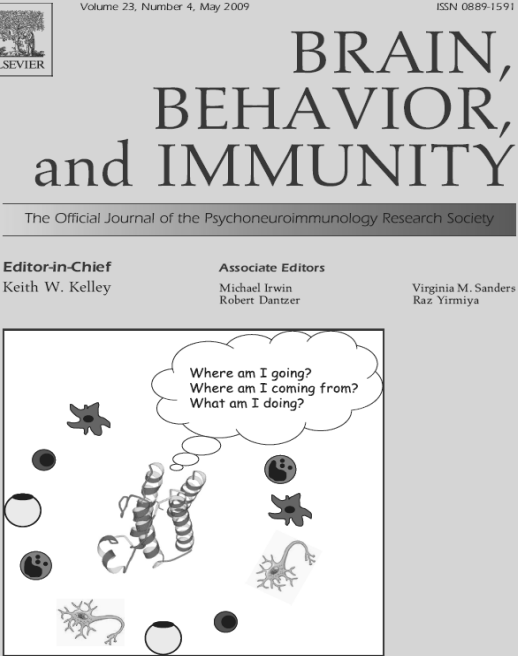


# The Role of Neuroinflammation in Chronic Illness

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**Integrative Immunology and Behavior Program**



Volume 23, Number 4, May 2009 ISSN 0889-1591

**BRAIN,  
BEHAVIOR,  
and IMMUNITY**

The Official Journal of the Psychoneuroimmunology Research Society

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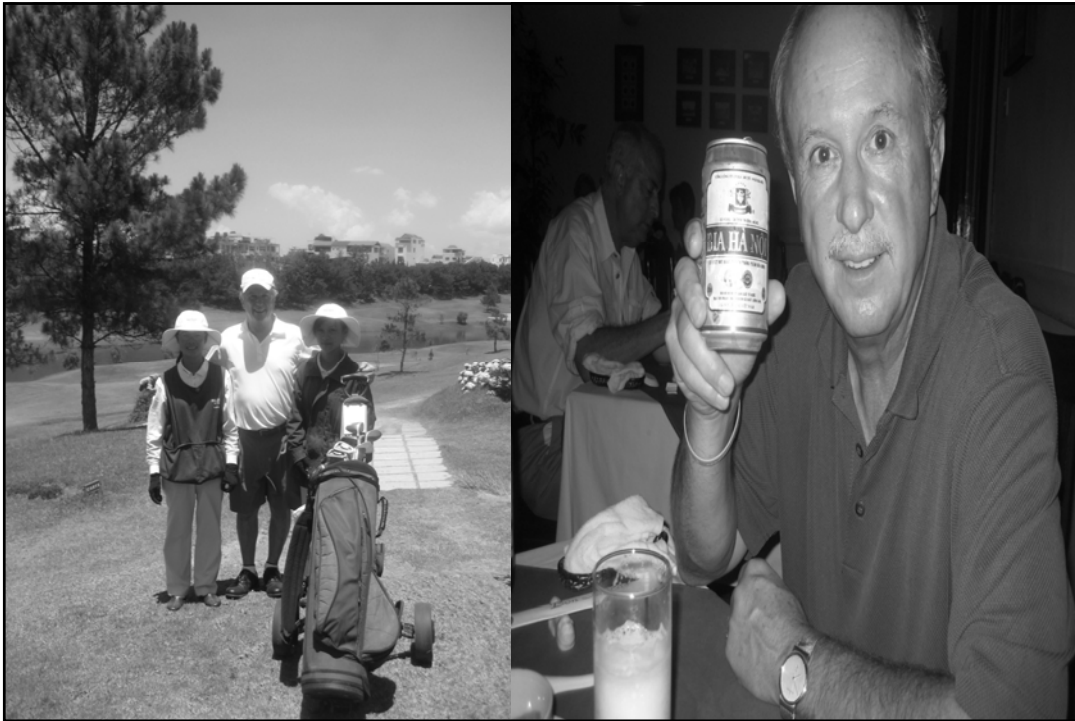
Where am I going?  
Where am I coming from?  
What am I doing?

“...international, interdisciplinary journal devoted to investigation of the physiological systems that integrate behavioral and immunological responses.”

## Why Am I Here at the Research Advisory Committee on Gulf War Veterans' Illness?

<u>Question</u>	<u>Answer</u>
- I enjoy flying through Chicago O'Hare?	No
- I like to ride the Blue Line of the Boston Subway?	No
- I like to eat shell fish?	No
- I have nothing better to do?	Maybe
- I like to have dinner with a former post-doc at Harvard?	Yes
- I have published some stuff on neuroinflammation?	Yes





## **Summary of Research Advisory Committee on GWI, November 3, 2008**

“Since 1994, ..expenditures of \$440 million as GWI research.”

“The biological basis for GWI is unknown, and there is no efficacious treatment.”

“GWI research effort has yet to provide tangible results... Few treatments have been studied and none have been shown to provide significant benefit for...ill veterans.”

“The 200,000 veterans with GWI complain of diffuse pain, headaches, difficulties in learning and memory, mood changes and unrelenting fatigue.”

## **What do I Want you to Remember?**

### **Hypothesis from RAC Report:**

“...neurotoxic Gulf War exposures may activate inflammatory processes in the brain and that increased brain levels of proinflammatory cytokines can produce a complex of multiple symptoms similar to GWI.”

### **Take Home Message:**

Given the lack of treatments for GWI, the neuroinflammation hypothesis is worth testing because FDA-approved drugs to reduce neuroinflammation and pre-clinical animal research models are available.

## **Minimal Requirements for Neuroinflammation**

- Microglial activation (ramified to amoeboid, MHC-II, NF $\kappa$ B)
- Pro- and anti-inflammatory cytokine synthesis
- Cox-1 & -2, iNOS
- Activation by peripheral immune signals
- No neutrophil or monocyte recruitment
- Neuronal dysfunction that does not require neuronal death
- Behavioral changes

## **The Experience of Just Being Sick:**

**Why do we feel sick and behave in a sick way when we are ill?**

## **VIEWPOINT**

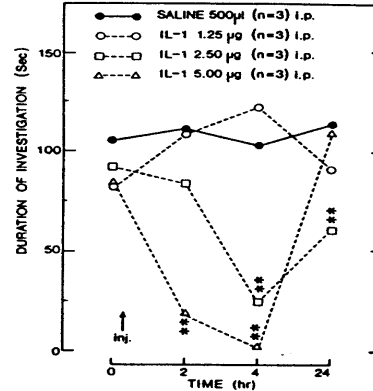
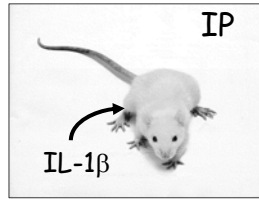
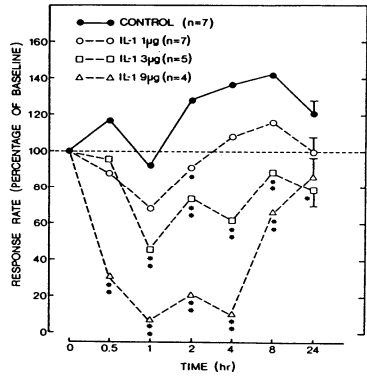
### **Sickness behavior as a new target for drug development**

Stephen Kent, Rose-Marie Bluthé, Keith W. Kelley and Robert Dantzer

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*Sickness behavior refers to the nonspecific symptoms (anorexia, depressed activity, loss of interest in usual activities, disappearance of body-care activities) that accompany the response to infection. Increasing evidence suggests that these symptoms are part of an organized defense response to antigenic challenge and that they are mediated by the neural effects of cytokines such as interleukin 1. An understanding of the mechanisms involved in these effects should permit development of new drugs aimed at decreasing sickness or promoting recovery processes. (Kent et al, 1992, TIPS, 13:24)*

## Exogenous IL-1 into the Brain Causes Sickness Behaviors

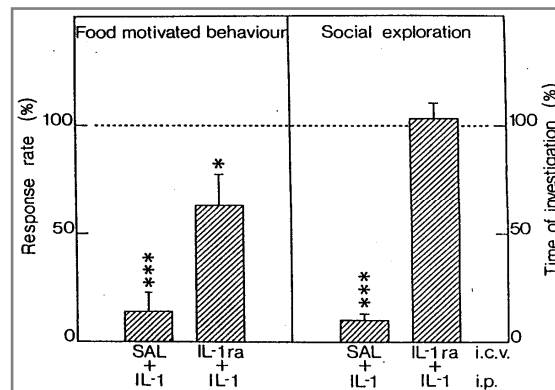
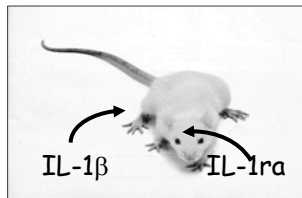


Operant responding for food  
 (Fixed ratio 10)

Social exploration of  
 a juvenile

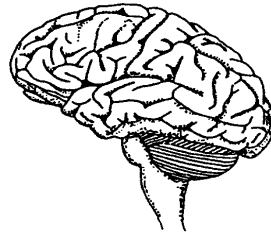
Kent et al, *Proc. Natl. Acad. Sci.* 1992, 89:9117

## The Sickness-Inducing Properties of Peripheral IL-1 are Mediated Centrally

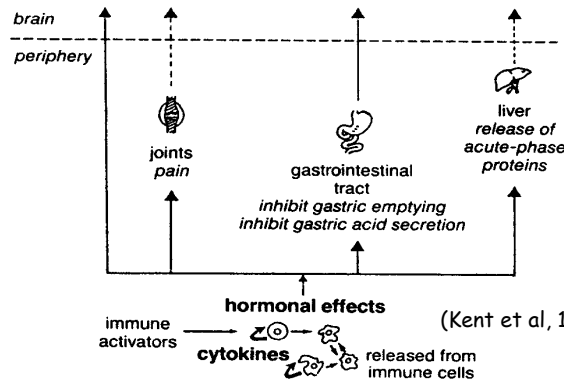


Kent et al, *Proc. Natl. Acad. Sci.* 1992, 89:9117

## Cytokines in the Periphery Act in the Brain

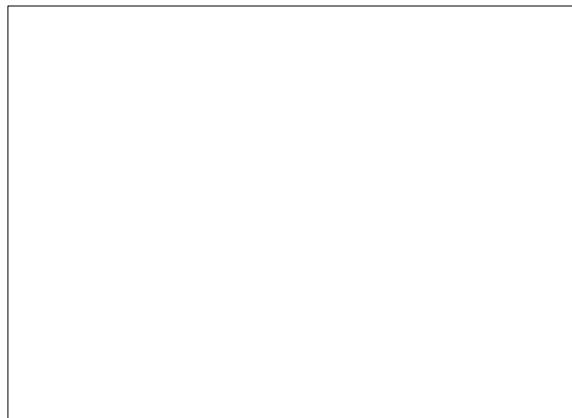
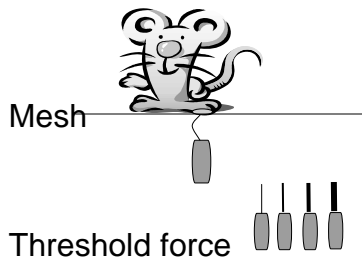


- central effects**
- activate pituitary-adrenal axis
  - ↑ thermogenesis
  - ↑ body temperature
  - ↑ slow-wave sleep
  - sickness behavior
    - ↓ body-care activities
    - malaise
    - ↓ locomotor activity
    - ↓ social exploration
    - ↓ food intake
    - ↓ food-motivated behavior



## Measurement of pain sensitivity

Mechanical sensitivity  
Von Frey test

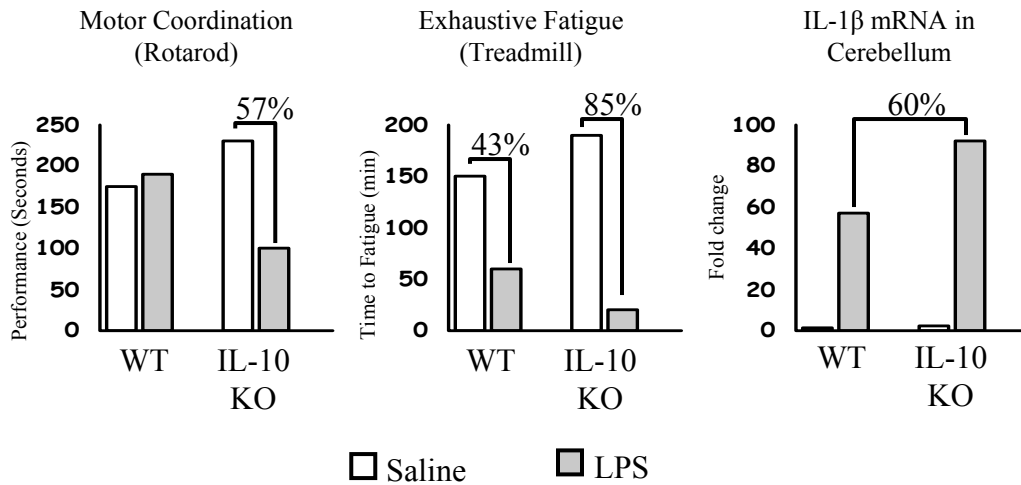


## "Fatigue: See How They Run, See How They Run"

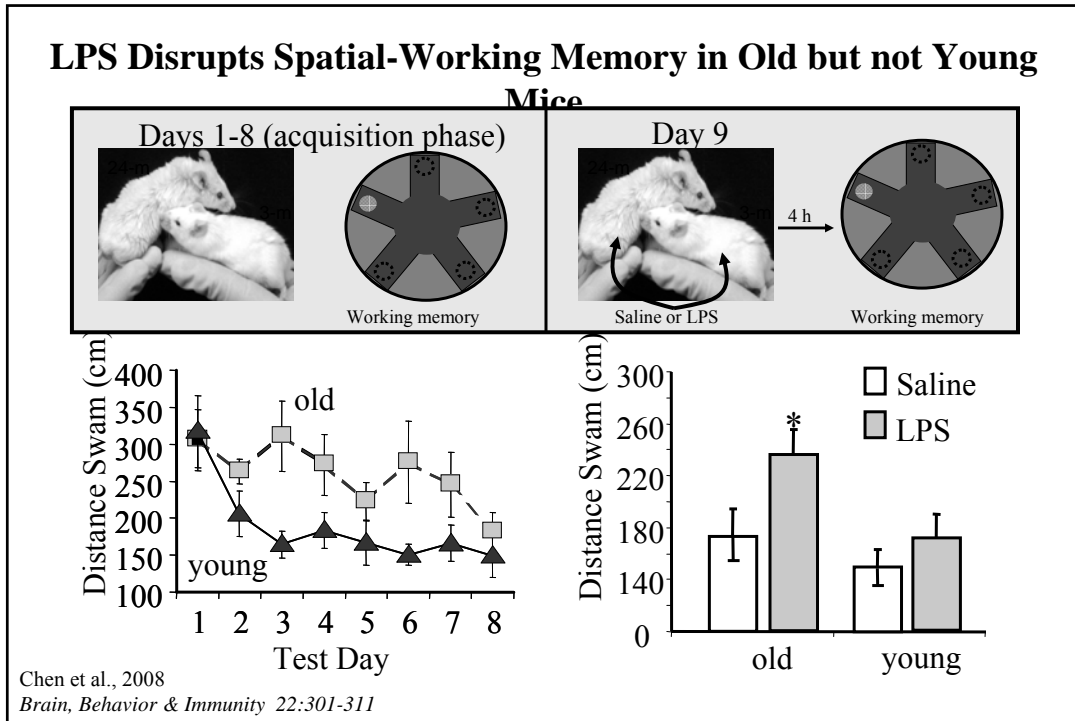


They are not blind, just blinded from view due to HIPAA!

## Fatigue and Deficits in Motor Coordination Induced by LPS are Exacerbated in IL-10 Knockout Mice





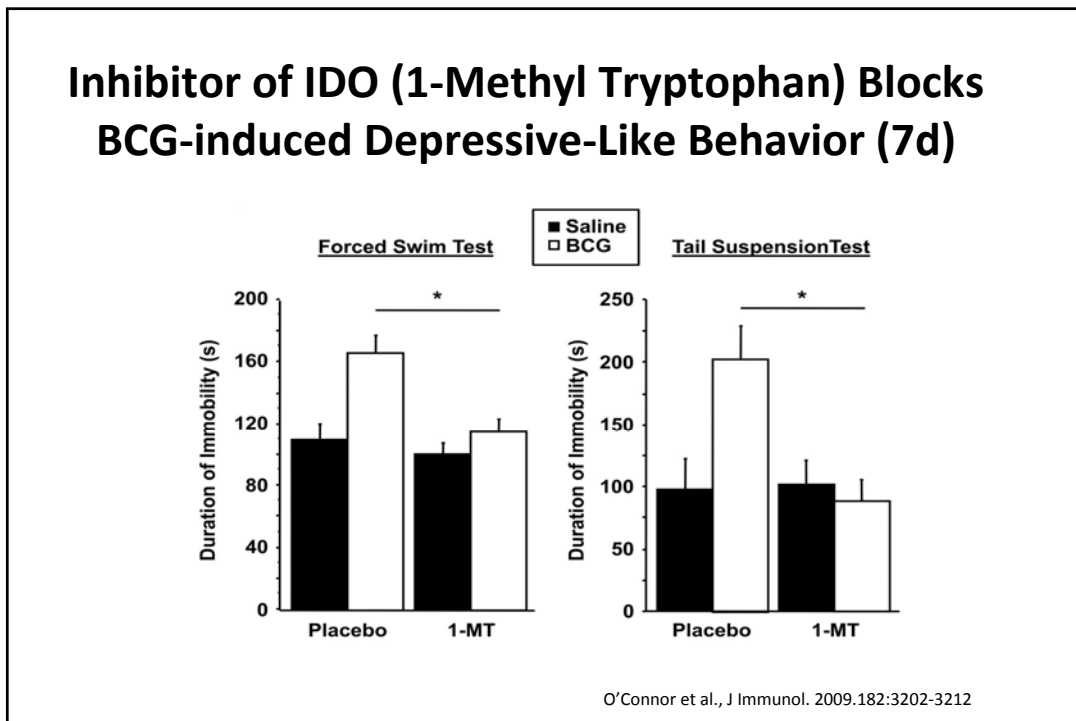
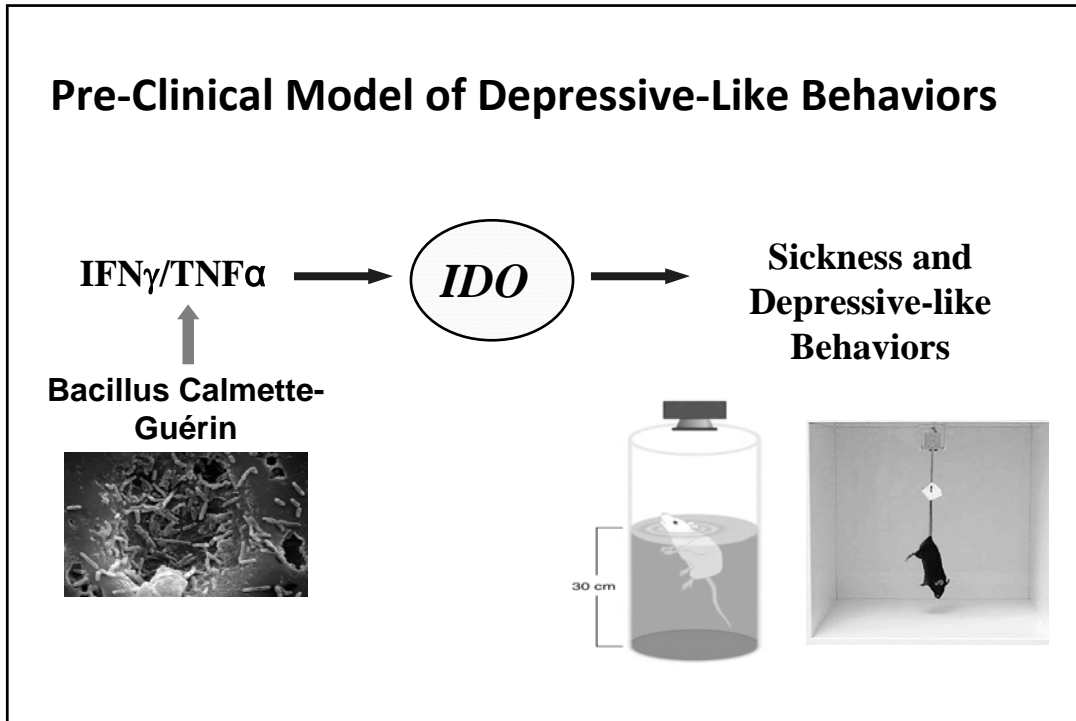


#### Major Depressive Episode (DSM-IV)

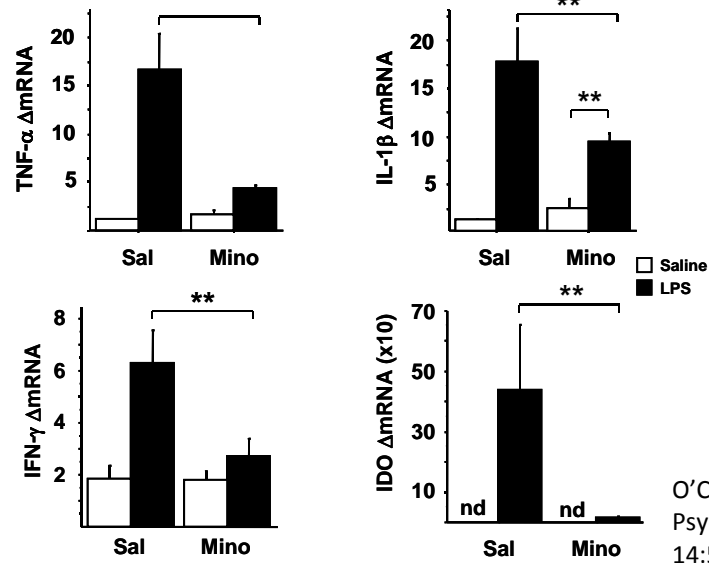
- Depressed mood
- Loss of interest / anhedonia
- Decreased concentration
- Worthlessness or guilt
- Suicidal thoughts
- Insomnia / hypersomnia
- Changes in appetite / weight
- Agitation / slowing
- Fatigue / anergia

#### Sickness Behavior

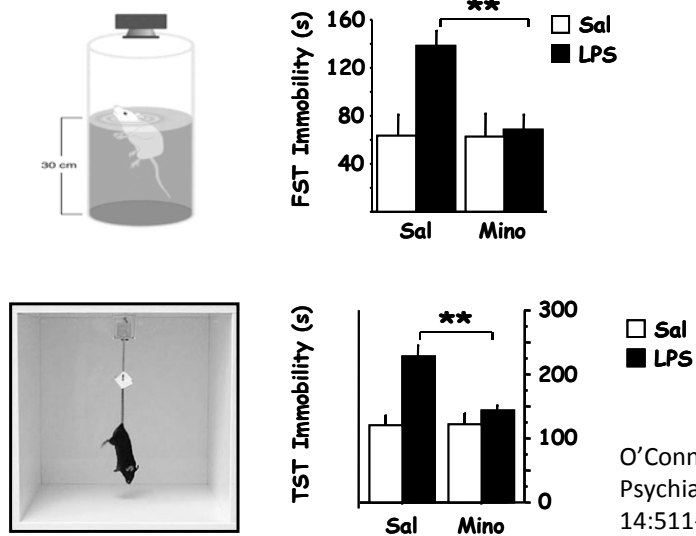
- ?
- Loss of interest / anhedonia
- Cognitive disturbances
- ?
- ?
- Altered sleep pattern
- Anorexia
- Reduced locomotor activity
- Lethargy

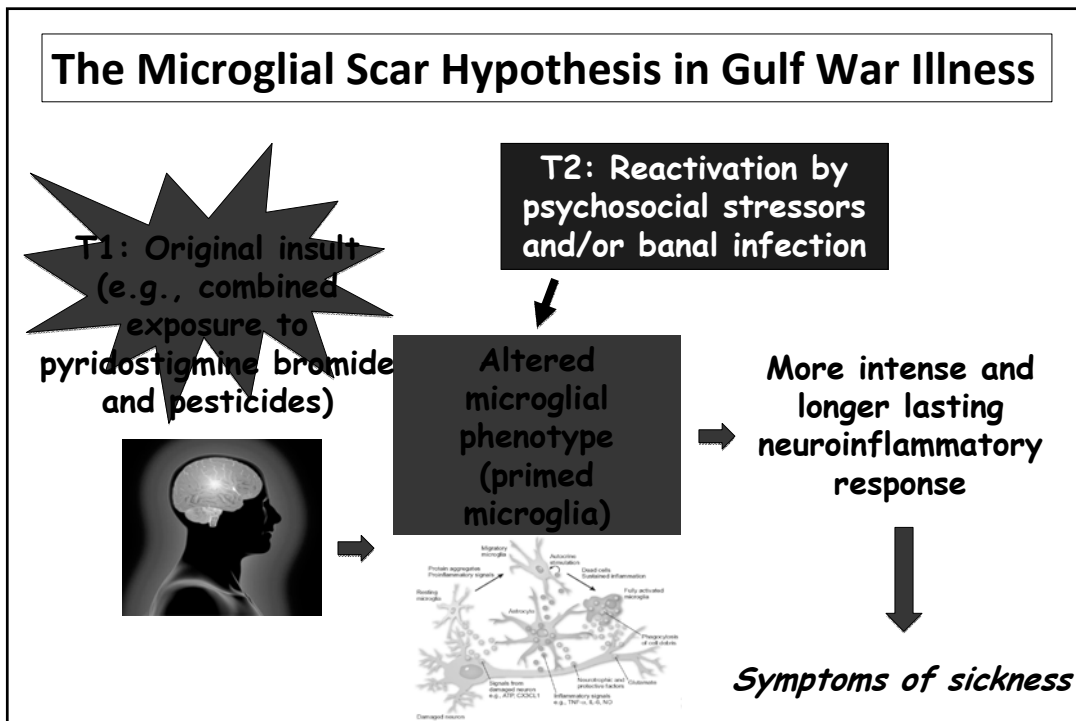
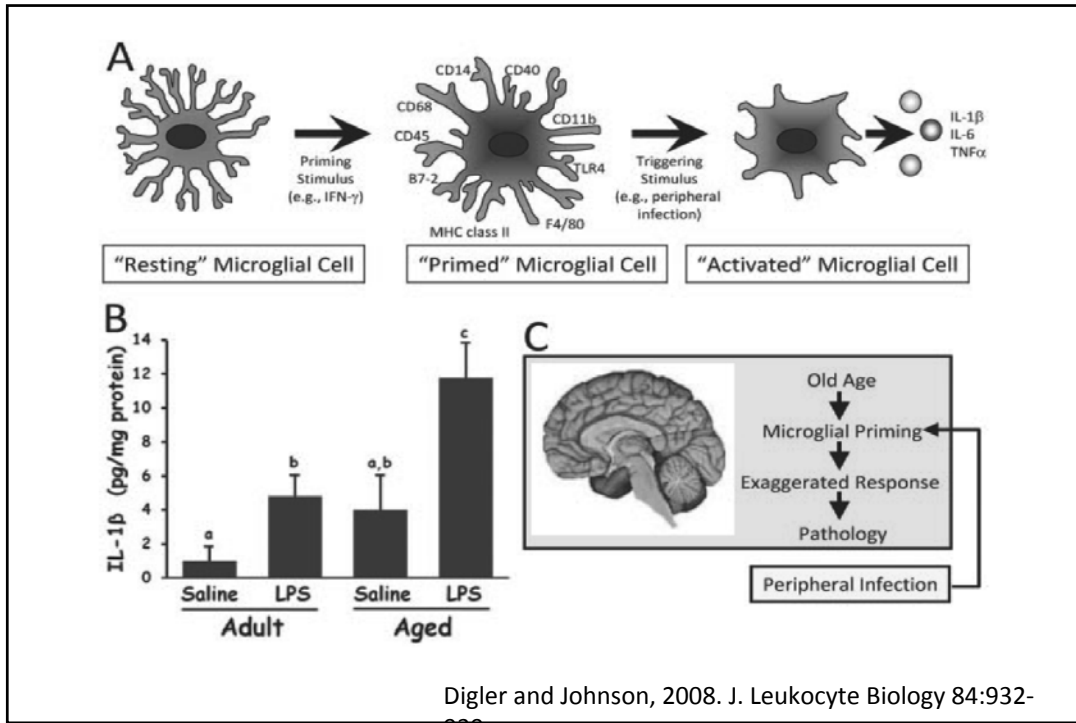


## Minocycline Reduces LPS-Induced Pro-inflammatory Cytokines in the Brain



## Minocycline Blocks Induction of LPS-Induced Depressive-like Behaviors





## Potential Existing FDA-Approved Approaches for Neuroinflammation in Gulf War Illness

- Antibiotics (Minocycline)
- New Drugs for Fibromyalgia (e.g., SNRI milnacipran)
- Botanicals (turmeric, resveratrol, luteolin)
- HMG-CoA reductase inhibitors (statins)
- Diet - Soluble Fiber like Pectin
- IDO Inhibitors now in Phase I clinical trials
- Exercise

## **Summary** **Neuroinflammation in Pre-Clinical** **Animal Models**

- Reduces Appetite and Motivation
- Increases Exhaustive Fatigue (Mental Fatigue?)
- Increases Sensitivity to Pain
- Causes Deficits in Learning and Memory
- Induces Depressive-Like Behaviors

## What do I Want you to Remember?

### Hypothesis from RAC Report:

“...neurotoxic Gulf War exposures may activate inflammatory processes in the brain and that increased brain levels of proinflammatory cytokines can produce a complex of multiple symptoms similar to GWI.”

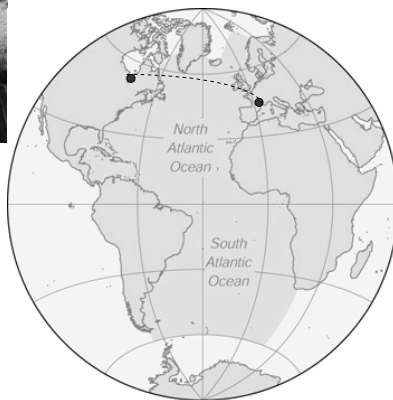
### Take Home Message:

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