

## **Efficacy of Fluoxetine and Resveratrol for Easing Memory and Mood Dysfunction in an Animal Model of Gulf War Illness**

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### **Gulf War Illness (GWI)**

#### ***Affected Population***

~33% of 700,000 Veterans who served in the 1991 Persian Gulf War-1 (PGW-1)

#### ***Symptoms***

Chronic multi-symptom health problem with multiple CNS impairments:

Learning and memory impairments  
Depression and anxiety  
Sleep problems  
Pain etc.

#### ***Potential Causes***

- (1) Intake of pyridostigmine bromide (PB)
- (2) Exposure to Pesticides such as DEET or permethrin (PM)
- (3) Low-level exposure to nerve gas agents, exposure to oil well fire smoke etc.

#### ***Multiple chemical exposure hypothesis***

*Emerged as one of the most likely causes of GWI*

*Concurrent exposure to chemicals PB, DEET and PM (with or without stress)*

## Rat Model of Gulf War Illness (GWI)

Generated through exposing rats to low doses of PB (1.3 mg/Kg), DEET (40mg/Kg), permethrin (0.13 mg/Kg) with or without 5 minutes of restraint stress for four weeks

### Pathophysiology

*Cognitive and Mood Dysfunction associated with Hippocampus pathology*

*Decreased levels of hippocampus neurogenesis – one of the substrates important for cognitive and mood function*

*Partial loss of hippocampal principal neurons*

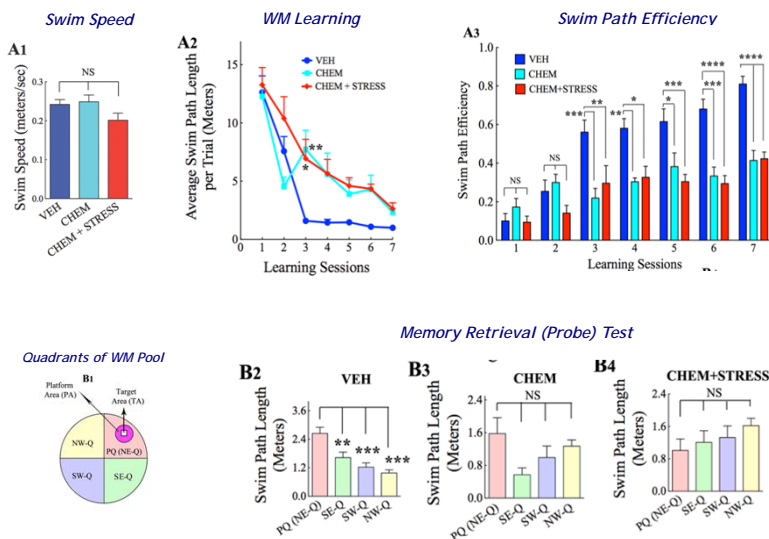
*Mild inflammation (reactive astrocytes and activated microglia)*

*Oxidative Stress*

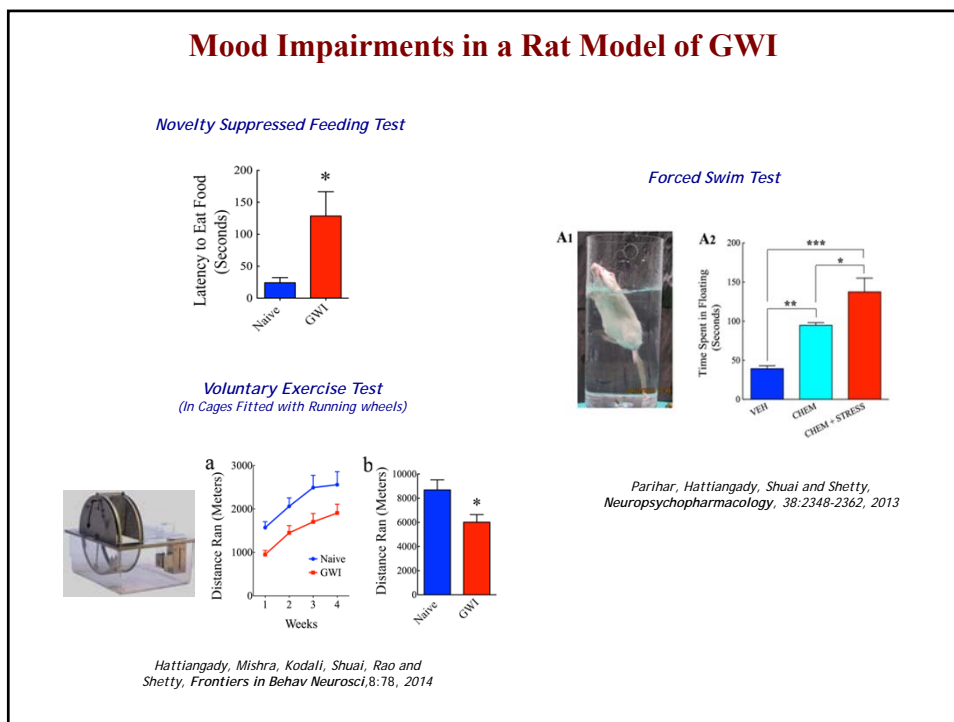
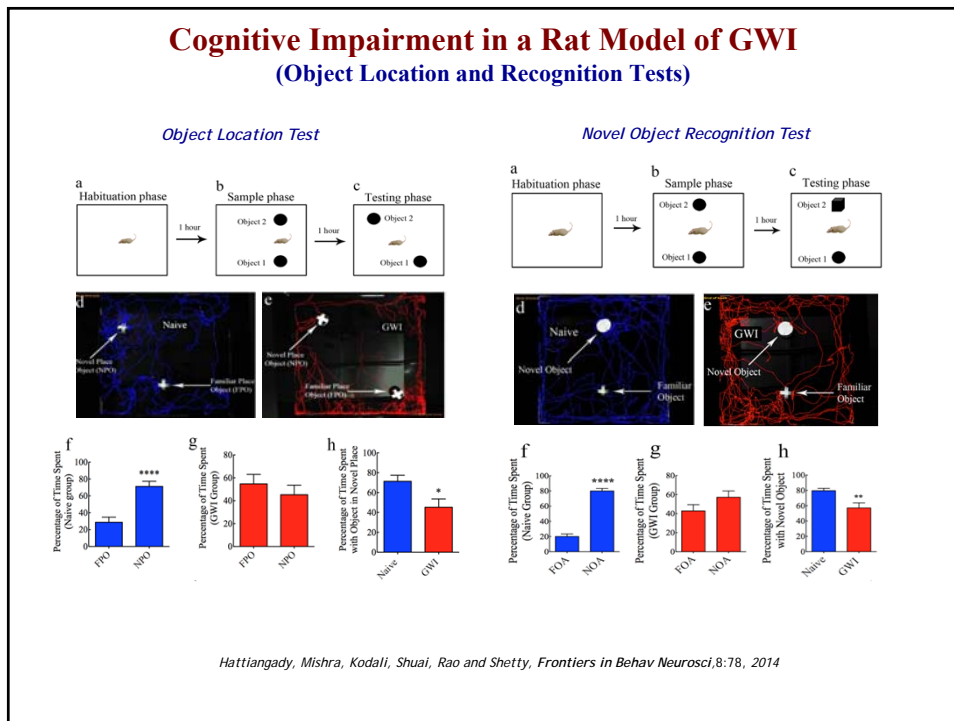
### Therapeutic Strategies Examined

*Administration of antidepressant Fluoxetine or an anti-inflammatory and antioxidant compound Resveratrol*

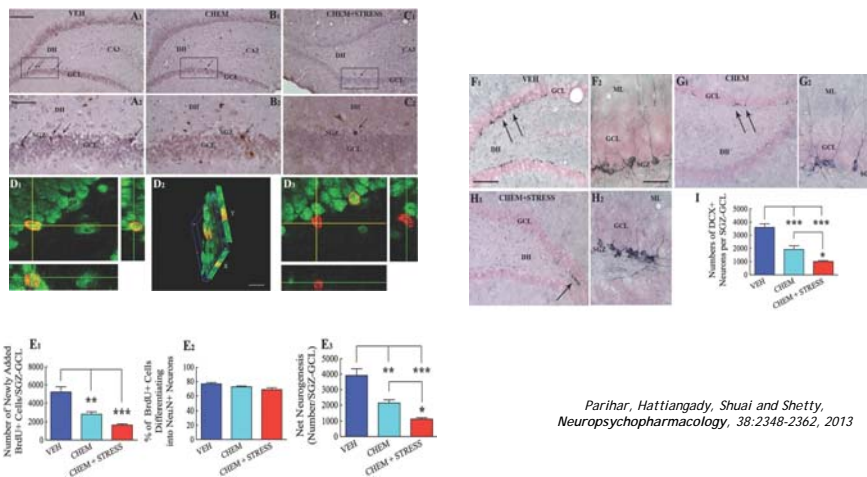
## Cognitive Impairment in a Rat Model of GWI (Water Maze Test)



Parihar, Hattiangady, Shuai and Shetty, *Neuropsychopharmacology*, 38:2348-2362, 2013

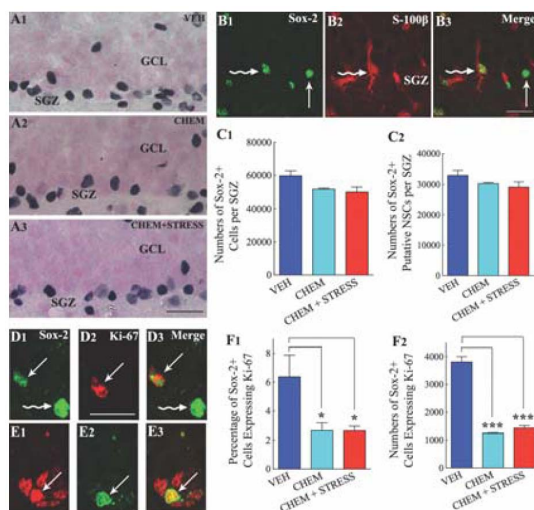


### Hippocampus Neurogenesis Impairments in a Rat Model of GWI



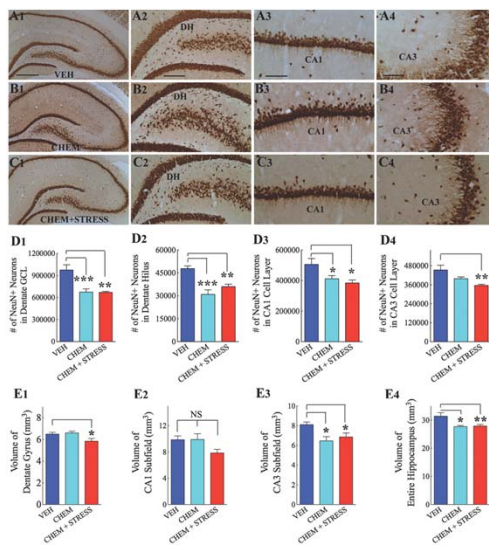
Parihar, Hattiangady, Shuai and Shetty, *Neuropsychopharmacology*, 38:2348-2362, 2013

### Stem Cell Proliferation Impairments in a Rat Model of GWI



Parihar, Hattiangady, Shuai and Shetty, *Neuropsychopharmacology*, 38, :2348-2362, 2013

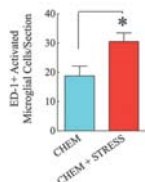
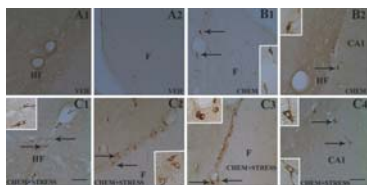
## Hippocampal Neuron Loss in a Rat Model of GWI



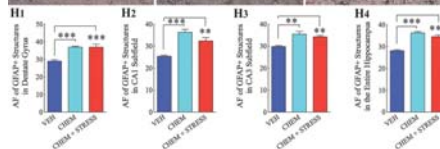
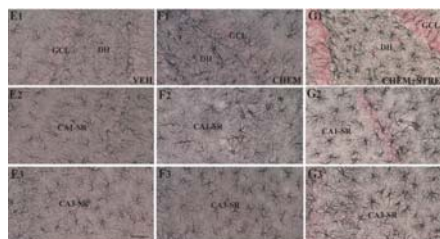
Parihar, Hattiangady, Shuai and Shetty, *Neuropsychopharmacology*, 38, :2348-2362, 2013

## Reactive Glial Cells in a Rat Model of GWI

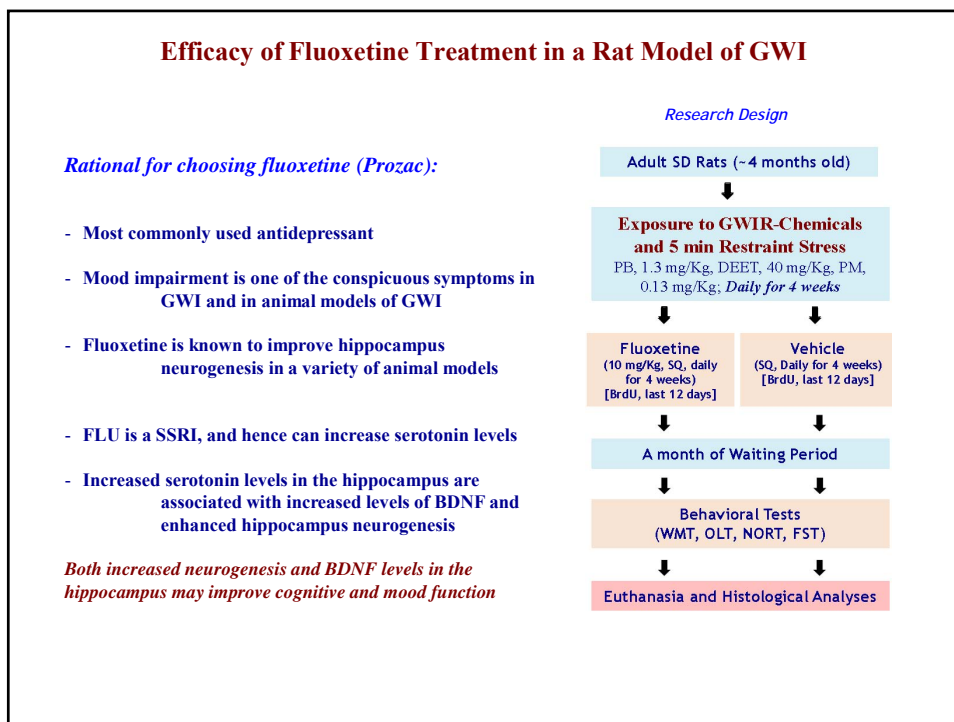
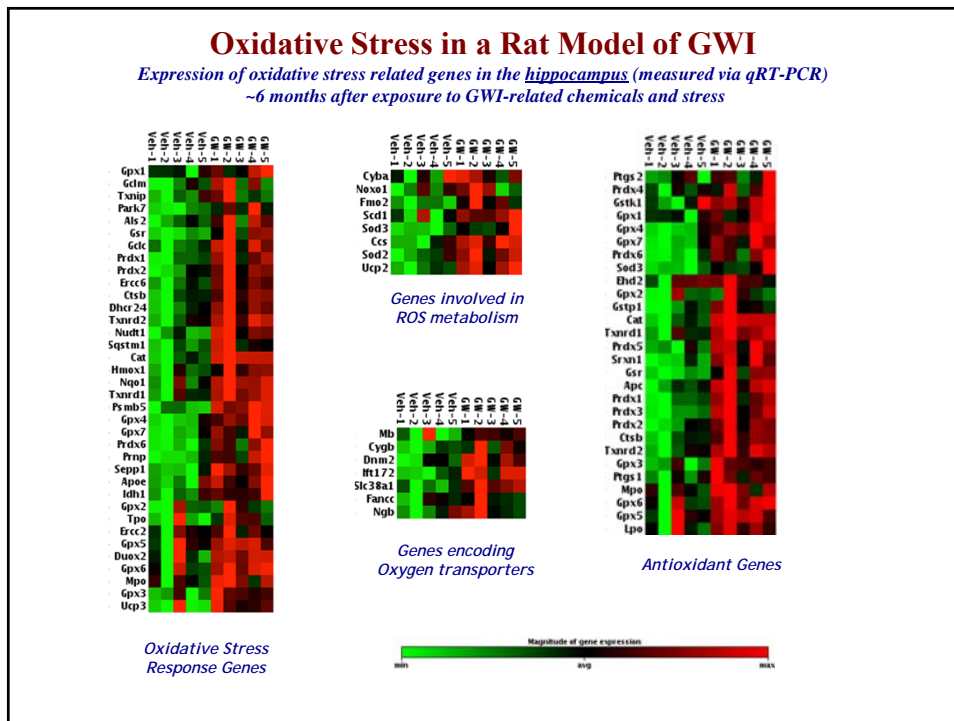
### Activated Microglia (ED-1+)

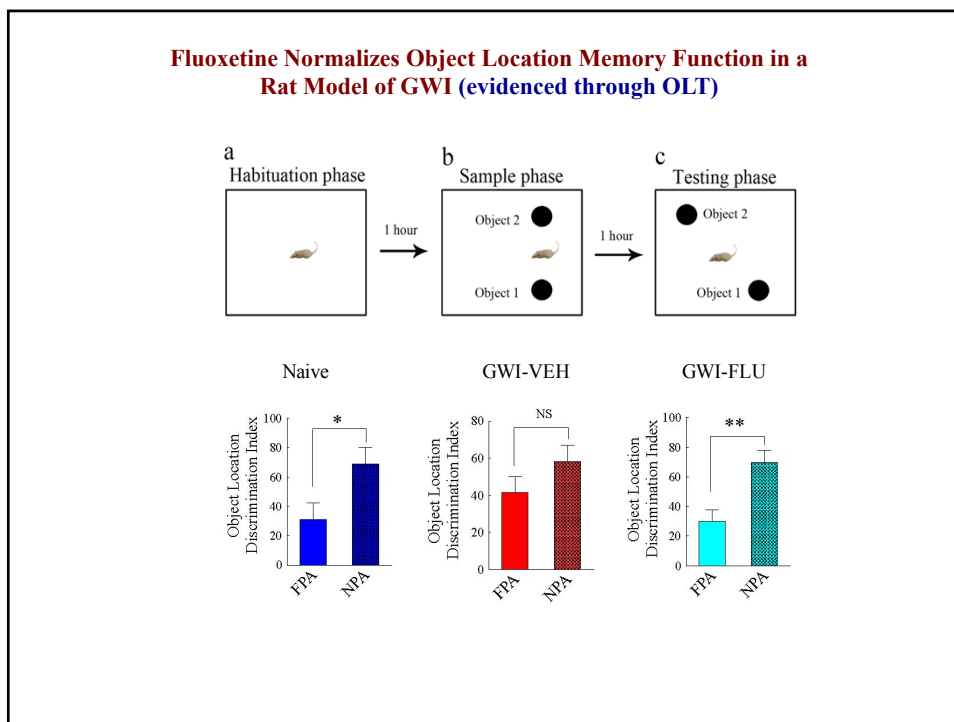
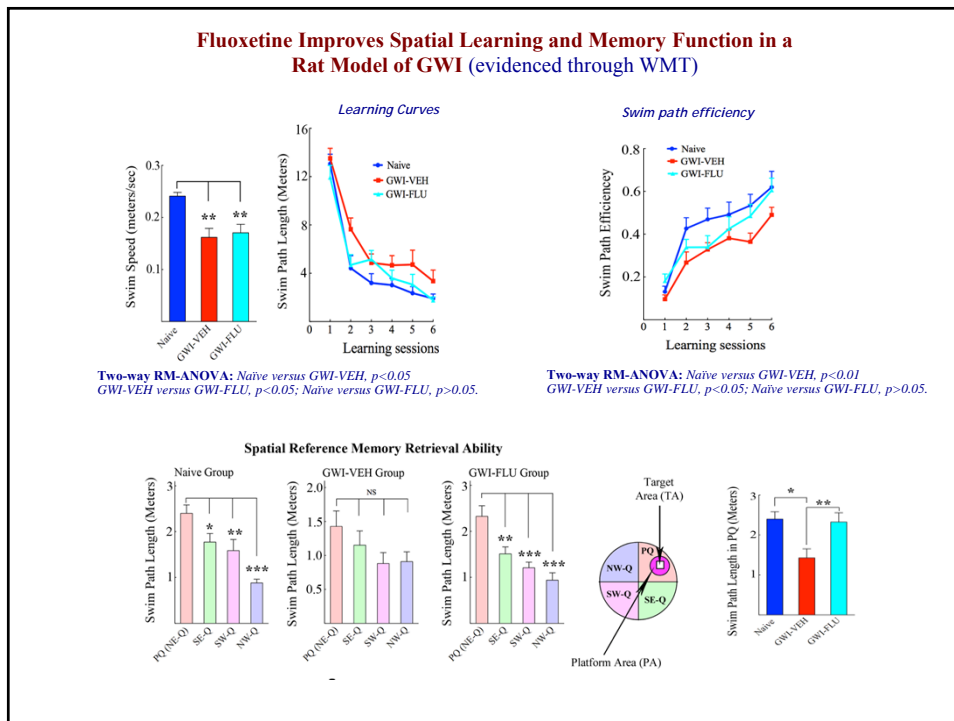


### Reactive Astrocytes

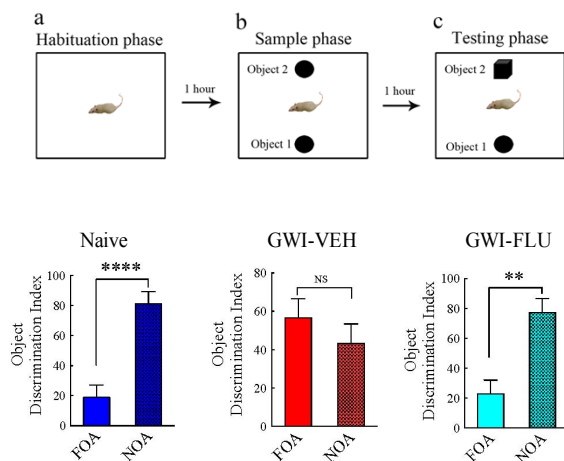


Parihar, Hattiangady, Shuai and Shetty, *Neuropsychopharmacology*, 38, :2348-2362, 2013

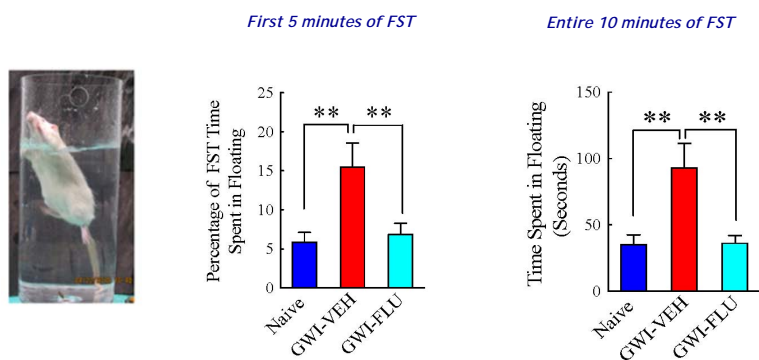




**Fluoxetine Normalizes Novel Object Recognition Memory Function in a Rat Model of GWI (evidenced through NORT)**

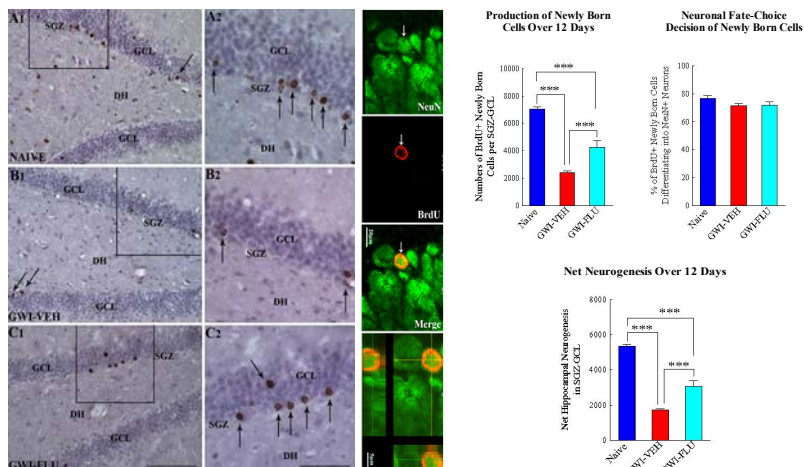


**Fluoxetine Reduces Depressive-like Behavior in a Rat Model of GWI (evidenced through FST)**

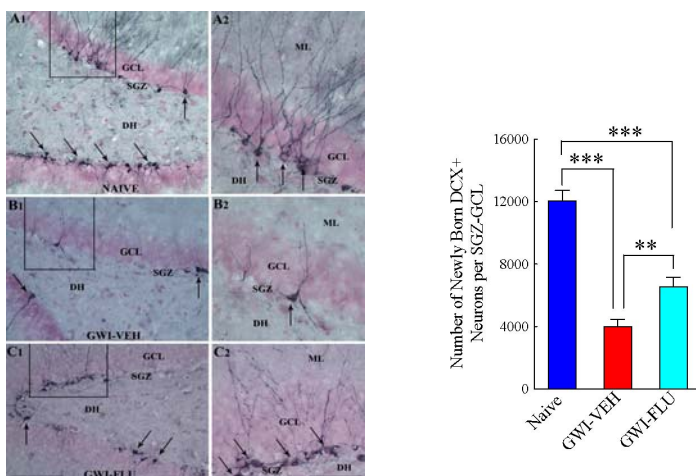




### Fluoxetine Improves Net Hippocampus neurogenesis in a Rat Model of GWI



### Fluoxetine Enhances the Generation of New Dentate Granule Cells (Doublecortin+ Cells in the Hippocampus) in a rat Model of GWI (Even after the termination of treatment)



### CONCLUSIONS

#### Efficacy of Fluoxetine for Easing Cognitive and Mood Dysfunction in GWI

Fluoxetine treatment to rats exposed to Gulf War Illness-related chemicals and stress:

- Normalizes hippocampus-dependent spatial learning and memory function
- Alleviates hippocampus-dependent object location memory dysfunction
- Normalizes novel object recognition memory function
- Eases mood dysfunction
- Enhances neurogenesis in the hippocampus

Considering the purported functions of hippocampal neurogenesis, increased neurogenesis at least partially underlies the beneficial effects mediated by fluoxetine

However, other mechanisms may be involved – need further studies!

### Efficacy of Resveratrol Treatment in a Rat Model of GWI

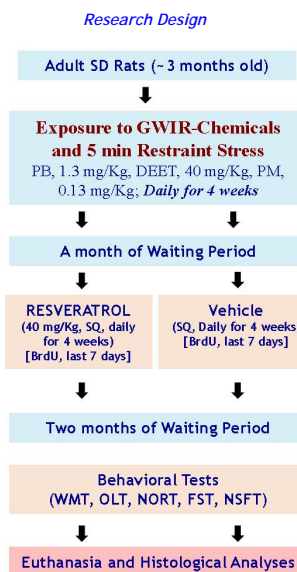
Resveratrol (RESV), a naturally occurring polyphenol found in skin of red grapes, red wine and some nuts

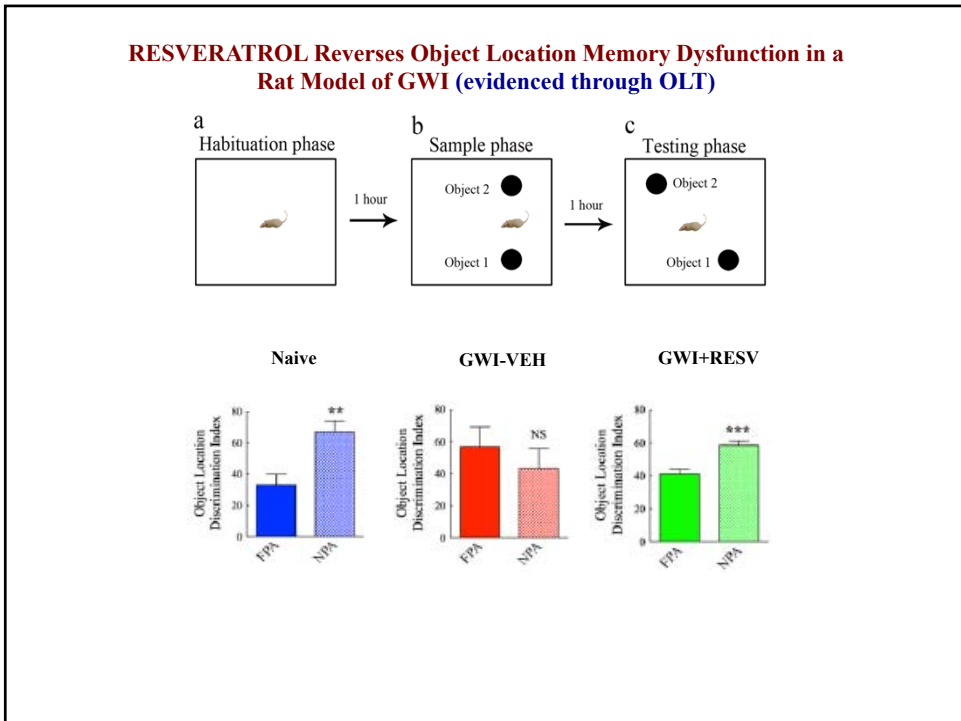
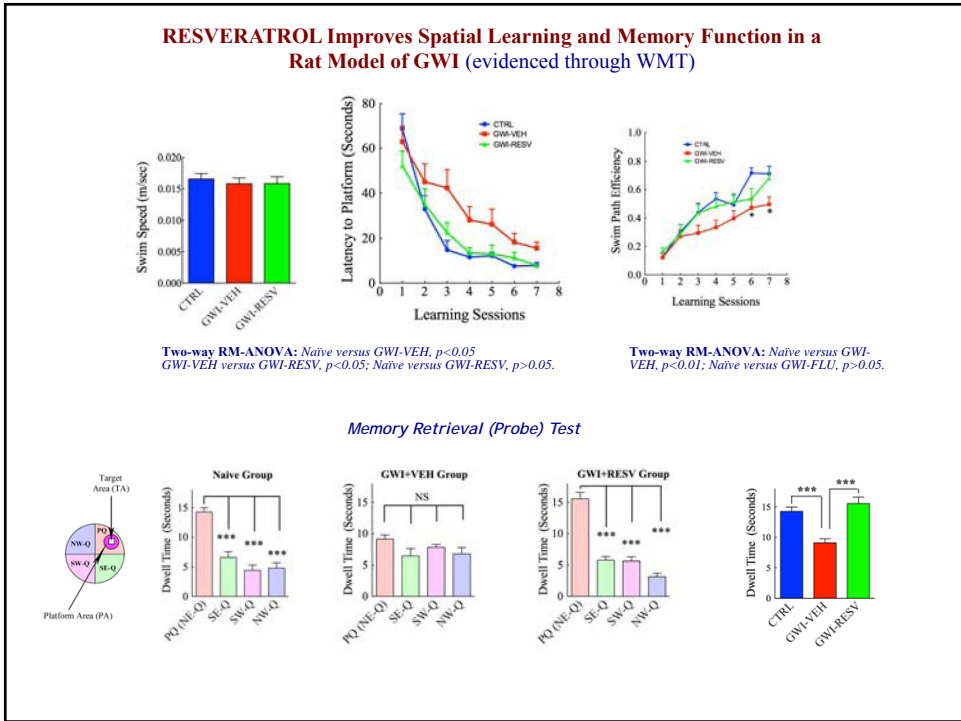
#### Rational for choosing Resveratrol:

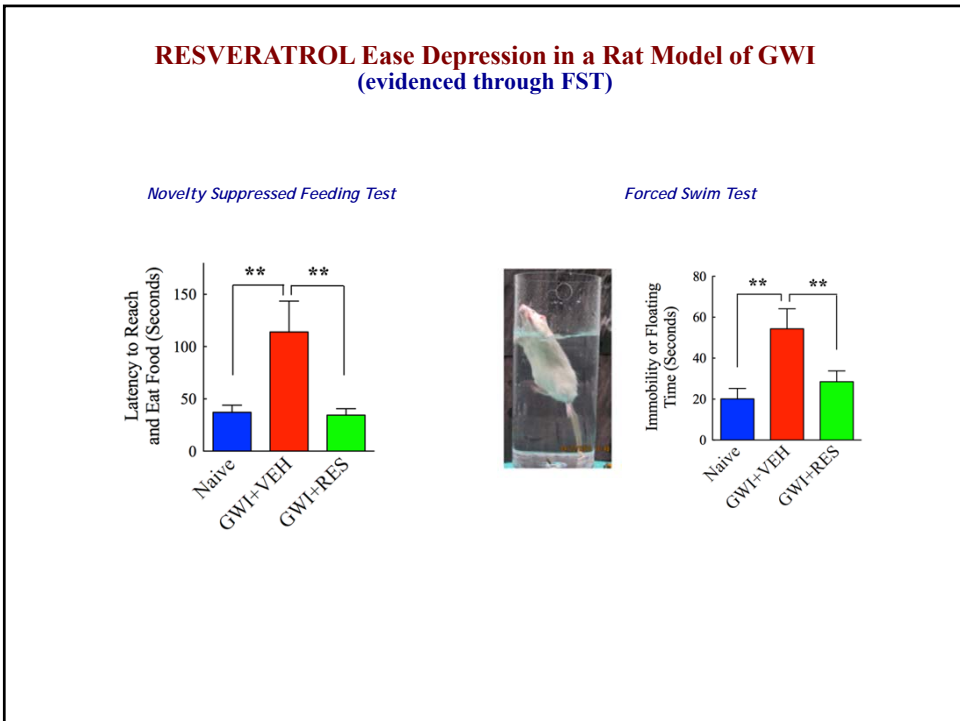
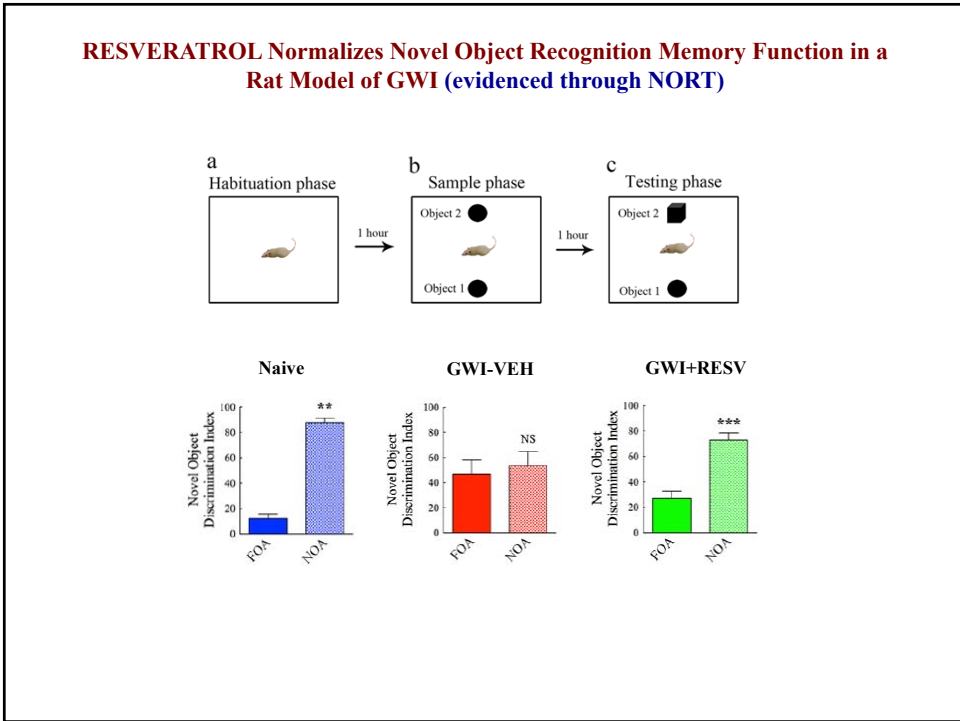
RESV has the ability for:

- Up-regulating SIRT1 (a longevity gene vital for maintenance of normal cognitive function and synaptic plasticity)
- Modulating inflammation
- Reducing Oxidative Stress

As our animal model of GWI exhibits inflammation as well as oxidative stress in the hippocampus, RESV appeared appropriate for easing symptoms of GWI.

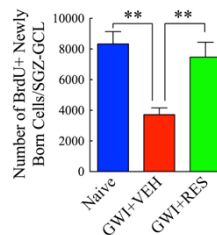
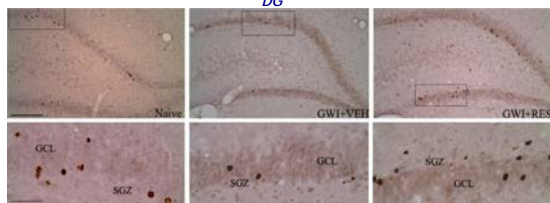




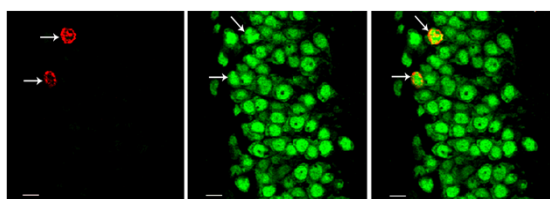


### RESVERATROL Improves Net Hippocampus Neurogenesis in a Rat Model of GWI

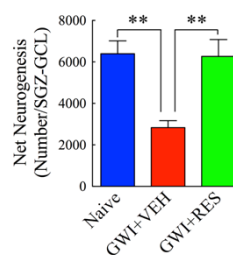
Newly Born Cells (BrdU+) in the DG



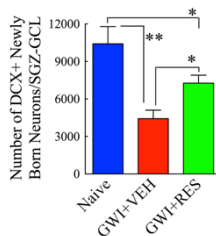
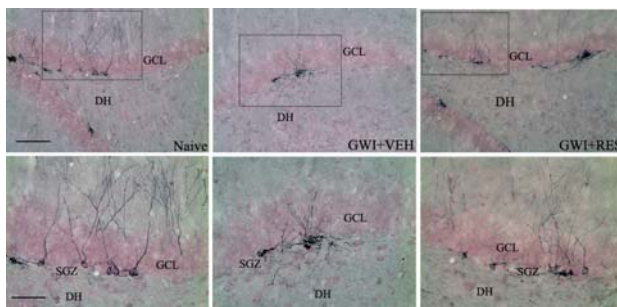
Newly Born neurons that mature into NeuN+ dentate granule cells

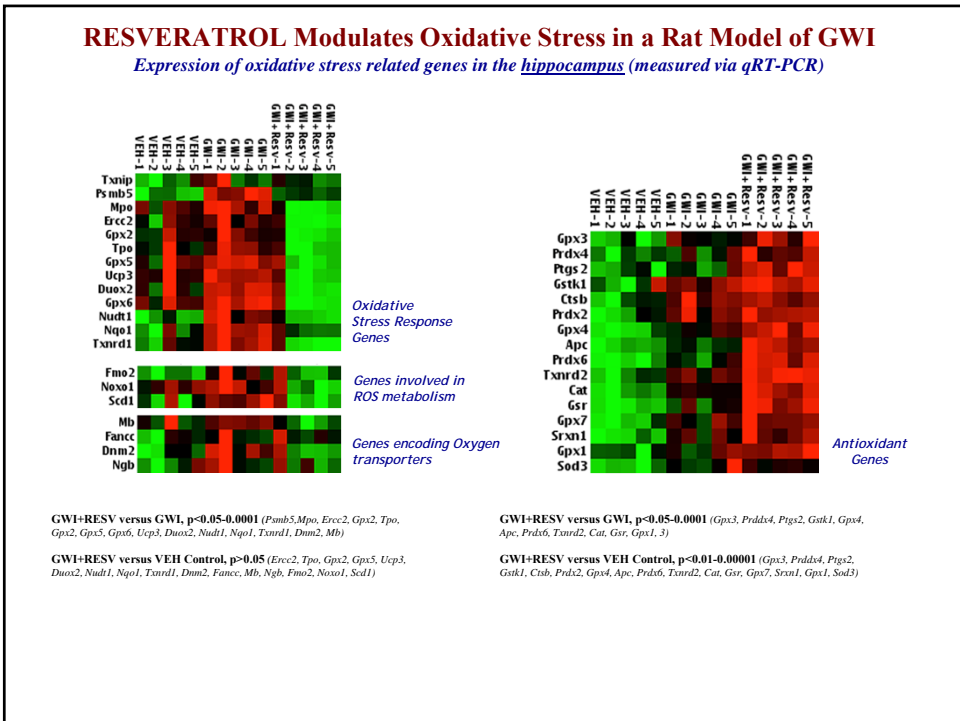
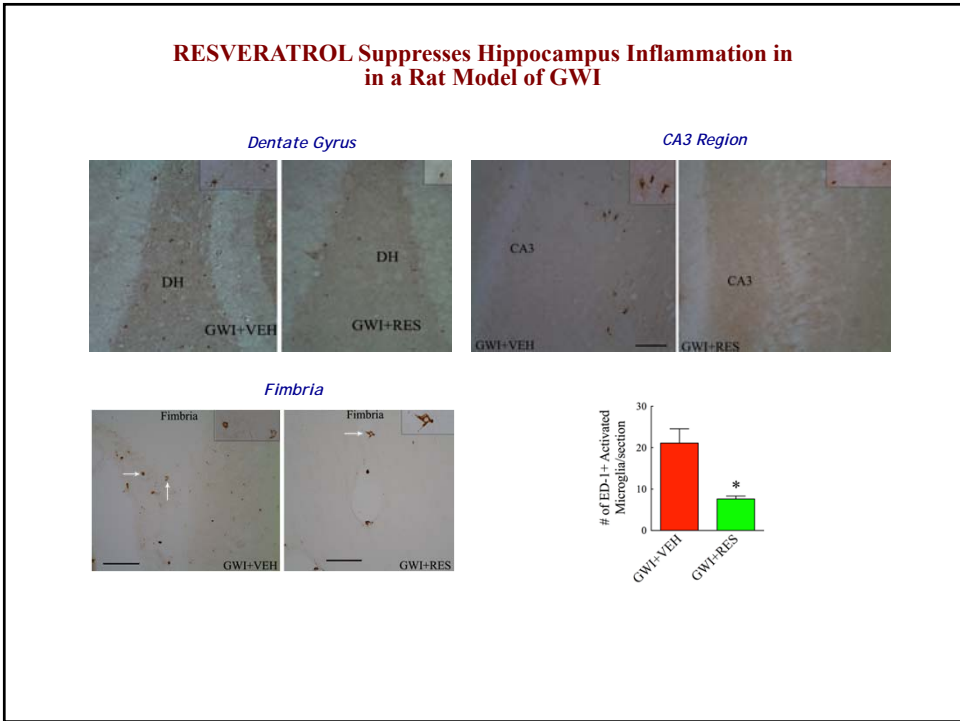


Net Hippocampus Neurogenesis



### RESVERATROL Enhances the Generation of New Dentate Granule Cells in a rat Model of GWI (even after the termination of treatment)





## CONCLUSIONS

### Efficacy of RESVERATROL for Improving Cognitive and Mood Function in GWI

#### Resveratrol treatment to rats exposed to Gulf War Illness-related chemicals and stress:

- Improves hippocampus-dependent spatial learning and memory function
- Relieves hippocampus-dependent object location memory dysfunction
- Normalizes novel object recognition memory function

-Reverses mood dysfunction

- Increases neurogenesis in the hippocampus
- Suppresses inflammation in the hippocampus
- Modulates oxidative stress in the hippocampus

It is likely that improved neurogenesis, decreased levels of inflammation and oxidative stress mediated by Resveratrol contributed to the beneficial effects observed in this study

However, other mechanisms (e.g. activation of SIRT1) may also be involved – Need further studies!

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## Acknowledgements

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