

Neurotoxicity or  
Medically  
Unexplained  
Symptoms

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# Summary

- Neuropsychological symptoms and abnormalities are nonspecific.
- The presence of neuropsychological abnormalities may be consistent with the presence of neurotoxicity, but they never are diagnostic of neurotoxicity.
- Neuropsychologists are dependent on experts in toxicology, because the dose makes the poison.

# MUS defined

- Related syndromes characterized more by disability, symptoms, and suffering than objective pathology.
- Objective findings outweighed by subjective complaints

# Subjective Cognitive Complaints

- Subjective complaints (Sx) are not equivalent to neuropsychological abnormalities
- Cognitive Sx are an index of affective distress, not neuropsychological abnormalities (various studies reviewed in Binder, 2005)

# Cognitive Symptoms

- In Gulf War Illnesses group, more related to Beck measures of anxiety and depression than to objective neuropsychological scores (Binder et al 1999)
- Similar findings in epilepsy surgery group (Westerveld et al, 1999) and in chronic fatigue (Tiersky et al, 1997)

# Examples of Labeling of MUS

- Fibromyalgia
- Chronic fatigue syndrome
- Silicone breast implant illness
- Gulf War Unexplained illnesses
- Sick Building Syndrome/Toxic mold
- Multiple chemical sensitivity

# Many MUS Are Unlabeled

- Problems during lifetime in community dweller:  
joint pains (36.7%), back pain (31.5%),  
headaches (24.9%), chest pain (24.6%), arm or  
leg pain (24.3%), abdominal pain (23.6%),  
fatigue (23.6%), and dizziness (23.2%). (Kroenke  
& Price, 1993)

# Unlabeled MUS -2

- Most symptoms (84%) were at some point considered major in that they interfered with routine activities or had led individuals to take medications or visit a physician.
- Nearly one third of symptoms were either psychiatric or unexplained (Kroenke & Price, 1993)

# Cognitive Complaints Don't Signify Presence of Disease or Injury

- Normal college students: memory loss 20%,  
Loss of interest 36%, temper problems 37%,  
fatigue 28% (Gouvier et al, 1988)

Litigants not claiming brain dysfunction:

Concentration 78%, Confusion 59%, Memory  
loss 53%, dizziness 44%, word finding 34%  
(Lees-Haley & Brown, 1993)



# Neurologic Complaints and Stress

- One week after SF earthquake in 1989:  
Dizziness 30%, concentration problem 71%  
(Cardena & Spiegel, 1993)
- One year after a flood, more neurological sx in exposed than in nonexposed persons (Escobar et al)

# MUS and Neuropsychology Overview

- Associated sometimes with NP abnormalities
- Cognitive sx often index affective distress
- Self report history may be inaccurate
- Emotions, family roles, motivation are important

# MUS and Neuropsychology

## Overview -2

- NP abnormalities do not signify neurologic disease but brain chemistry and perhaps structure are altered by stress

# Neuropsych Abnormalities are Common in Normals

- Heaton et al (2004) defined abnormality as score  $> 1 \text{ SD} < \text{mean}$  of 1189 normals after demographic correction.
- 25 measures in extended HRB
- 13% had zero abn
- 46% had  $> 3$  abn.
- 30% had  $> 5$  abn.
- All percentages estimated from Figure 9

# Neuropsychological Abnormalities Occur in Conditions Other than the Condition of Interest

- Learning disabilities
- Psychiatric Disorders
- Motivational problems
- Various medical problems: sleep apnea, COPD, hypertension, diabetes, liver disease

Neuropsych  
abnormalities  
are nonspecific

# Mental Disorders Are Common

## Eschleman et al (1994)

- structured interview prevalence study.
- 48% reported at least one lifetime disorder and 29.5% reported a disorder within 12 months.
- 10% had major depression (MD) in past year, 13% of females and 8% of males.
- In lifetime, 17% overall and 21% of females had MD.

# Characteristics of Disabling MUS (DMUS) 1

- Self Diagnosis
- Symptom Amplification - disabled role
- Belief in serious illness with bad outcome
- Skepticism with mainstream medicine
- Shopping for professionals who believe in an organic explanation
- Rejection of psychological explanations
- Biomedical explanation preferred



# Characteristics of DMUS 2

- Normal viewed as abnormal. Symptoms interpreted as signifying disease.
- Sick role and disability
- Self help groups – internet and support
- sensationalized media coverage, e.g. Gulf War, silicone breast implants
- Overlapping conditions: chronic fatigue, fibromyalgia, silicone breast illness, MCS

# Shorter's Historical View - 1

- Historical eras and culture shape the mind and symptoms.
- The culture considers some symptoms legitimate and others illegitimate, selectively rewarding some symptoms

# Shorter's Historical View - 2

- Medical authority is declining in influence
- Media, internet, and support groups are increasing in influence
- Social isolation is increasing, and this may increase idiosyncratic explanations of symptoms. The wisdom of relatives is less available.
- Normal symptoms such as fatigue are viewed as disease.

# Pseudoneurologic Disease

- Neurologic symptoms without objective evidence of neurologic disease
- Often associated with NP deficits
- Slater (1965) showed hysteria was overdiagnosed, but newer studies show much lower rate of neuro disease at followup (Kent et al; Couprie et al - 7%)

# Nonepileptic Seizures (NES) Best model of pseudoneurologic illness

- Neuro disease is ruled out
- NP deficits
- Associated with psychiatric illness
- Common - above 30% prevalence in EEG monitoring populations
- Bad historians sometimes - deny verifiable stressors

# NES and ES Don't Usually Coincide

- Consistent with the experience of our group, Martin et al 2003 found that only 5% of over 500 patients with NES also had ES.

# Neuropsychology of Nonepileptic seizures 1

- Our group found that epileptic and nonepileptic seizure patients did not differ on most neurocognitive variables, but MMPI-2 showed striking differences with nonepileptic patients about 10 points higher on HS and HY
- Our study replicated others

# Neuropsychology of NES 2

- Associated with trauma and PTSD, but presence or absence is not diagnostic
- Clearcut cognitive deficits in NES that are nearly as dramatic as in ES.
- Deficits on WAIS-R, Trails, memory measures, WCST, etc. as severe as in ES



# Wilkus, Dodrill, & Thompson 1984

- Standardized battery of measures with cutoff scores developed in the UW seizure population
- ES group averaged abnormalities on 46% of the measures. NES group averaged abnormalities on 51%. (non-significant difference between ES and PS groups)

# Binder, Kindermann, Heaton, & Salinsky

- Arch of Clin Neuropsychology, 1998, 513-522.
- Both seizure groups impaired relative to controls obtained from Heaton's normative sample. No control data for some tests.
- Differences between NES and ES groups were NS, except on BNT

# NES

# ES

WRAT-R Read	94.8	■ 92.1
WAIS-R FSIQ	92.0	■ 90.6
Boston	52.7	■ 46.7 *
COWAT	34.0	■ 32.1
RAVLT Total	44.6	■ 42.0
RAVLT Delay	8.3	■ 7.6
Trails B seconds	93.0	■ 97.2

# NES ES

■ Gr Pegs dom sec 84.6      ■ 96.9

## WMS-R LM percentiles

■ LM I                      30.1      ■ 34.4

LM II                      33.8      ■ 31.5

■ LM Savings %    79.3      ■ 69.5     $p = .09$

■ CVMT Total        72.0      ■ 72.4

■ WCST PR            26.0      ■ 31.3

# Brown, Levin (1991)

	NES	ES
■ Age	37.1	33.2
■ Educ	13.5	13.3
■ Boston Naming	48.9 (8.8)	45.3 (10.9)
■ FAS	31.1 (12.4)	30.4 (10.2)
■ Similarities	8.0 (2.9)	8.9 (2.5)
■ Block Design	7.6 (2.3)	8.3 (2.3)
■ Digit Span	7.5 (3.4)	8.7 (3.5)
■ LM Immed (WMS)	11.3 (4.3)	12.1 (4.4)
■ LM Delayed	10.2 (5.3)	10.6 (4.7)

# Explaining Abnormalities in NES

- Brown et al: qualitative effort problems
- Measures of effort show NES deficits
- Memory scores are related to PDRT
- NES mean 51/72
- ES mean 59/72
- Word Memory Test scores usually invalid (Williamson, Drane et al)

# Clinical Aspects of NES -1

“I’d rather die of cancer than be told my seizures were caused by a psychological problem”

(young, well educated female NES patient to her neurologist as he conveyed what he thought was the good news of having ruled out epileptic seizures)

# Clinical Aspects of NES - 2

Young adult with both ES and NES denied any psychosocial stressors and specifically denied problems with her father who lived out of state. Her mother reported that her NES began around the time her dad remarried and that the patient felt her dad cared only for his stepchildren.



# MMPI-2 Conversion V Interpretation

- High Hs and Hy and low D
- Emphasis on somatic complaints
- Denial , poor insight (why would a person admit psych problems if she would rather die of cancer?)
- Stress may cause physical complaints
- Dramatic presentation with dependency needs

# Clinical Aspects of NES - 3

- Modal psych dx is conversion disorder – no evidence of any other psych disorder
- MMPI -2 and diagnostic data lead to the conclusion that many of these patients lack insight and try to deny psychological problems, preferring physical explanations for their illness.
- Fortunately, some are willing to accept a psychological explanation.

# Clinical Aspects of NES - 4

- History of physical and sexual abuse in childhood and adulthood is common
- Psychiatric problems, esp. panic attacks and suicidal behavior, are common.
- Hypothesized cause may be old, current, or unknown
- Evidence for treatment effect is anecdotal. Some evidence that careful followup and psychotherapy is helpful. Studies are underway.

# *Generalizations from NES to other MUS*

- Neuropsychological abnormalities are non-specific and occur in non-neurological conditions
- People with MUS often do not show evidence of an Axis I disorder, other than a somatoform category disorder
- People with MUS often lack insight

# Somatization and Denial of Psych Sx

- In psychiatric samples, acknowledgment of somatic sx is not associated with denial of psych disorder (Hotopf & Wadsworth)
- MUS can occur with or without the acknowledgement of psychiatric distress

# Commercial Announcement

INS in Portland, February 2007.

Come on down to the Rose City.

# Animal Models of Stress

- In animals, early stress causes chronic alterations in hypothalamic-pituitary-adrenal (HPA) axis function, negative emotions, and alarm reactions
- Social support from monkey peers leads to fewer alarm reactions than in monkeys raised in isolation
- Physiology & environment are important

# Immune System and Psychological Function

- Immune system activation of cytokines by salmonella affected emotions and memory, even w/o physical symptoms (Reichenberg et al)
- Depression associated with large changes in immunity, e.g. lower natural killer cell activity, change in WBCs, etc. (Herbert & Cohen, 1993)



# Immune System and Psych Function - 2

- Immunosuppression associated with past PTSD-Ss with no current psych disorder (Kawamura et al 2001)

# Emotional Expression and Health

- Expressing emotions was good for immune system functioning. Thought suppression was bad for immune functioning. (Petrie, et al., 1998)
- Infirmary visits of imprisoned sex offenders decreased by trauma writing exercise (Richards, et al., 2000).

# Emotional Expression and Health-2

- Inhibition of thoughts and feelings takes physiological work.
- Short term effect of inhibition is increased autonomic activity.
- Long term effect of inhibition is cumulative pathophysiologic stressor increasing probability of psychosomatic disease (Pennebaker & colleagues)

# PTSD: Psychological Findings

- Exposure to stressors causes PTSD in a minority
- Associated with NP deficits
- Caused by abuse

# Effects of Trauma

- Medical illness, at least for Vietnam PTSD
- Somatization including NES
- Psych problems
- Substance abuse
- Dissociative symptoms (some, as measured by DES, are neuropsychological symptoms)

# Emotional Trauma and Somatization

- 3-4 times more likely (Andreski, et al)
- Panic disorder and somatization strongly related (Katon, 1991)
- Trauma and natural disasters (earthquake, flood) associated with neurologic symptoms (Cardena & Spiegel, 1993; Escobar et al., 1992)

# Vietnam related PTSD and health

- Vets seen an average of 17 years after combat were diagnosed with a structured interview. Illnesses reported by Ss to have been diagnosed by doctor.
- Circulatory, digestive, musculoskeletal, nervous system, respiratory, and infectious disease related to PTSD

# Vietnam PTSD and Health -2

- PTSD unrelated to STDs, cancers, or genitourinary and skin diseases, suggesting that positive findings were not an artifact of response bias
- The study controlled for SES, substance abuse, tobacco, and other factors
- (Boscarino, 1997)



# Individual Biological Differences in Emotional Processing

- The intensity of negative affect is related to individual differences in electrophysiology, immune system functioning, and autonomic activity (Richard J. Davidson)
- Early environmental manipulation leads to individual differences in reactivity, brain circuitry and vulnerability to psychopathology (Davidson and David Barlow)

# Neurotoxicity Debunked?

- Persian Gulf War Unexplained Illnesses
- Silicone Breast Implant Disease
- Solvent Encephalopathy (see Albers & Berent, Neurologic Clinics, 2000)
- Toxic Mold
- Umatilla Army Depot outbreak of mass illness

# Multiple Chemical Sensitivities

- Associated with psychiatric disease
- Characterized by allergic like sensitivity to various common chemical odors such as common cleansers, gasoline, and perfume
- Symptoms include fatigue, confusion, dizziness, and respiratory
- Little controlled evidence of cog impairment (Bolla; Fiedler et al; Simon)

## Comparison of Neuropsychological Studies, Shown as Raw Scores (+-SD), in Patients with Multiple Chemical Sensitivity and Controls with Musculoskeletal Injury

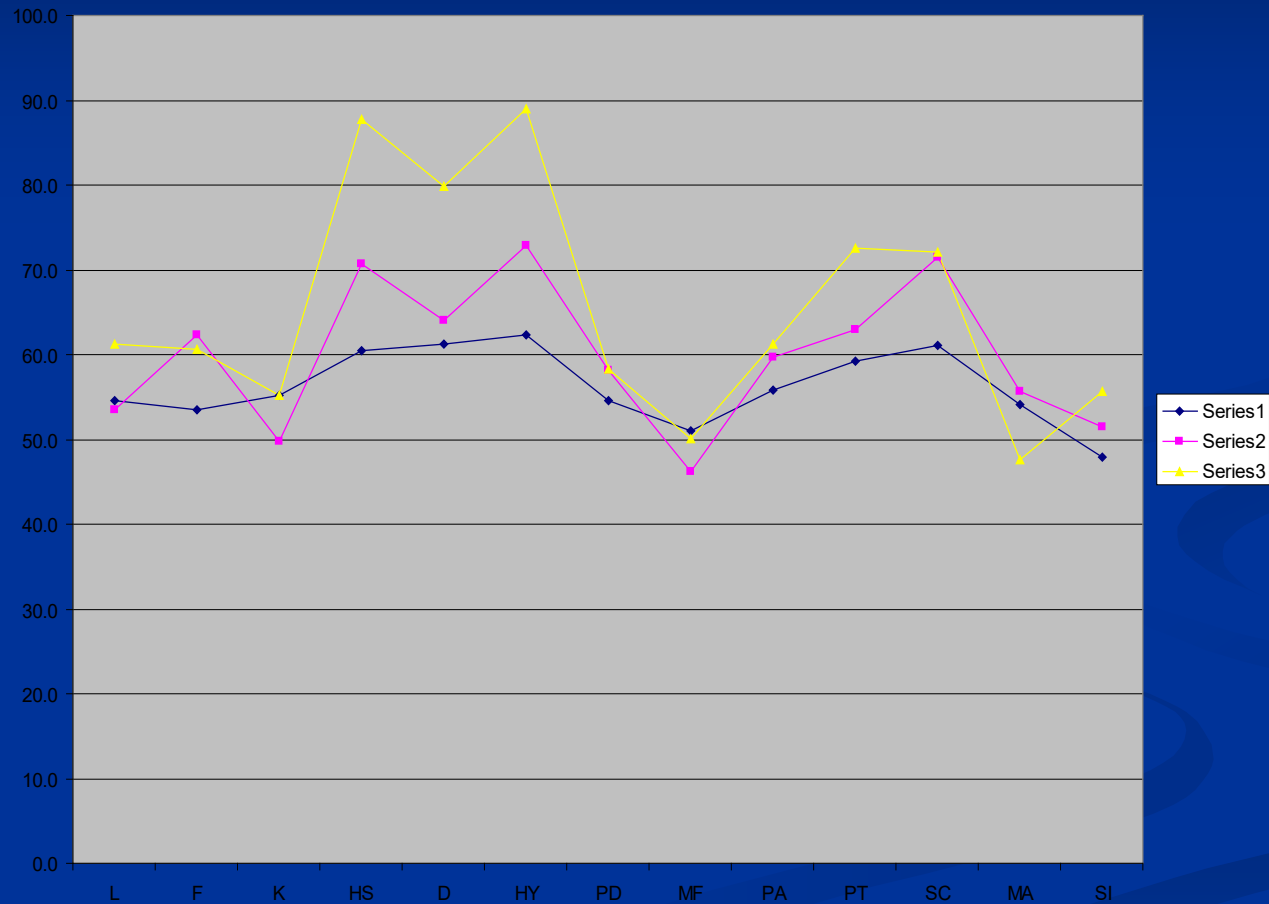
Study	Normal	Cases ( <i>n</i> = 41)	Controls ( <i>n</i> = 34)	95% CI for Difference	<i>P</i> Value
<b>Attention</b>					
WAIS-R Digit Span*	10.0	10.6 (±2.5)	11.1 (±2.3)	(-0.6 to 1.6)	>0.2
<b>Verbal memory</b>					
WMS-R Logical-Immediate†	24.3	22.8 (±6.4)	26.0 (±6.3)	(1.9 to 4.5)	0.04
WMS-R Logical-Delayed†	20.5	18.9 (±7.4)	21.6 (±7.2)	(-0.4 to 6.0)	0.1
Rey Auditory Verbal‡	11.3	9.3 (±2.8)	10.5 (±2.7)	(-0.1 to 2.5)	0.06
<b>Visual memory</b>					
WMS-R Visual-Immediate†	32.1	32.8 (±5.0)	33.0 (±5.8)	(-2.1 to 2.5)	>0.2
WMS-R Visual-Delayed†	29.6	28.6 (±6.7)	30.3 (±7.3)	(-2.5 to 3.9)	>0.2
<b>Visuomotor speed</b>					
WAIS-R Digit Symbol*	10.0	10.0 (±2.7)	10.2 (±2.8)	(-1.0 to 1.4)	>0.2
Trails A, <i>s</i>	31.3	32.6 (±12.3)	35.6 (±15.8)	(-3.4 to 9.4)	>0.2
<b>Mental flexibility</b>					
Trails B, <i>s</i>	74.5	75.2 (±31.6)	77.6 (±31.4)	(-11.9 to 16.7)	>0.2

\* Age-adjusted scale score.  
† Raw score, number of items recalled.  
‡ Trial VII, postdistraction.

Simon, G. E. et. al. Ann Intern Med 1993;119:97-103

# Litigated MCS and MMPI-2

## Binder Storzbach & Salinsky 2006



# Litigated MCS

MMPI-2 profiles more elevated than nonepileptic seizures

Conclude that there is a massive psychological component

# MCS after pseudo-nerve gas exposure in Umatilla

- Chemical Weapon incinerator construction
- Facility stored Sarin and Mustard gas
- Climate of fear: concern about faulty alarm systems
- Mass outbreak of largely respiratory symptoms but most workers at site unaffected

# Umatilla incident: No nerve gas symptoms

- None of the characteristic symptoms of acute organophosphate exposure (constricted pupils, tears, vomiting, increased urinary frequency, coma, convulsions, depressed respiration and heart rate)



# Umatilla incident

- No Organophosphate-induced delayed neuropathy
- No dermatologic sx consistent with Mustard gas. Mustard is classified as a blistering agent.
- No evidence of discharge of chemical weapons from storage

# Umatilla incident outcome

- 26 went to hospital emergently
- About 50 filed lawsuits
- Several had neuropsychological exams
- Nonspecific neuropsychological findings – alternative explanations existed for all abnormalities: LD, diabetes, poor effort, recent ETOHism, MS, etc.

# Umatilla incident and MCS

- MCS in 7/13 of the neuropsychological sample. All had dx of “reactive airway disease”
- 3/7 with MCS continued to smoke despite MCS (1/3 smokers had quit by neuropsychological exam)
- tobacco smoke provokes symptoms in asthmatics, so why did 3 examinees continue to smoke?

# MCS Explained ?

- Plastic workers with environmental illness
- Illness predicted by preexisting panic attacks, depression, and medically unexplained physical symptoms (Simon, et al., 1990)

# MCS and Classical Conditioning

- Conditioned stimulus = odor
- Unconditioned stimulus = unrelated pathogen, e.g. upper respiratory infection
- Response of illness is conditioned

# MCS and Expectancy

- In an experiment, participants level of subjective physical symptoms was related to the warnings given about the odors (healthy, neutral, unhealthy) Dalton et al 1999
- No evidence that people who believe they are chemically sensitive are really challenged by the chemicals that they believe are noxious

# MCS and Umatilla Incident Causation

- combination of scary environment, mass hysteria, expectancy, perceived coverup, and opportunism.
- People with respiratory or other illnesses may have been classically conditioned
- Cannot conclude that MCS without financial incentives has same causes as MCS with financial incentives

## **CNN: 2003**

**A woman was arrested for dousing herself with perfume, spraying the house with bug killer and disinfectant, and burning scented candles in an attempt to seriously injure her chemically sensitive husband, prosecutors said.**



David Taylor, 46, is disabled due to allergies that resulted from exposure to toxic mold and hazardous chemicals as a construction worker, his doctors say. That exposure netted him \$150,000 in a recent workers compensation settlement. Lynda Taylor's attorney, Karen Steger, said the charge was a misuse of the criminal justice system. "The guy's a faker," she said. "He just wants to gain an advantage in the divorce case." Legal outcome is unknown.

# Toxic Mold

- Mold is everywhere
- Fungi are not volatile and the odors cannot pass through walls
- Except for severely immuno-compromised persons and some other well-defined diseases, no good evidence of serious health effects

# Neuropsychology of Toxic Mold

- Existing neuropsychological studies of TM showing impairment are uncontrolled
- The only controlled study of sick building syndrome showed no neuropsychological effect (Hodgson et al)
- Neuropsychological sx are nonspecific
- Attributing neuropsychological sx or findings to toxic mold is junk science (Lees-Haley, 2003)

# MCS and Toxic Mold Conclusion

NP findings may be the most objective abnormality, but no evidence that there is neurologic disease in classical sense

# Bradford Hill Causal Criteria

- Strength of association
- Consistency of evidence
- Specificity
- Temporal relationship
- Biological gradient – dose response relationship
- Biologic rationale
- Experimental evidence

# Diagnosis of Neurotoxicity

In the absence of neurotoxicological expertise, neuropsychologists can go no farther than stating that the findings are consistent with brain dysfunction. The dose makes the poison. Neurotox expertise is required to assess the dose. Competing explanations of cognitive deficits should be ruled out.

# Accuracy of Self Report-1

- Subjective cognitive impairment is weakly or not predictive of objective findings and is more related to distress
- “Good old days” phenomenon: Premorbid health overestimated after injury (Ferguson et al; Hilsabeck et al) and probably after illness onset

# Accuracy of Self Report-2

- Many adults who were sexually abused or otherwise traumatized during childhood or earlier in adulthood fail to report abuse/trauma when directly asked (Widom)
- 35-40% rate of denial of childhood sexual or physical abuse at 20-yr followup



# Accuracy of Self Report-3

- Well documented stressors, medical, & mental health history imperfectly recalled (Harlow & Linet; Simon & VonKorff)

# Accuracy of Self Report-4

- No significant overlap between self report of depression in structured interview and in a self report instrument administered a year later. Results were “Disheartening.... Wherever possible, use of records of past depression is to be strongly preferred over a reliance on respondent recall.” Coyne et al.2001

# Accuracy of Self-report - 5

- Mental health sometimes illusory. Clinician ratings may not agree with self report scale. Those with illusory mental health showed greater maximal and mean coronary reactivity and greater defensiveness on a phrase association test. (Shedler et al., 1993)

# Accuracy of Self-report - 6

- 1008 New Zealand 18 year olds who had participated in a longitudinal study had inaccurate recollections of items such as family conflict at various ages as reported earlier by mother, self report of hyperactivity, self report of depression Henry et al., 1994

# Accuracy of Self-report - 7

- Acute illnesses and sick leave not accurately reported. Illness usually underreported Rogler et al., 1992

# Accuracy of Self Report – 8

- Neuropsychological symptoms are nonspecific
- Negative emotions are more strongly predictive of cognitive symptoms than are objective cognitive deficits
- MUS: cognitive complaints more severe than objective deficits

# Accuracy of Self Report – 9

- Normal college students' symptoms (Gouvier et al 1988)
- Memory loss 20%
- Loss of interest 36%
- Temper problems 37%
- Many symptoms as common in normals as in TBI patients

# Accuracy of Self-Report 10

- Litigation is associated with complaints despite absence of neuro hx (Lees-Haley & Brown, 1993)
- Concentration 78%
- Confusion 59%
- Memory loss 53%
- Dizziness 44% Word Finding 34%



# Accuracy of Self-report 11

- Depressives had more physical and mental sx than normal or MHT participants (Trahan et al, 2001)

Concentration 54%, HA 37%, Fatigue 68%

Also more trouble with shortness of breath and remembering names

# Accuracy of Self-report 12

- Patients with MUS had significantly more incorrect reports of previous medical diagnoses than patients with confirmed neurological diagnoses (Schrag et al, 2004)

# Accuracy of Self-Report: Lies and Untruths

- Not all misstatements are lies
- GPA and years of schooling are commonly exaggerated
- Less frequent but more colorful exaggerations of education, athletic feats, military service, etc.

# Extreme Exaggerations

- College degrees
- Military: Combat, Special Forces
- Athletics
- Blatant Denial of past medical and psychiatric history
- Criminal history: denial of convictions, actual guilt.

# Detection of Extreme Exaggerations

- They can be detected by comparing and contrasting records that may show conflicting information, and by obtaining additional records. Educational attainment can be ascertained by phone or the internet.

# Clinical Implications of Extreme Exaggeration

- People who outrageously exaggerate their past accomplishments or who outrageously minimize past problems are untruthful. Their reports of current problems and their effort should be closely scrutinized.

# Accuracy of Self-report: Implications for Practice -1

Obtain records

Ask historical questions more than once, in more than one way

# Accuracy of Self-report: Implications for Practice - 2

- Disclosure of emotions is healthy
- Patients often incapable of accuracy
- Unreported stressors may be the most damaging to physical and mental health
- Disclosure of trauma must be titrated - too much disclosure can be traumatic for some people



# Implications for Practice - 3

- “I hope the doctor finds something wrong so that I will have a reason to stop hating you.”  
(comment before exam of wife to patient who had no objective evidence of NP deficits)
- Some families and patients prefer physical explanations for symptoms

# Implications for Practice - 4

## patient behavior

- Outcome after treatment not always related to accepting a psych cause. Changing attitudes about the illness sometimes more important
- Increase exercise
- Change to belief that the illness not life threatening

# Implications for Practice - 5

- Physicians are more likely to err on the side of diagnosing symptoms as medically explained rather than unexplained.
- This practice is beneficial to patients who truly have disease, and it is harmful to patients who truly have MUS.

# Implications for Practice - 6

- Cognitive behavior therapy, including self disclosure demonstrably effective with FM and Gulf War Illnesses, by implication, for others where fatigue or pain are symptoms
- Pain clinic approach
- Other psychotherapeutic interventions have powerful anecdotal support. Their applicability is limited by preference for a medical explanation.

# Existential Themes in MUS

P. Feldman

- Do I have the right to exist?
- Do I have the right to have my needs met?
- Can I be in control of my life?
- Much of these themes is related to premorbid adjustment issues.