Presentation 3 – Iris Bell

TIME-DEPENDENT SENSITIZATION IN CHEMICAL INTOLERANCE AND GULF WAR ILLNESSES

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Chemical Odor Intolerance

- negative hedonic response in the host
- illness symptoms from low levels of chemicals tolerated by most people
  - headache
  - nausea
  - difficulty concentrating
  - dizziness

Prevalence of Chemical Intolerance

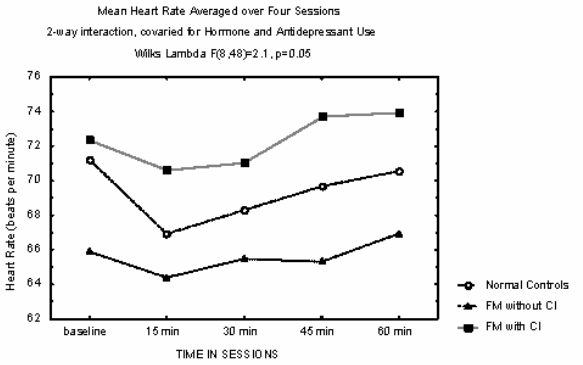
- *15-30%* of general population, mild, usually without disability
- *4-6%* of general population, MCS, severe, usually with disability

Rates of Worsened Symptoms from Environmental Chemicals

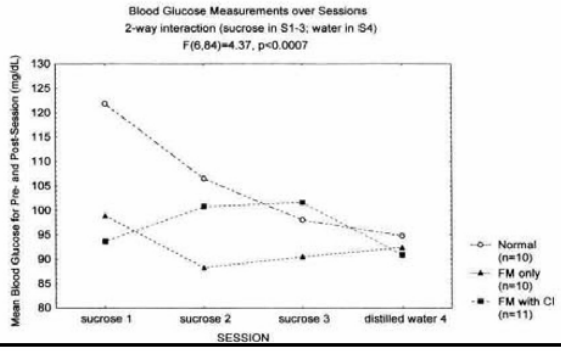
(Buchwald & Garrity 1994)

	CFS	FM	MCS
pollution/ exhaust	53%	60%	97%
cigarette smoke	57%	64%	87%
gas/paint/ solvent fumes	67%	67%	97%
perfumes	57%	46%	90%

Chemical Intolerance Modifies Heart Rate Physiology of Fibromyalgia *(Bell et al, 2001)*



Chemical Intolerance Modifies Blood Glucose Response to Sucrose Ingestion over Time in Fibromyalgia *(Bell et al, 2001)*



Medical Comorbidities in Chemical Odor Intolerance

- ovarian cysts/breast cysts
- menstrual disorders
- migraine headache
- irritable bowel syndrome
- food intolerances
- sinusitis
- rhinitis

Family Histories in Chemical Odor Intolerant Individuals

- hypertension and heart disease
- diabetes mellitus
- rhinitis/"allergies"
- substance abuse, esp. paternal alcoholism

Phenomenology of Low Level Chemical Intolerance

- multiple symptoms in multiple systems
- different agents trigger similar symptoms in an individual patient (non-specificity)
- non-specific symptoms, with no clear relationship to toxicological properties of a specific chemical
- single symptom in all cases is "cacosmia," i.e., illness from low level chemicals with negative hedonic rxn

Representative Initiating & Eliciting Agents in Chemical Intolerance

Initiating	Eliciting
▪ solvents/VOCs	▪ solvents/VOCs
	▪ cleaning products
▪ pesticides	▪ pesticides
	▪ tobacco smoke
	▪ perfumes
	▪ automotive exhaust
	▪ natural gas
	▪ new carpet

Working Hypotheses

- Chemical odor intolerance is a manifestation of neural sensitization.
- Individuals high in chemical odor intolerance are especially sensitizable.
- The capacity to demonstrate sensitization in chemically intolerant persons requires proper experimental design (2 or more sessions).

Two Step Dynamical Process

Initiation

Elicitation

Neural Sensitization Definition

- neural sensitization is the progressive increase in the size of the host's response to repeated, intermittent exposures to an initially novel stimulus.
- animal model for multiple chemical sensitivity, chronic fibromyalgia pain, temporal lobe epilepsy, craving in drug addiction, PTSD, recurrent depression

Neurochemistry of Sensitization: Neural Plasticity

- Mesolimbic dopaminergic pathway - from ventral tegmental area to nucleus accumbens (reward pathway)
- Prefrontal dopaminergic pathways and limbic excitatory amino acid pathways modulate process

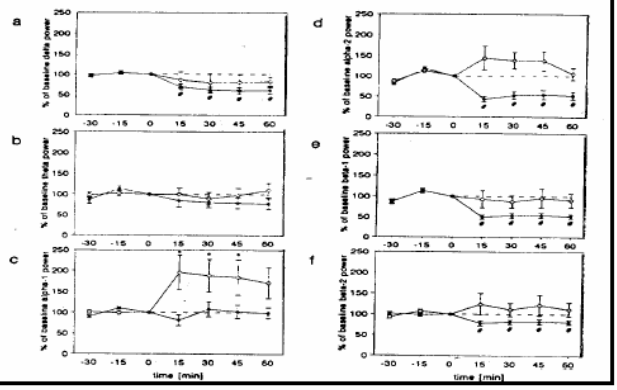
Animal Studies Showing Sensitization to Chemicals over Time

- formaldehyde (Sorg et al. 1996, 1998)
  - psychomotor activity to cocaine
- toluene, peppermint (Kay 1996)
  - limbic field potential 15-30 hertz activity
- toluene (vonEuler et al. 1994; Beyer et al 2001)
  - psychomotor activity to apomorphine, cocaine
- ethanol (Antelman et al. 1991; Grahame et al. 2000)
  - haloperidol-induced catalepsy
- lindane (Gilbert 1995)
  - electrical kindling of amygdala

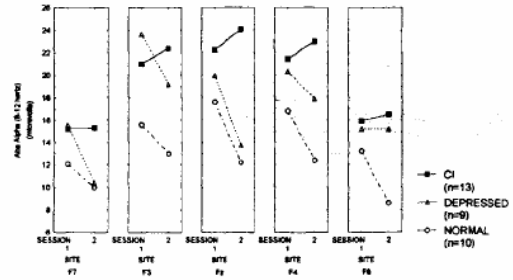
Agents that Favor Mesolimbic Sensitization

- cocaine, amphetamine
- physical or psychological stress
- lindane *(pesticides)*
- ethanol
- toluene *(solvents)*
- formaldehyde *(other VOCs)*
- interleukin-2; substance P agonists *(endogenous mediators)*

EEG Alpha-1 Sensitization by Repeated Cocaine Exposures (20 mg/kg) *(Ferger et al 1996)*



EEG Alpha Magnitude Sensitizes over Time in Women with Chemical Intolerance *(Bell et al. 1998)*



Odor Sensitization in Women with CS or SA

- EEG Alpha Highest in CS
- EEG Alpha sensitized in CS & SA

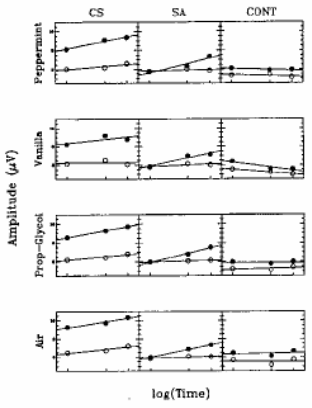
* * *

CS = Chem Sensitive

SA = Sexually Abused

Cont = Norm Controls

(Fernandez et al 1999)

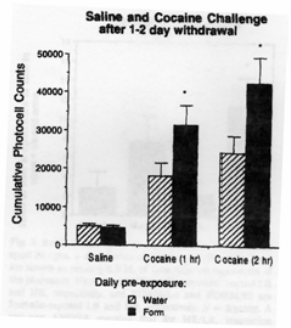


Cross-Sensitization: Agent "Nonspecifity"

- Definition. One agent initiates the sensitized state of heightened reactivity over repeated intermittent exposures, then a different, structurally-unrelated agent elicits the same level of reactivity upon its first exposure
  - Stress with amphetamine or cocaine
  - Cocaine with amphetamine
  - Cocaine with morphine
  - Formaldehyde with cocaine
  - Toluene with apomorphine or cocaine
  - Sucrose with amphetamine or cocaine

Formaldehyde Cross-Sensitizes with Cocaine

(Sorg et al. 1996)

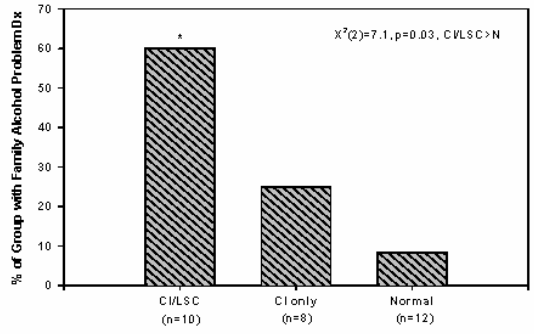


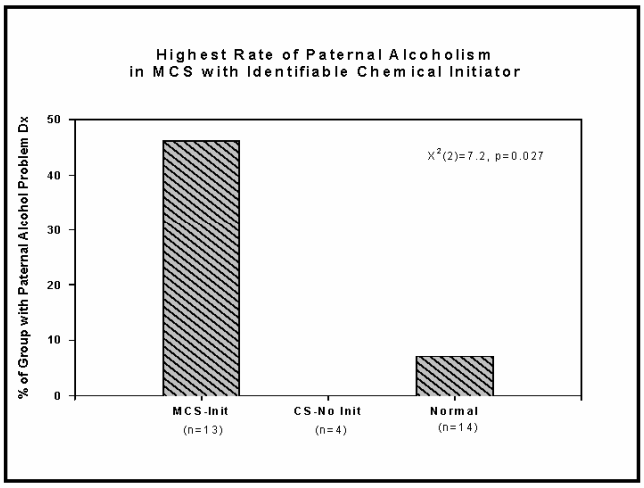
Host Factors in Animals that Increase Sensitizability

- genetic vulnerability
- sucrose/sweet preference
- hyperreactivity to novelty
- female gender
- lateral asymmetry (leftward turning)

Human Evidence for Mesolimbic Neural Sensitization Model in CI

- increased family histories of drug or alcohol problems in CI
  (genetic vulnerability)
- increased scores on Carbohydrate Addicts Test in CI
  (increased sucrose intake predicts sensitizability)
- Altered resting EEG alpha & beta activity in CI
  (cf., alcoholics' offspring & in stimulant drug-sensitized animals)
- more women than men report CI
  (female animals are more sensitizable than males)





Different Rates of Psychiatric Comorbidity by Group

(Fiedler et al. 1996)

Current Psychiatric Disorders (p=.002)

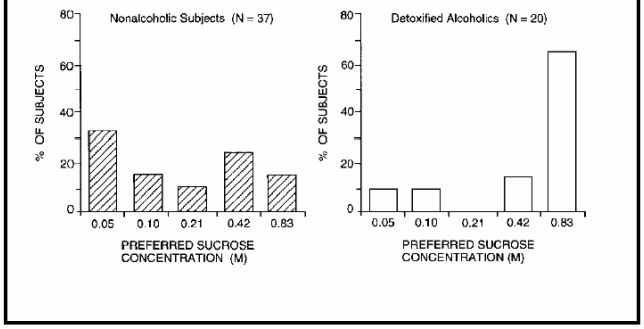
- MCS (identifiable chem initiator) 26%
- CS (no identifiable initiator) 62%
- CFS 39%

Lifetime Psychiatric Disorders (p=.004)

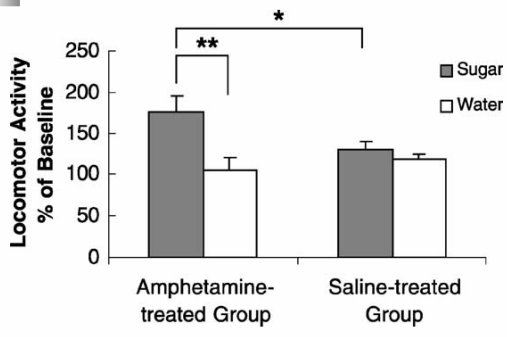
- MCS (identifiable chem initiator) 43%
- CS (no identifiable initiator) 69%
- CFS 72%

Detoxified Alcoholics Prefer Very High Sucrose Concentrations

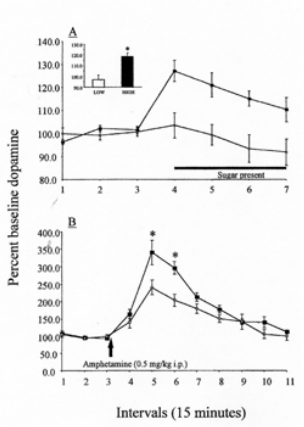
(Kampov-Polevoy et al. 1997)

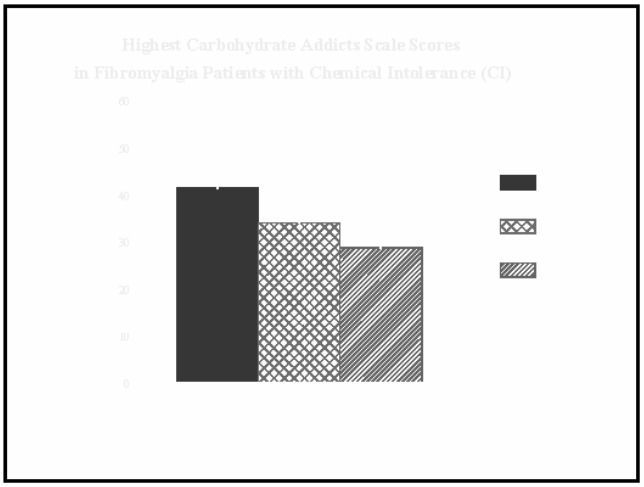


Sucrose & Stimulants Cross-Sensitize *(Avena & Hoebel 2003)*

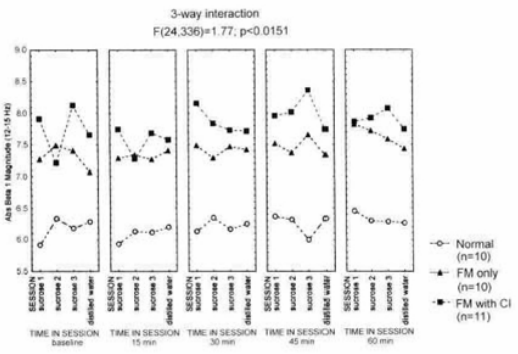


Sucrose Enhances Dopamine in Nucleus Accumbens of High vs Low Sugar Feeders
(Sills et al. 1998)





EEG Beta 1 Sensitization/Oscillation in Fibromyalgia after Lab Sucrose Ingestion
(Bell et al. 2001)



PGW Study Subjects

- 4 groups:
  - Unhealthy (ill) Gulf vets *with* chemical intolerance (CI) (n=22)
  - Unhealthy (ill) Gulf vets *without* chemical intolerance (n=24)
  - Healthy Gulf veterans (n=23)
  - Healthy veterans in military at same time but not deployed to Persian Gulf (Era vets) (n=20)

PGW Study Design I

- 4 sessions, once/week, same procedures for all subjects
- 1st 3 sessions – jet fuel (JP-8) or clean air sham; 4th session - perfume
- 15 randomized trials of acoustic startle stimuli during sessions for all subjects in all sessions

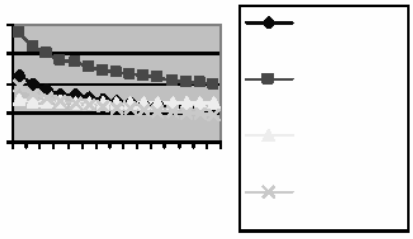
PGW Study Design II

- Parallel groups, randomized, double-blind assignment:
  - ½ of each group received 3 sessions of sub-olfactory threshold JP-8 jet fuel exposures;
  - ½ of each group received 3 sessions of clean air
- All groups received perfume exposure in Session 4 (cross-sensitization test)

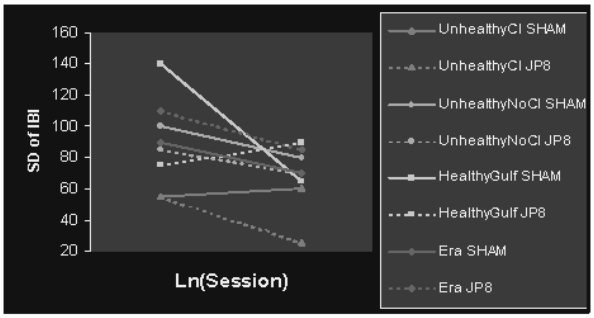
Descriptive Characteristics of Veteran Sample

- Mean age 40 SD 8 years, 85% male
  - Era veteran controls were older than the other 3 groups ($p<0.01$)
- More Hispanic veterans in ill Gulf veteran groups (both with and without chemical intolerance
- No group differences for education, gender distribution, marital status, employment status/income

Novelty Hyperreactivity in Unhealthy Gulf Vets with Chemical Intolerance:
Initial Blink Hyperreactivity to Noise AND Chemical Exposure (JP-8 jet fuel)



Unhealthy Gulf Vets with CI Start Low and Decrease HR Variability over Three JP-8 Jet Fuel Exposure Sessions *(Bell et al. 2003)*



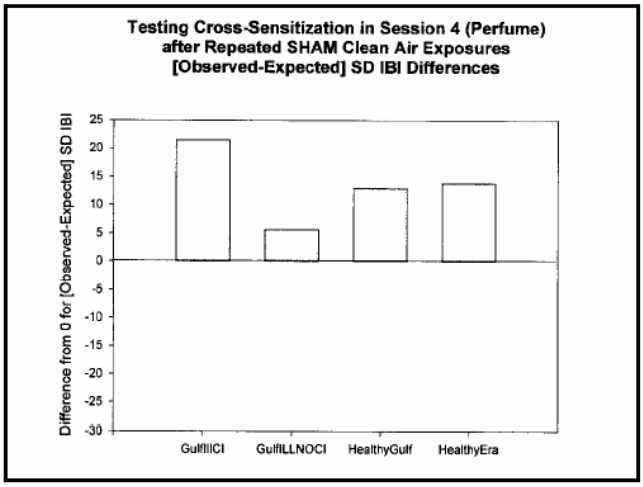
Gulf War Study: Heart Rate Variability Conclusions

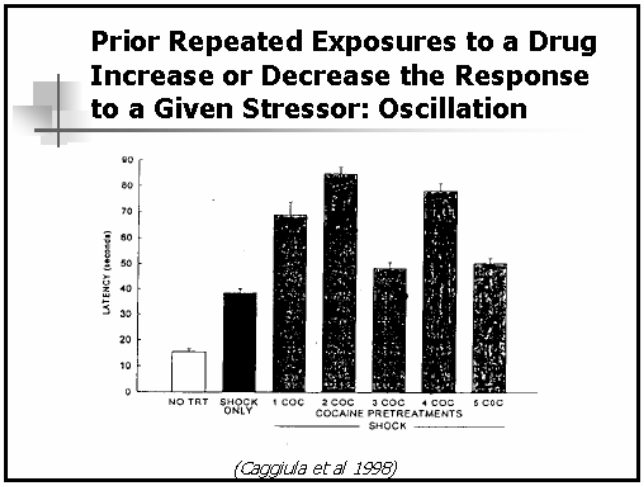
- As a function of JP-8 jet fuel exposure vs SHAM clean air over Sessions 1-3, all 3 contrasts for HR variability (SD IBI) differed significantly, after controlling for covariates:
  - Unhealthy Gulf Veterans with CI differ from Unhealthy Gulf Veterans without CI
  - Healthy Gulf Veterans differ from Healthy Era Veterans
  - Combined Unhealthy Gulf groups differ from Combined Healthy groups

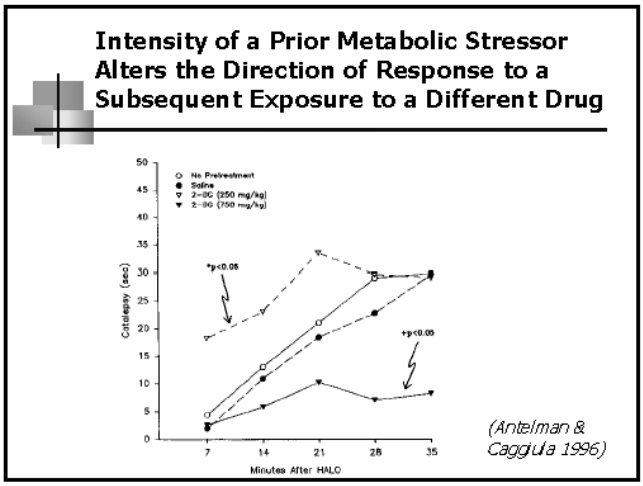
Cross-Sensitization

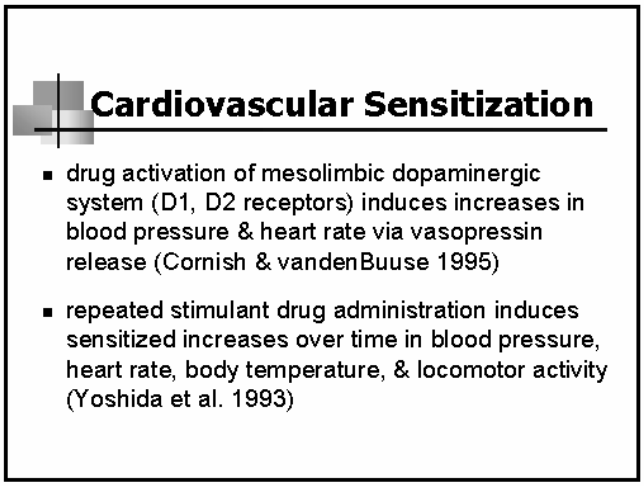
- Replicated animal studies demonstrate that stress and drugs (stimulants) cross-sensitize
- Replicated animal studies demonstrate that drugs (cocaine) and environmental chemicals (formaldehyde, toluene) cross-sensitize

Testing Cross-Sensitization in Session 4 (Perfume) after Repeated JP-8 Fuel Exposures [Observed-Expected] SD IBI Differences

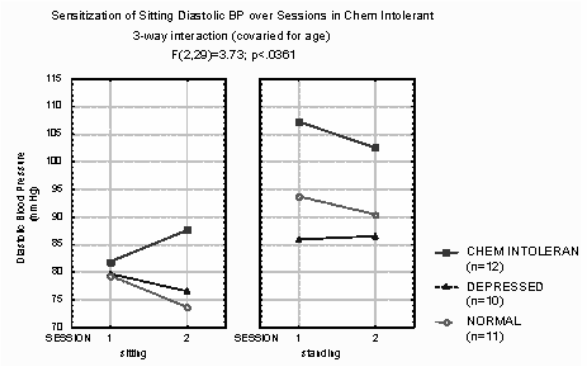

Testing Cross-Sensitization in Session 4 (Perfume)
after Repeated SHAM Clean Air Exposures
[Observed-Expected] SD IBI Differences
Difference from 0 for [Observed-Expected] SD IBI
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
GulfIIICI
GulfILLNOCI
HealthyGulf
HealthyEra


Prior Repeated Exposures to a Drug
Increase or Decrease the Response
to a Given Stressor: Oscillation
LATENCY (seconds)
NO TRT
SHOCK ONLY
1 COC
2 COC
3 COC
4 COC
5 COC
COCAINE PRETREATMENTS
SHOCK
(Caggiula et al 1998)


Intensity of a Prior Metabolic Stressor
Alters the Direction of Response to a
Subsequent Exposure to a Different Drug
No Pretreatment
Saline
2-DG (250 mg/kg)
2-DG (750 mg/kg)
Catalepsy (sec)
*p<0.05
*p<0.05
7
14
21
28
35
Minutes After HALO
(Antelman &
Caggiula 1996)


Cardiovascular Sensitization
drug activation of mesolimbic dopaminergic system (D1, D2 receptors) induces increases in blood pressure & heart rate via vasopressin release (Cornish & vandenBuuse 1995)
repeated stimulant drug administration induces sensitized increases over time in blood pressure, heart rate, body temperature, & locomotor activity (Yoshida et al. 1993)

Sitting Diastolic Blood Pressure Sensitization in CI *(Bell et al. 1998)*



Conclusions - MCS/CI

- Chemical intolerance may be a nonspecific marker of heightened sensitizability
- Chemical intolerance is physiologically different from depression or prior abuse
- Chemical intolerance may reflect in part dysfunction of limbic & mesolimbic pathways
- Past exposure history matters: chemicals, drugs, or life stressors may all initiate subsequent chemical intolerance
- Dietary factors, e.g., sucrose, facilitate time-dependent sensitization in susceptible persons

Gulf War Study Collaborators

- Carol M. Baldwin, RN PhD
- Mercedes Fernandez, PhD
- Susanne Haugebak, BA
- Audrey Brooks, PhD
- Aurelio J. Figueredo, PhD
- Gary E.Schwartz, PhD

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