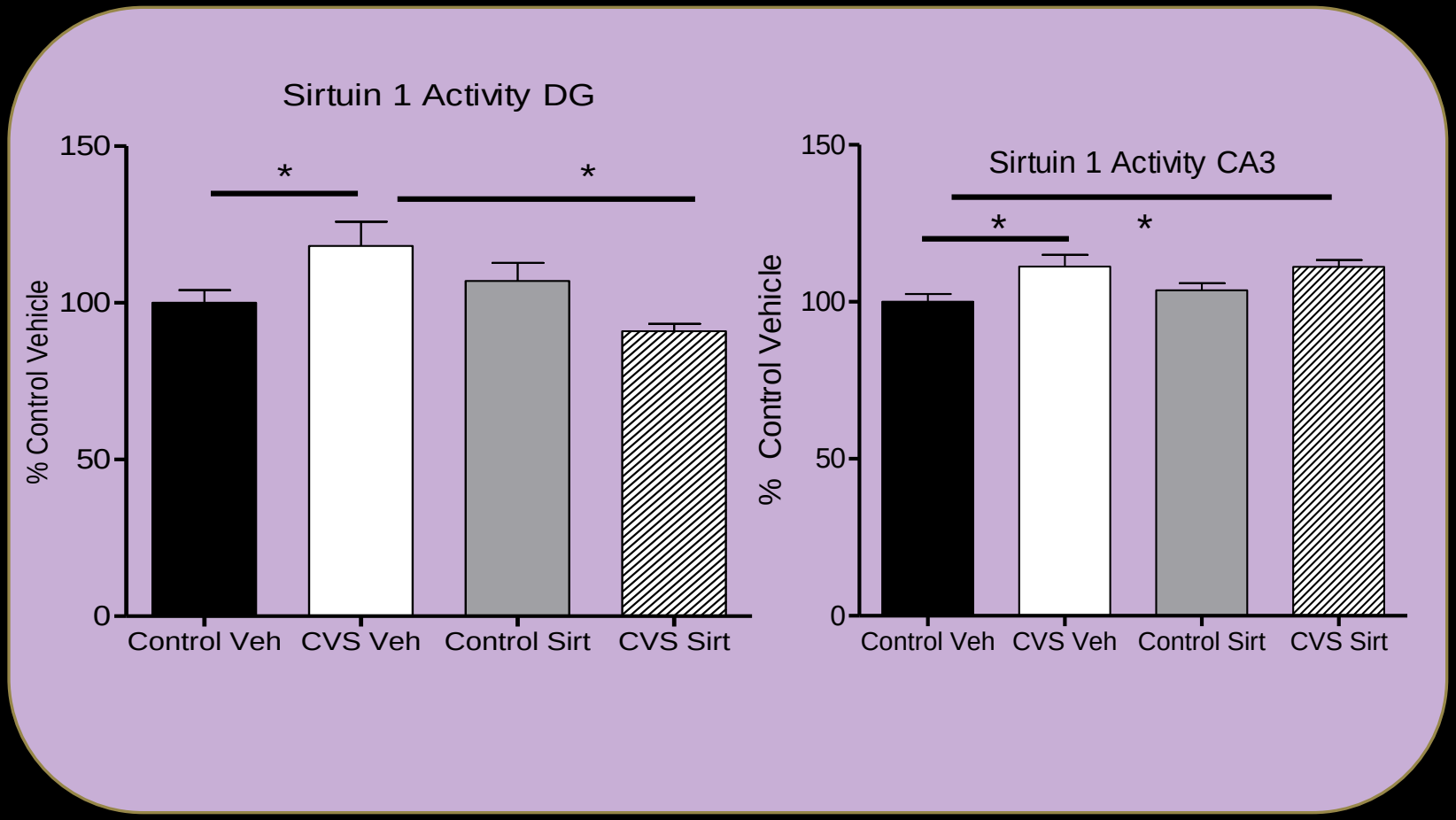
-10 -6 1 9 10 11 12 13 14 15 16

Day of Protocol

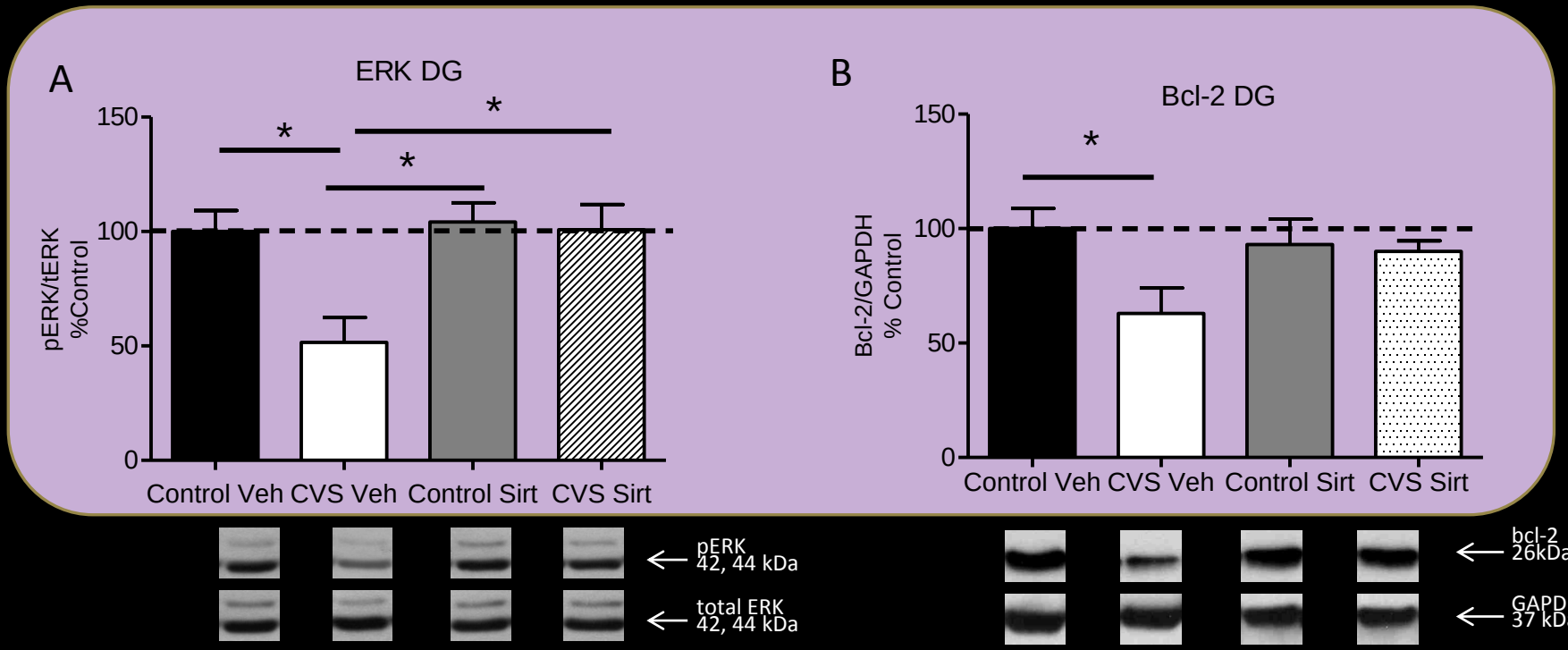
Habituation

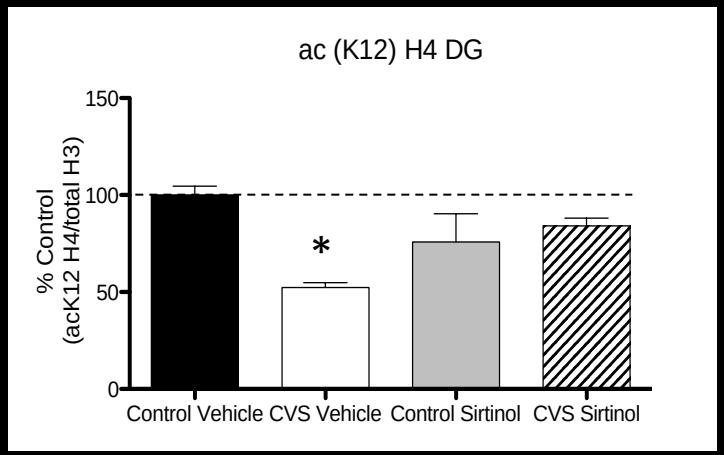
Done in Collaboration with Paul Colombo

Infusion of sirtinol, a sirt1 inhibitor, decreased sirt1 activity in the DG

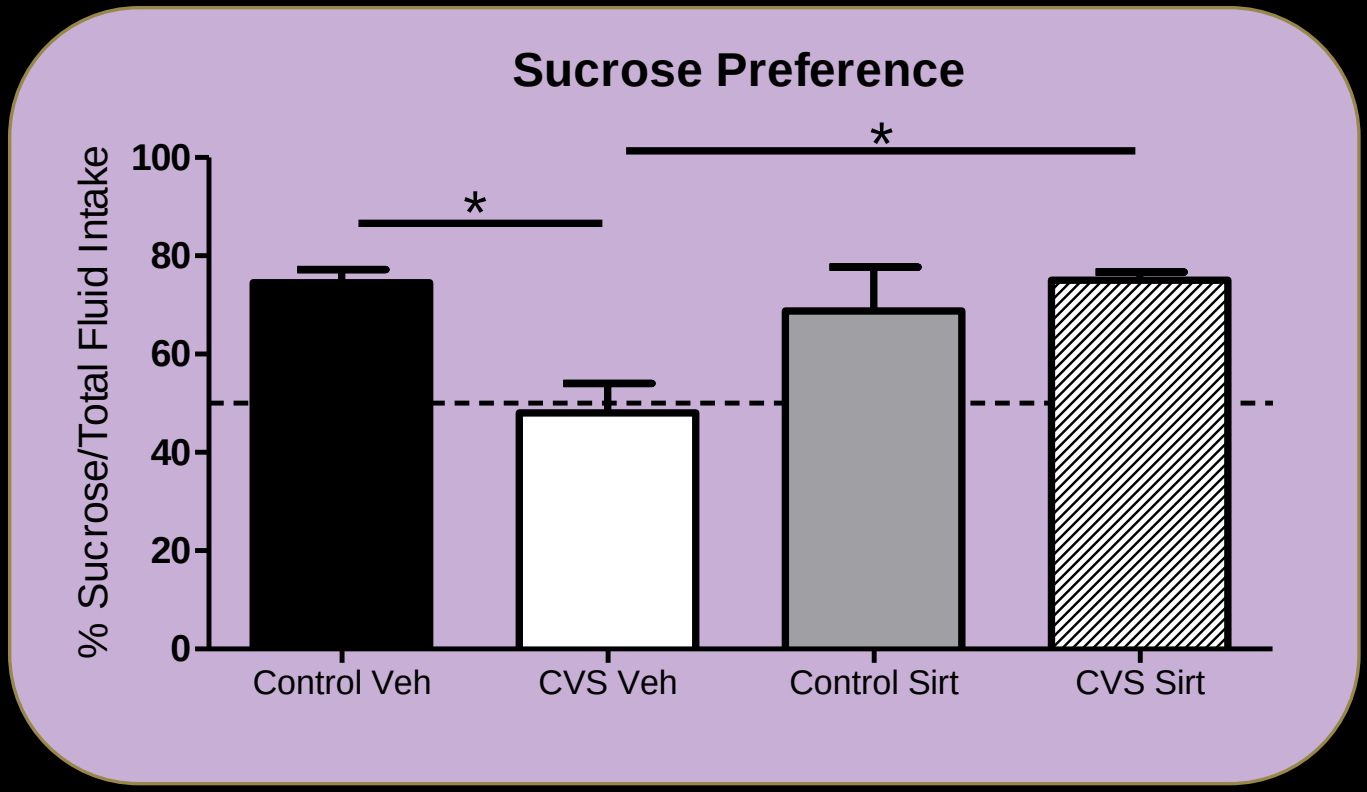


Sirt1 inhibition reversed the molecular effects of CVS in the DG

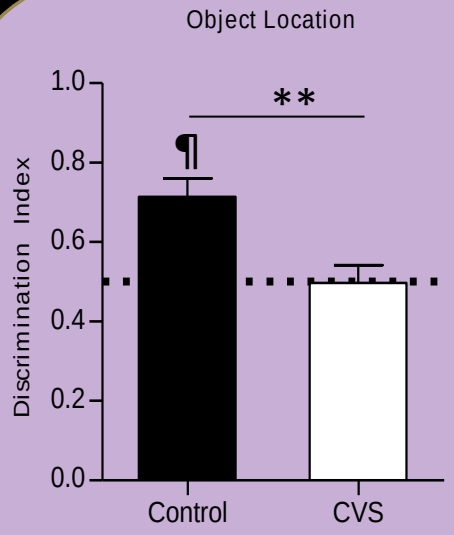


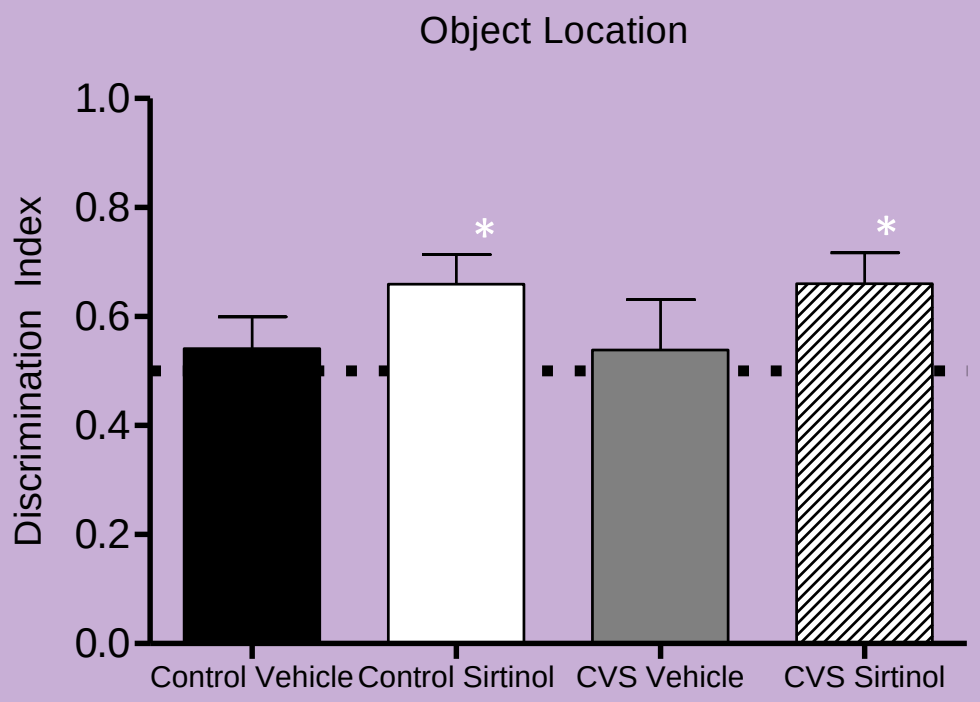


Sirt1 inhibition reversed the anhedonic behavior caused by CVS

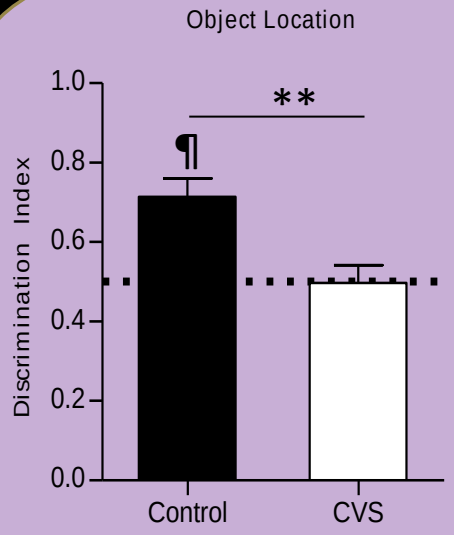


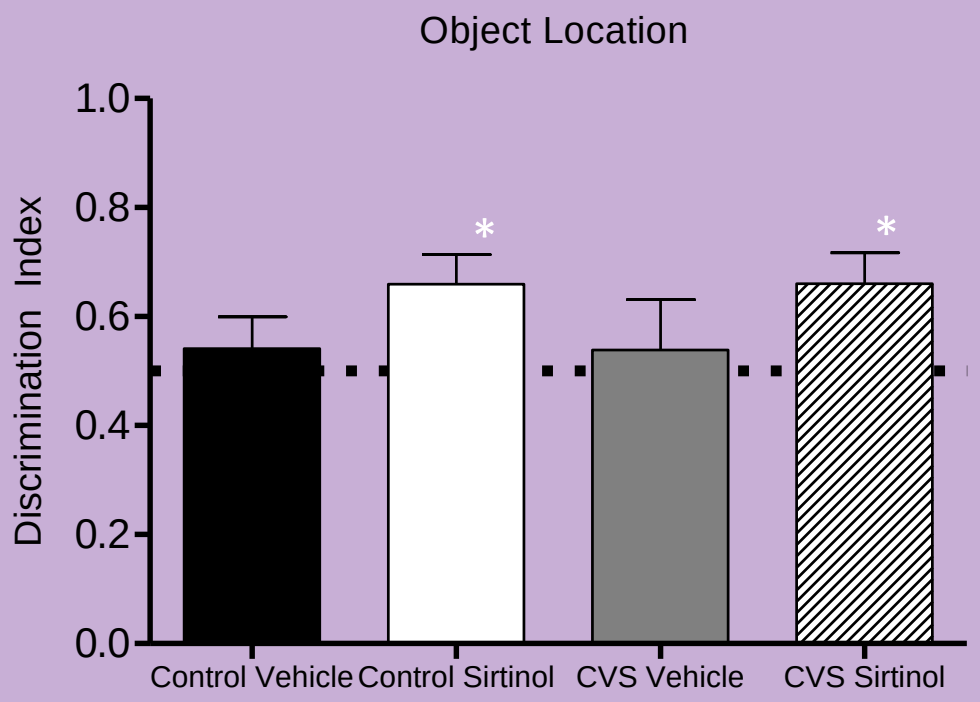
Sirt1 inhibition reversed the memory deficit caused by CVS



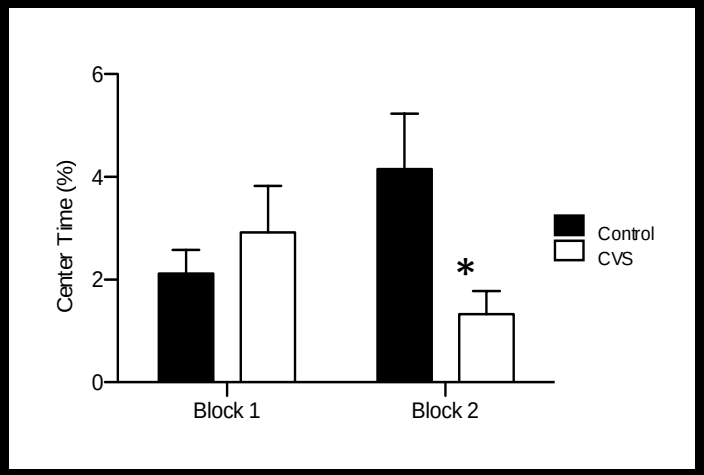


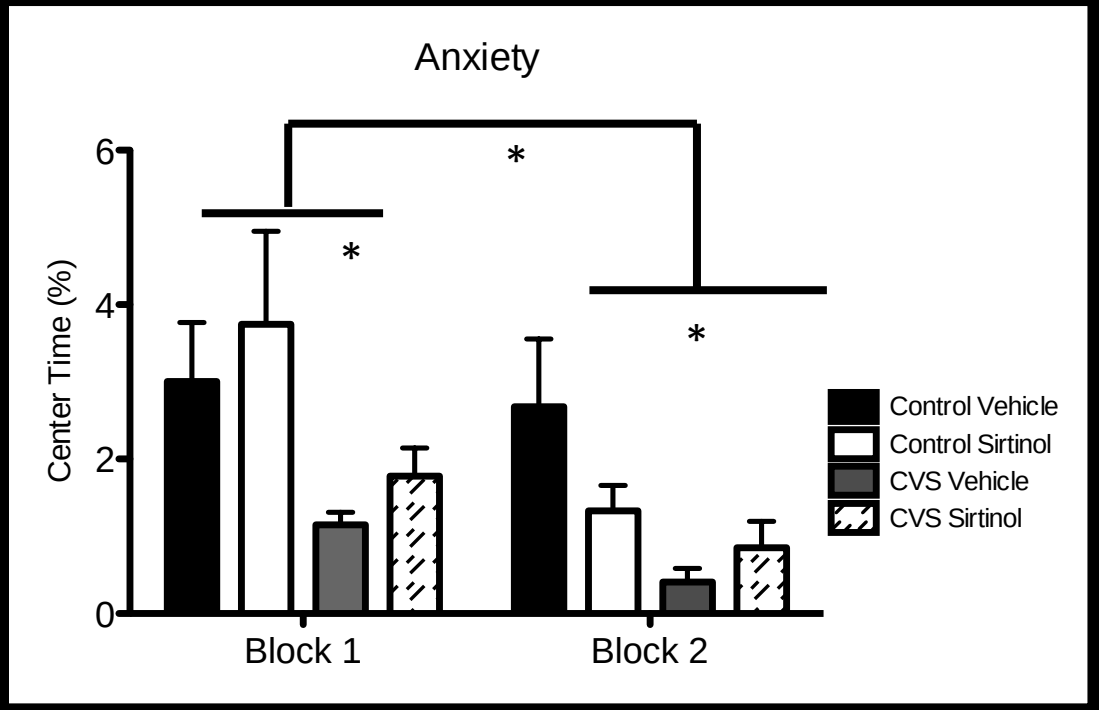
Sirt1 inhibition reversed the memory deficit caused by CVS





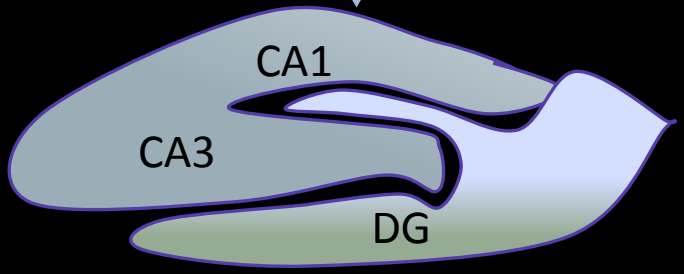
Sirt1 inhibition did not reverse the increased anxiety caused by CVS





STRESS

corticosterone



Sirt1 activity

Ac K12H4

ERK/MAPK

Bcl-2

Decreased hippocampus-dependent memory

Anhedonia

Paul Colombo, PhD

Brett East

Gary Dohanich PhD

Wayne Hawley, M.S.

Elin Grissom, M.S.

Chantelle Ferland

Nicole Theiler

Alex Buras

Emily Evans

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