

# **The Cause(s) of Chronic Multisymptom Illnesses Following the First Gulf War**

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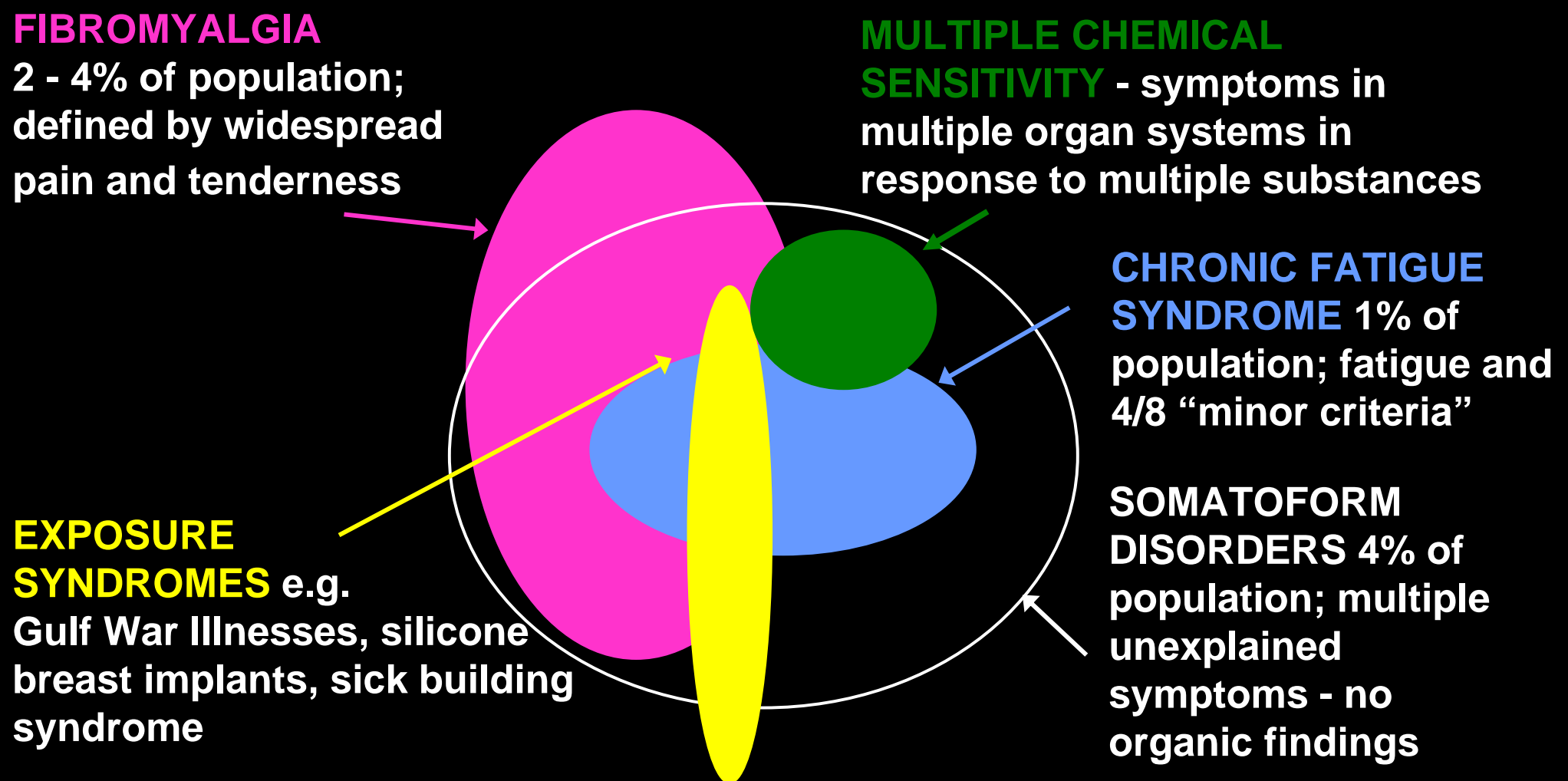
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# ***Chronic Multi-symptom Illnesses (CMI)***

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- **Term coined by the CDC in 1999 to describe multiple somatic symptoms in Gulf War veterans (Fukuda et. al. JAMA 1999)**
- **This study and subsequent studies in the general population using factor analytic techniques (e.g., Doebbling et. al. Am J Med 2000) identified 3 – 4 symptom factors that cluster in the populations**
  - Multifocal pain
  - Fatigue
  - Cognitive difficulties
  - Psychological symptoms
- **This and subsequent studies demonstrated that approximately 10 – 15% of the population suffers from a syndrome characterized by two or more of these symptoms**

# “Systemic” Chronic Multisymptom Illnesses



# Regional Chronic Multisymptom Illnesses

Tension/migraine headache

Affective disorders

Temporomandibular joint syndrome

Constitutional

Weight fluctuations

Night sweats

Weakness

Sleep disturbances

Irritable bowel syndrome

Nondermatomal paresthesias



Cognitive difficulties

ENT complaints (sicca sx., vasomotor rhinitis, accommodation problems)

Vestibular complaints

Multiple chemical sensitivity, "allergic" symptoms

Esophageal dysmotility

Neurally mediated hypotension, mitral valve prolapse

Non-cardiac chest pain, dyspnea due to respiratory mm. dysfunction

Interstitial cystitis, female urethral syndrome, vulvar vestibulitis, vulvodynia

# In Addition to the CMI Seen Commonly in the General Population, is There a Superimposed “Neurological Damage” Disorder?

	Yes	No
Population-based		
Case-control neurological study		
Abnormal functional imaging		
Abnl autonomic fxn.		

# What Causes CMI?

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- **Genetics**
- **“Triggers”**
- **Mechanisms**
  - Relationship between physiologic and psychologic factors
  - Disordered sensory processing
  - Autonomic/neuroendocrine dysfunction

# Genetics of Fibromyalgia

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- **Clearly is a strong *familial* predisposition**
  - Most recent work by Arnold, Hudson, et. al. suggest > 8 OR for first degree relatives, and much less familial aggregation (OR 2) with affective disorders
- **Genes that may be involved**
  - 5 HT 2A receptor polymorphism T/T phenotype (Bondy 1999)
  - Serotonin transporter (Offenbaecher 1999)
  - COMT (Catecholamine O-Methyl Transferase)
    - Shown to be involved in pain transmission (Zubieta 2002)
    - Slightly different in FM (Gursoy 2003)

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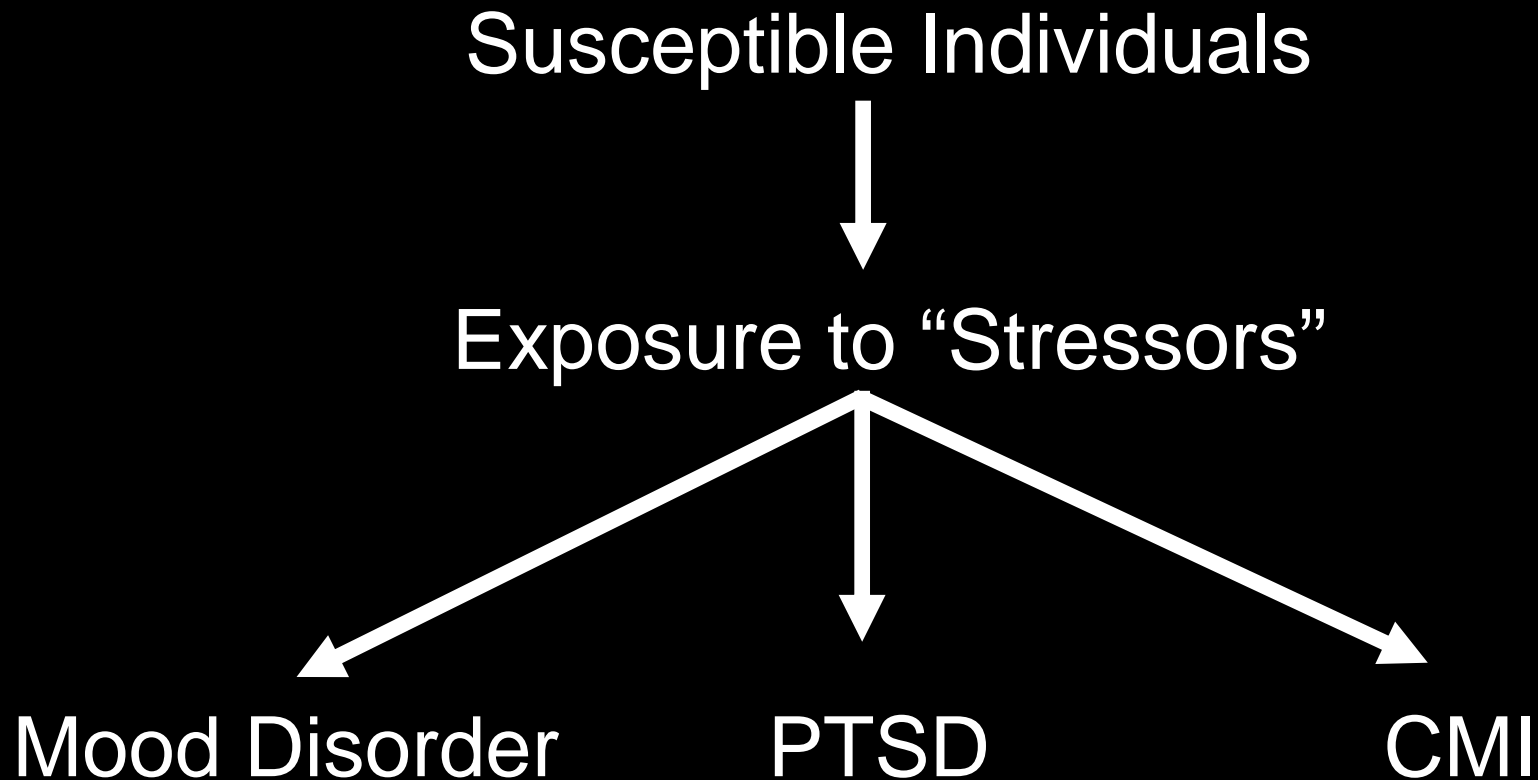
# “Stressors” capable of triggering these illnesses – supported by case-control studies

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- Infections (e.g., parvovirus, EBV, Lyme, Q fever; not common URI)
- Physical trauma (automobile accidents)
- Psychological stress / distress
- Hormonal alterations (e.g., hypothyroidism)
- Drugs
- Certain catastrophic events (*war, but not natural disasters*) (Clauw, Engel, Aronowitz, Jones, Kipen, Kroenke, Ratzan, Sharpe, Wessely. *J Occup Environ Med*, 2003)

# “Stress” Related Syndromes

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# The Physiological / Psychobehavioral Continuum



Population

Primary Care

Tertiary Care

## ***Neurobiological***

- Abnormal sensory processing
- Autonomic dysfunction
- HPA dysfunction

## ***Psychosocial factors***

- Decreased activity / isolation
- General “distress”
- Cognitive factors
- Maladaptive illness behavior
- Secondary gain issues

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# Summary (Scientific)

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- **Recent research is giving significant insights into the underlying mechanisms of Chronic Multisymptom Illnesses such as Fibromyalgia, Irritable Bowel Syndrome, TMD syndrome**
  - **CNS disorder**
  - **Triggered by a variety of “stressors”**
  - **Abnormalities in brain function, especially in**
    - **Sensory processing**
    - **Autonomic nervous system**
    - **Hypothalamic pituitary adrenal axes**
- **Very few mechanistic studies have compared GWV to those with CMI that are in general population, but this is an essential “control” group to interpret findings of physiological studies in GWV**

# Summary (Personal)

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- The notion that the Gulf War and other post-deployment syndromes are *either*
  - “Psychological” or “physiological”
  - Due to “stress” or “toxins”is both inaccurate and counter-productive
- Psychological = Physiological
- The evidence that purely psychological stressors are responsible for triggering or worsening CMI is weak
- Stress is a toxin, and toxins are stressors

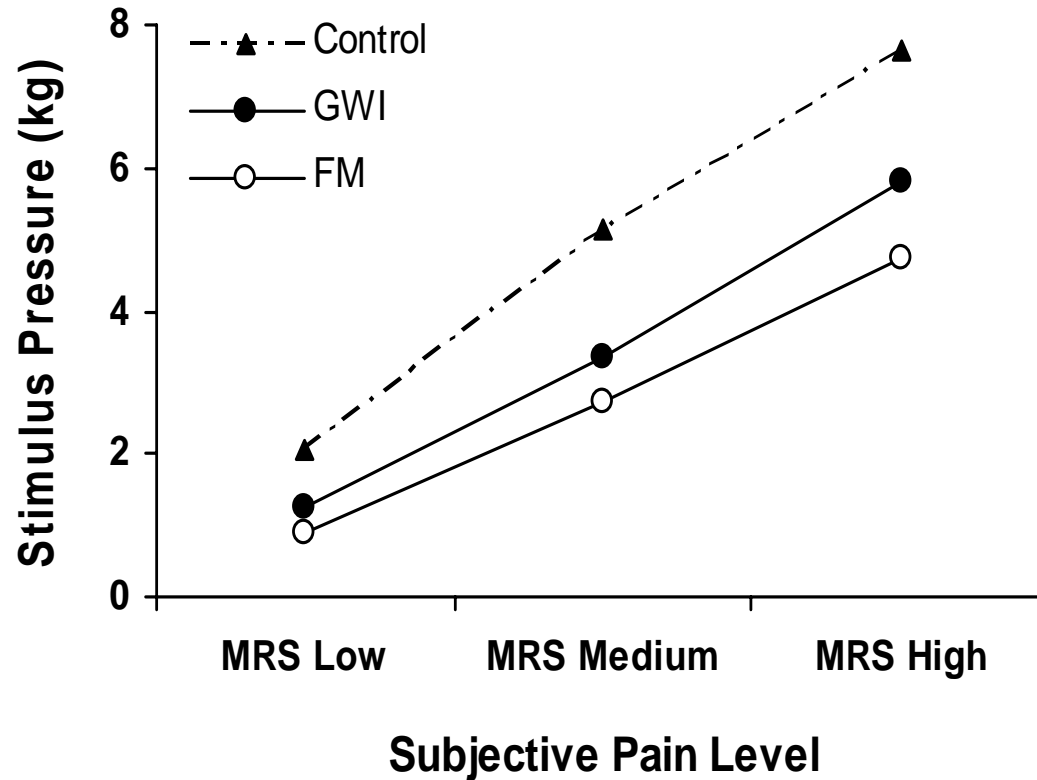
# Studies of Physiology of Gulf War Veterans vs. Healthy Controls, with FM as “Positive Control” Group

- Sensory processing
- Autonomic function

# Sensory Processing in Gulf War Veterans

- **Quantitative sensory testing for pressure pain threshold**
  - 20 GWI participants with chronic multisymptom illnesses
  - 36 age- and gender-matched controls
  - 27 individuals with fibromyalgia
- fMRI in a representative cohort from above

# Pressure Pain Threshold



## Gulf War Veterans

Brain Region	X coord.	Y coord.	Z coord.	z score
Anterior Cingulate	-2	-32	24	3.85
S1	44	-26	55	4.88
S2	65	-24	21	5.17
Ipsilateral S2	-61	-17	19	3.38
Inferior Parietal Lobule	51	-34	53	4.74
Cerebellum	-30	-52	-21	5.01
Inferior Frontal Gyrus	40	62	6	4.90

## Fibromyalgia Patients

## Fibromyalgia

Brain Region	X coord.	Y coord.	Z coord.	z score
Putamen	-24	4	7	3.83
S1	55	-18	32	4.27
S2	59	-34	18	3.33
Ipsilateral S2	-59	-21	12	3.22
Inferior Parietal Lobule	53	-38	57	4.13
Cerebellum	-30	-54	-23	3.21
Inferior Frontal Gyrus	38	61	-10	3.45

## Healthy Controls

Brain Region	X coord.	Y coord.	Z coord.	z score
S2	63	-20	21	3.53

# Studies of Physiology of Gulf War Veterans vs. Healthy Controls, with FM as “Positive Control” Group

- Sensory processing
- Autonomic function

# Heart Rate Variability as a Surrogate Measure of Autonomic Function

- Subjects included 26 (19F,7M) with FM, 11 (6M,5F) with GWI and 36 (18M,18F) normal controls. HRV was determined from Holter recordings obtained in the Clinical Research Center.
- In FM and in GWI females, HRV was significantly lower than in FM and GWI males. HRV was similar in male and female controls. When HRV was compared by group within gender, HRV was significantly decreased in female FM and GWI and no significant differences were seen for males with these conditions.
- Decreased HRV in FM and GWI appears to be gender-dependent. Results suggest that different mechanisms may be operative in symptom expression in males and females with this spectrum of illness.