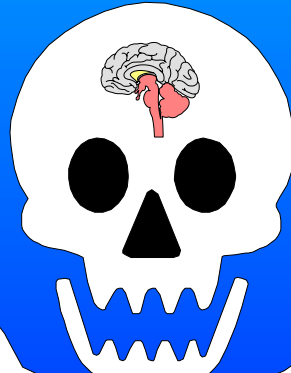


Pain, The Brain* and Neuropsychological Function



*(Pain Sensor Organ)

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International Neuropsychological Society, St. Louis, 2005

PHENOMENOLOGY OF PAIN: A BIOPSYCHOSOCIAL CONCEPTUALIZATION

- IASP (1986): "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"
- Complex Multidimensional SUBJECTIVE EXPERIENCE
 - SENSORY VS AFFECTIVE
 - ACUTE VERSUS CHRONIC
 - PAIN MAINTENANCE PATTERNS

PAIN DISTINCTIONS

Chronic

- **> 6 months**
- **Ambiguous Connections Between CNS and Injury Site**
- **Useless Old Information**
- **Perpetuates Maladaptive Protection**

Acute

- **< 6 months**
- **Relatively Discrete Neuroanatomic Connections to Injury Site**
- **Useful New Information**
- **Survival Value Signaling Need for Corrective Action**


CHRONIC PAIN

- **There can be Injury without Pain & Pain without Injury**
- **An estimated 5% is Psychogenic (e.g., conversional)**
- **An estimated 20% is Exaggerated, Malingered and/or Primarily Psychologically Mediated**
- **Correlates Between Physical Signs and Pain Complaint are Generally Weak**
- **With Time, Pathways Connecting Injury Site to CNS change and Lead to Emotional Distress, Energy Decrease and Neurohormonal changes**
- **ACC, Basal Ganglion and Limbic System, HPA Dysfunction is Typically Found**
- **Subjective Cognitive Complaints are Common**
 - ▶ **Multiple Lines of Evidence Suggest Objective Cognitive Impairment Can and Does Occur**

CHRONIC PAIN *(continued)*

- Depression is a Common Sequelae
 - ▶ Multiple Lines of Evidence Indicate an Association with Cognitive Impairment
- Sleep Disturbance is a Common Sequelae
 - ▶ Sleep Deprivation Strongly Associated with Cognitive Impairment
- Women are More Likely to Complain of Pain
- Certain Cultural Groups Complain More
- Depressed, Anxious Complain More (serotonin relevant in all)
- 33% Never Seek Treatment
- 45 to 90 Million Americans Are Affected
- Most Patients Do Not Improve After Legal Settlement

HEADACHE...

 *A Pain in the
Brain that can
drive you Insane*

Unknown Author

Alice in Wonderland?

Post Traumatic Headache (PTHA)

- ▶ PTH, or HA following trauma to head, brain and/or neck (or PTH) - most common post traumatic symptom after mild TBI, whiplash
 - Incidence of early or "acute": 50 - 90%
 - Incidence at 6 mos (chronic PTH): 15 - 45%
 - Incidence at 4 years: 10 - 20%
- ▶ PTHA is more Treatment Resistant than HA
- ▶ Brain Injury considered least likely cause
- ▶ PTH associated with greater subjective complaints of cognitive interference than other chronic pain types

ETIOLOGIES

- ▶ CEREBRAL, CRANIAL &/OR CERVICAL INJURY
- ▶ CATEGORIES
 - ➔ Musculoskeletal
 - ➔ Vascular
 - ➔ Mixed
 - ➔ Neuroma / Neuritic
 - ➔ Other Causes
- ▶ SOURCES OF HEAD PAIN
 - ➔ Intracranial
 - ➔ Extracranial

OVERLAPPING POST TRAUMATIC DIAGNOSES

- Post Concussion Syndrome
- Post Trauma Syndrome
- Accident Neurosis
- Post Traumatic Headache

CCCV

Methodologic Considerations

- **Functional vs Testing vs Response Bias**
 - ▶ 1. Pain 2. Cognitive Function & Performance
- **Assessment Methodology: NP, Experimental, etc.**
- **Litigation v Clinical**
- **With or Without Neurologic Insult**
- **Pain Meds and Type**
 - ▶ 1. Schedule v prn; 2. Reported v Not; 3. Synergistic Effects...
- **Depression, Anxiety and PTSD** as frequently comorbid after pain inducing injury or repetitive pain experience... producing ANS / CNS hyperarousals; Uniformity Myths
- **Sleep Deprivation and Type**
 - ▶ Partial, Total, Duration, etc.
- **Combinations & Interactions...**

Posttraumatic Headache (PTH) and Neuropsychological Performance

Martelli, Grayson and Zasler, 1999

- Given sensitive neuropsychological measures, significant neuropsychological effects often found
- Information processing speed and complex attention are most frequently observed
- Cognitive flexibility, verbal associative fluency and learning deficits often noted and may be secondary.
- Other chronic pain: More chronic pain and more pain related symptomatology typically produce impaired performances on select neuropsychological tests

Posttraumatic Headache (PTH) and Neuropsychological Performance

*Martelli, Grayson and Zasler, 1999 (continued)**

- Abnormal SPECT findings are typical in persons with many chronic pain syndromes.
- Pattern of neuropsychological impairments appeared similar to that produced by MTBI, posing a differential diagnostic dilemma. Validity and utility of neuropsychological test based inferences regarding brain injury necessarily depend on assurances that the effects of chronic headache and other chronic pain symptoms are taken into consideration.
- Successful resolution of PCS may frequently hinge on successful resolution of, or adaptation to PTH

Relationship of Pain, Cognition and TBI

Nicholson, 2000

- Effect of pain, acute or chronic, with or without possible MTBI, most evident on aspects of attention, memory, speed of processing, and executive control (cf. MTBI).
- Numerous functional neuroimaging studies indicate disruption of brain processes
- Differential diagnosis concerns greatest in suspected TBI with pain problems
- Previous studies of MTBI, esp. PPCS, may have been confounded by pain related problems

Relationship of Pain, Cognition and TBI

Nicholson, 2000 (continued)

- Problems discriminating cognitive - behavioral effects of brain injury from pain, other factors, potentially limits utility of neuropsych assessment
- Considerable variability in studies noted, along with confounding effect of associated problems such as fatigue, depression, anxiety, medication side effects, or other factors.
- Onset, maintenance, exacerbation or severity of pain problems may be related to a process of central sensitization associated with psychological factors or pre-existing vulnerability

Chronic Pain & Neuropsychological Functioning: *Hart, Martelli and Zasler, 2000*

- Cognitive impairment associated with higher pain intensity, involvement of head and neck areas ("cervicoencephalic syndrome")
- Studies tended to support an association between cognitive impairment and other concomitant symptoms: mood change, increased somatic awareness, sleep disturbance, and fatigue.
- Further studies needed to clarify variables mediating impact of pain on neuropsychological functioning and the unique role of various symptoms often associated with chronic pain.

Review of Reviews of Effect of Pain on Neuropsychological Functioning

Martelli, Zasler, Nicholson and Hart, 2001 (JCMC)

- Pain and pain related symptomatology can, often do produce impaired neuropsychological performances: attentional capacity, processing speed, psychomotor speed, executive functions.
- Pattern of neuropsychological impairment appears similar to that in MTBI.
- Functional neuroimaging abnormalities consistent with observed cognitive decrements
- In cases of putative MTBI, pain and concomitants must be considered.

Review of Reviews of Effect of Pain on Neuropsychological Functioning

Martelli, Zasler, Nicholson and Hart, 2001 (continued)

- CPain doesn't always cause cognitive impairment
- Neurophysiologic changes are probably pain reactive, reversible
- Associated symptoms (e.g., depression, sleep disturbance, fatigue, anxiety and pain vigilance) & premorbid coping vulnerabilities, likely play a predominant role in mediating impact of Cpain on cognitive functioning
- Cpain and its concomitants represent a source of performance variance and caution is warranted in interpreting decrements in neuropsychological test scores as signs of neurologic sequelae of brain disease or injury in patients with chronic pain

The Evidence: Summary

- (A) Experimental animal and human information processing / attentional capacity literature indicates that distractors less aversive than pain disrupt attention, as does pain
- (B) experimental rhodent and mammal studies showing disrupted maze and other learning for both appetitive (e.g, food reward) and avoidant (eg, shock) stimuli
- (C) experimental rhodent studies showing improved performance with cessation of pain
- (D) experimental rhodent and mammal studies showing improved performance after administration of pain relieving medications known to disrupt cognition
- (E) experimental human studies showing improved cognitive (controlled vs. automatic processes; other cognitive) performance after discontinuation of pain stimulus and administration of opiod pain relievers

The Evidence *(continued)*

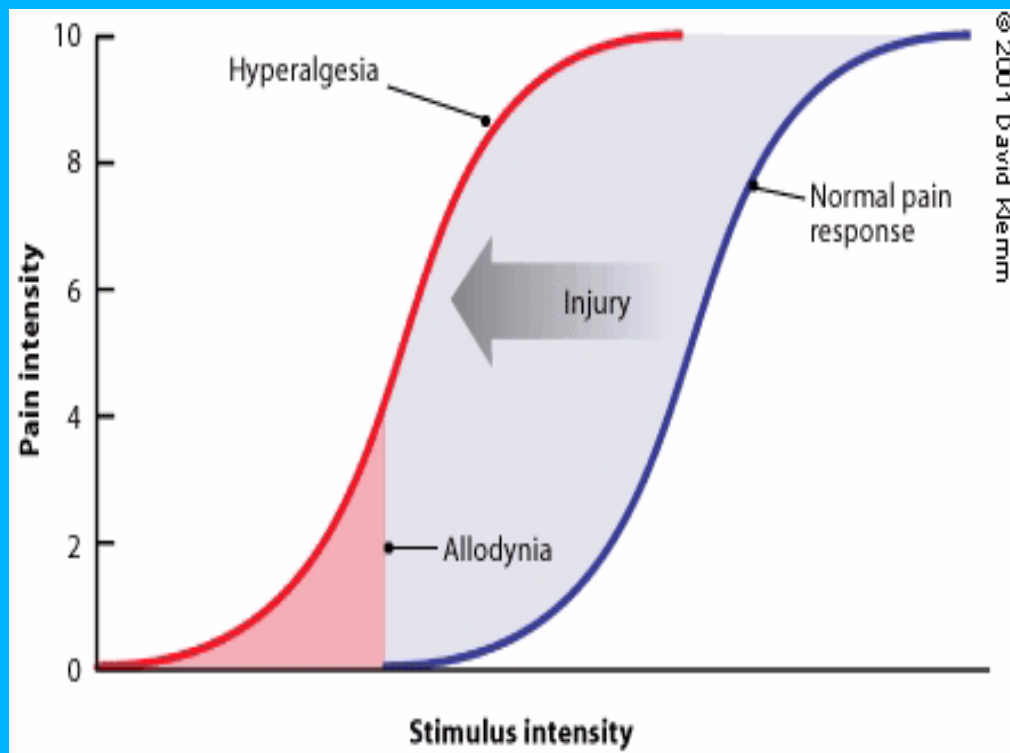
- (F) clinical studies showing improved cognitive (controlled vs automatic processes; other cognitive) performance after discontinuation of pain stimulus and/or administration of opioids
- (G) animal studies showing that stress (including chronic pain) is associated with damage to the hippocampus, inhibition of neurogenesis, and deficits in hippocampal-based memory function.
- (H) PTSD findings of deficits in hippocampal-based declarative verbal memory associated with smaller hippocampal volume.
- (I) recent preclinical evidence showing that SSRI's promote neurogenesis, reverse effects of stress on hippocampal atrophy, improve cognitive deficits observed in OCD and depression, etc.
- (J) a majority of studies indicating at least attention dysregulation, in chronic and acute pain patients. *Although many of these did not employ explicit response bias measures for pain or cognition, some designs circumvented this (e.g., experimental pain, neuropathic pain, reward designs), some included neurophysiologic measures, combination neuropsych and neurophysiologic measures, and new ones are addressing this more diligently.*

The Evidence *(continued)*

- (K) consistent neurophysiologic studies showing very specific neurophysiologic (i.e., ACC) patterns associated with chronic pain and attentional disruption, superimposed over more general patterns, consistent with other disorders with reasonable evidence of cognitive impairments and similar neurophysiologic expressions
- (L) neural plasticity / cerebral reorganization associated with chronic pain showing functional cerebral changes (e.g. Flor's studies showing expansion of sensory cortex),
- (M) neuroendocrine and HPA perturbation in and chronic pain and evidence that pain and chronic stress (and depression) are linked via chronic stress-induced HPA dysfunction (along with evidence of combined muscle energy depletion and serotonin deficiency (peripherally, but also centrally), along with depressed levels of somatomedin C, caused by deficit of stage 4 sleep dependent release of GH, and elevated NE response levels in fibro, etc.;

The Evidence *(continued)*

- (N) amassing neurophysiologic evidence of central sensitization (inc. Am Acad of Pain Mgmt definition: "chronic neuromuscular pain") and disrupted pain inhibitory mechanisms associated with dysfunctional ACC functioning of both anterior / ventral and posterior/ dorsal quadrants (associated with cognitive and affective regulation, respectively), with evidence that less severe and less disruptive chronic pain is associated with a greater habituation response to painful stimuli (vs. sensitization) and not associated with cognitive disruption. The newest integration of these findings link a biopsychosocial model where genetics, learning history and psychological variables interact, with a clear role played by anxiety and avoidance conditioning to produce a pattern of pain arousal that mimics OCD, chronic or severe depression, PTSD or high trait anxiety, with hypoaroused inhibition (ACG hypofunction) of pain, obsessive thoughts, anxiety, somatic concerns, intrusive associations/ memories) and disrupted allocation of attentional resources.



The Evidence *(continued)*

- (O) evidence that the concomitants of chronic pain most likely account for cognitive disruption, given that many of them, singularly, account for cognitive impairment: sleep disturbance / deprivation (e.g., metaanalytic studies showing impaired attention and psychomotor function - more impaired compared to alcohol intoxication); pain medications; depression and anxiety; and likelihood that combinations are additive.
- (P) consistent findings showing both normalization of neuropathophysiology and cognitive function (for performance and self reported improvements in cognition) after effective pain reduction interventions

Pain & Cognition Review: Significance of Stress

Hart, Wade and Martelli, 2003


- Psychological distress assoc'd with cognitive impairment, esp for pain-related negative emotions & variables mediating suffering (activity interference, somatic vigilance)
 - independent of pain intensity.
- Probable underlying neurophysiologic substrates:
 - ▶ 1. ACC (pain processing & affective-motivational experience) mediates impact of pain-related emotional distress on cognitive functioning through allocation of attentional resources.
 - ▶ 2. Maladaptive physiologic stress responses and HPA dysregulation negatively effects hippocampal function and memory.
 - Anticipation of unpredictable pain symptoms, esp in ind's with high trait neuroticism, presents significant stressor repeatedly activating HPA and ACC areas, thereby disrupting cognitive efficiency.

PAIN. *In Press*. Hyperalgesia versus response bias in fibromyalgia. Roger B. Fillingim

*The findings of Petzke et al. (2003) further indicate that individuals with FM process nociceptive information differently than controls. There are inevitably multiple biopsychosocial factors that interact in complex ways to produce these alterations in pain sensitivity. The results of their research suggest that **measures of pain sensitivity that are freer of response bias still demonstrate enhanced pain responses in FM.** The mechanisms underlying the enhanced pain responses of FM patients remain to be determined, but the careful and **systematic research described by Petzke et al.(2003) informs us that the enhanced pain sensitivity in FM is not an artifact of response bias.** A more thorough understanding of the hyperalgesia observed in FM will help elucidate its **pathophysiology**, ultimately leading to more effective diagnosis and treatment of this complex and disabling syndrome.*

RESPONSE BIAS: REPORT OF PAIN

Chronic pain disability exaggeration/malingering and submaximal effort research (review 1961-1999). *Fishbain et al, Clinical Journal of Pain. Vol 15(4), 1999, 244-274.*

 "It is concluded that there is no reliable detection of malingering or of degree of pain."

Malingering Pain in the Medicolegal Context. (review). *Mendelson & Mendelson, Clinical Journal of Pain. 20(6):423-432.*

 "**There are, however, no valid clinical methods of assessment of possible malingering of pain.** In our view, the ultimate issue of the veracity of the plaintiff is for the Court to decide, and epithets such as "malingerer" have no place in reports prepared for legal purposes by health care professionals."

Fishbain (2004) Metaanalysis on Waddell signs:

- Not correlated with psychological distress or secondary gain
- Do not discriminate organic from nonorganic problems
- May represent an organic phenomenon
- Associated with greater pain levels and poorer treatment outcomes

Other False Positives Indicators: Pain Relief by DISTRACTION, Nondermatomal, MMPI, etc.!!!

Waddel Signs: Prevalent But Unsupported

1. **Overreaction:** *Guarding/limping, bracing, rubbing, grimacing, sighing.*
2. **Tenderness:** *Widespread sensitivity to light touch of superficial tissue.*
3. **Axial Loading:** *Light pressure to skull of standing patient should not significantly increase low back symptoms.*
4. **Rotation:** *Back pain is reported when shoulders and pelvis are passively rotated in the same plane.*
5. **Straight Leg Raising:** *Marked difference between leg raising in the supine and seated position*
6. **Motor and Sensory:** *Giving way or cog wheeling to motor testing or regional sensory loss in a stocking or non dermatomal distribution (R/O PeriphNervDysf)*

Response Bias: Symptomatic Late post-Whiplash Pts *(Schmand et al)*

- ➔ **Malingering group (ASTM) performed similarly to Severe CHI**
- ➔ **Non-maling group > Maling, CHI < Controls**
- ➔ **...a significant proportion of post-whiplash patients underperformed**
 - ➔ **Clinical:**
 - ➔ **Litigation:**
- ➔ **Both malingering and non-malingering patients scored below normal controls on memory and concentration tests.**
 - ➔ **malingering post-whiplash patients performed as poorly as the patients with closed head injury.**
- ➔ **Replicates earlier findings of compromised memory and attention in late post-whiplash patients.**

Neuropsych Test Scores

Schmand et al JNNP, 64, 339-343

	<i>Whiplash non-malingering (n=65) group 1</i>	<i>Whiplash malingering (n=43) group 2</i>	<i>Closed head injury (n=20) group 3</i>	<i>Normal controls (n=46) group 4</i>	<i>Scheffé p value <0.05</i>	
Fluency animals	55.0 (9.8)	49.0 (10.2)	51.2 (9.2)	56.2 (6.6)	**	2<1<4
Professions	53.6 (9.9)	48.5 (8.8)	50.6 (8.0)	54.4 (8.0)	*	
WAIS substitution	57.9 (10.3)	49.5 (13.0)	50.7 (10.7)	64.0 (8.8)	***	2,3<1<4
Stroop card 1	47 (13)	59 (30)	51 (11)	41 (6)	**	2>1,4 3>4
Stroop card 2	63 (17)	78 (32)	68 (17)	54 (7)	***	2>1,4 3>4
Stroop card 3	99 (30)	140 (83)	112 (38)	86 (17)	***	2>1,4
Trail making A	35 (13)	50 (28)	40 (19)	30 (10)	**	2>1,4
Trail making B	69 (23)	114 (57)	88 (45)	60 (22)	***	2>1,4 3>4
AVLT learning	48.6 (8.8)	37.7 (8.8)	37.6 (11.0)	54.9 (8.2)	***	2,3<1<4
AVLT recall	10.6 (2.8)	6.7 (3.0)	7.0 (4.0)	12.3 (2.5)	***	2,3<1<4
AVLT recognition	28.4 (2.7)	25.2 (3.4)	26.8 (3.4)	29.7 (0.9)	***	2,3<1<4
Logical memory	9.8 (3.6)	7.9 (3.1)	8.1 (2.6)	11.9 (1.5)	***	2<1 1,2,3<4
Logical memory recall	8.3 (3.9)	5.8 (2.9)	5.8 (3.2)	10.1 (1.7)	***	2,3<1<4

Neuropsychological impairment in fibromyalgia: Relation to depression, fatigue, and pain *Suhr, J, Psychosomatic Res, 55, 321-329*

Measure (range)	FM (n=23)		Chronic pain (n=22)		Healthy controls (n=21)		Effect size ^a
	Mean (S.D.)	EMM ^b	Mean (S.D.)	EMM	Mean (S.D.)	EMM	
COWA (21-82)	37.5 (8.1)	37.9	37.9 (9.9)	37.9	47.4 (14.1)	46.9	.11
DS (6-17)	10.2 (2.5)	10.7	10.5 (2.5)	10.3	11.8 (2.3)	11.3	.03
SS (7-19)	11.3 (2.3)	11.3	11.8 (2.9)	11.8	12.2 (2.9)	12.0	.01
TMT A (14-64)	28.0 (9.3)	30.1	27.7 (10.3)	27.0	24.7 (6.9)	23.1	.06
TMT B (29-182)	68.9 (28.7)	66.9	72.0 (36.1)	72.3	52.3 (11.2)	54.1	.07

Neuropsychological Impairment (Suhr, cont)

- FM Cog C/o > NP Perf
- Dep related to Memory Perf
- Fatigue related to Psychomotor Speed
- NP Tests didn't add to variance in subjective cog c/o after accounting for Dep, Pain, Fatigue.

➤ EFFORT EFFECT

- AVLT Index Failure: 5/28 FM; 5/27 Chronic Pain
- Reported Less Cog C/o than Effortful Pts?

PAIN EFFECT

➤ Impaired Scores:

- FM = .9; CP = .9; Control = .6
- No Effect after Controlling for Dep, Pain, Fatigue

CONCLUSION: Psych factors, particularly effort, depression, and fatigue, important in understanding subjective c/o and objective cognitive impairment in FM and chronic pain disorders.

Sleep Deprivation & Cognition

- **U Penn Study (NIH, 2003): S's slept 4-6 hours for 14 nights**
 - ▶ Cog Perf Deficits equiv to 3 days w/o sleep
 - ▶ S's reported not feeling sleepy (Impaired Percept/Aware.)
- **Cognitive Performance Problems:**
 - ▶ **Attention Regulation**
 - ▶ **Information Processing Speed & Efficiency**
 - ▶ **Multi-tasking**
 - ▶ **Memory, mathematical skills, and many other skills**
- **Sleep deprivation reduces REM sleep**
 - ▶ **Learning reduced with REM reduction (Troczel, 2000)**
 - ▶ **Brain areas activated during daytime learning reactivated during sleep (Larkin, 2000)**
- **Reasoning/Problem Solving (Stickgold, 2004)**
 - ▶ Half participant imbibed before bed
 - 40% worse vs. Non Imbibers on Re-test
 - ▶ ETOH suppresses REM sleep / memory



Sleep and Functional Performance

• Driving

- 6 hrs/night reduce Coord, RT & Judgment, driving performance "as much as alcohol"
- Performance @ 17-19 hrs awake worse than BAL of .05
- Night Driving, Longer Driver = Worse (Phillips, 1999).

• Medical, Aeronautic, Military, Other Work Perf.

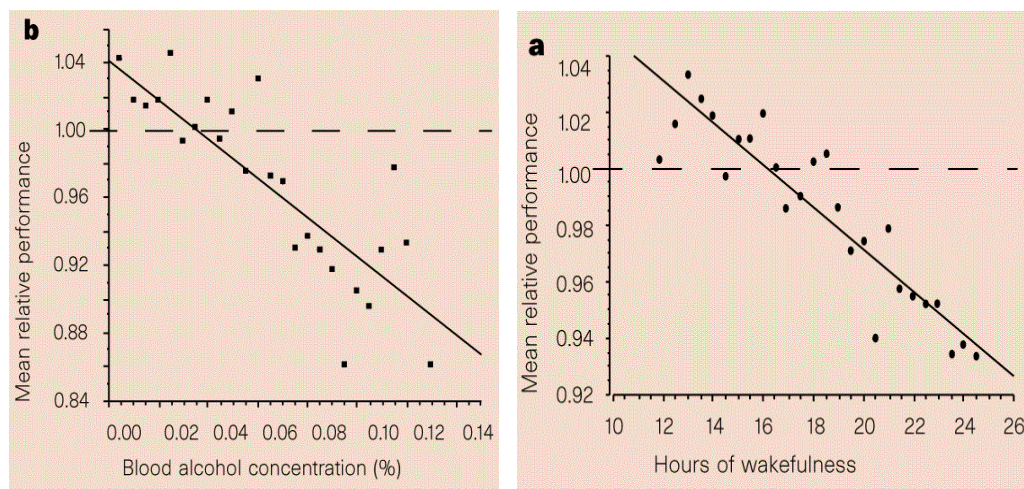
- Landrigan CP, Rothschild JM, Cronin JW, et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. N Engl J Med 2004;351(18):1838-48.
- Lockley SW, Cronin JW, Evans EE, et al. Effect of reducing interns' weekly work hours on sleep and attentional failures. Engl J Med 2004;351(18):1829-37.
- Wu AW, Folkman S, McPhee SJ, Lo B. "Do house officers learn from their mistakes?" JAMA, 1991; 265: 2089-94.
- See Bibliography and Abstracts at villamartelli.com

Determinants of the behavioural and performance effects of sleep loss

<p>Sleep and circadian influences</p> <p>Prior sleep amount and distribution Length of time awake Circadian time</p>	<p>Subject characteristics</p> <p>Age Personality and psychopathology</p>
<p>Arousal influences</p> <p>Activity, bright light, noise, temperature, posture, drugs, interest, motivation, history of exposure to sleep loss</p>	<p>Test characteristics and types</p> <p>Length of test, knowledge of results, test pacing, proficiency level, difficulty or complexity of test, short-term memory requirement, subjective vs objective measures, EEG measures (MSLT)</p>

Bonnet (2000)

Effects of Sleep Deprivation on Functioning



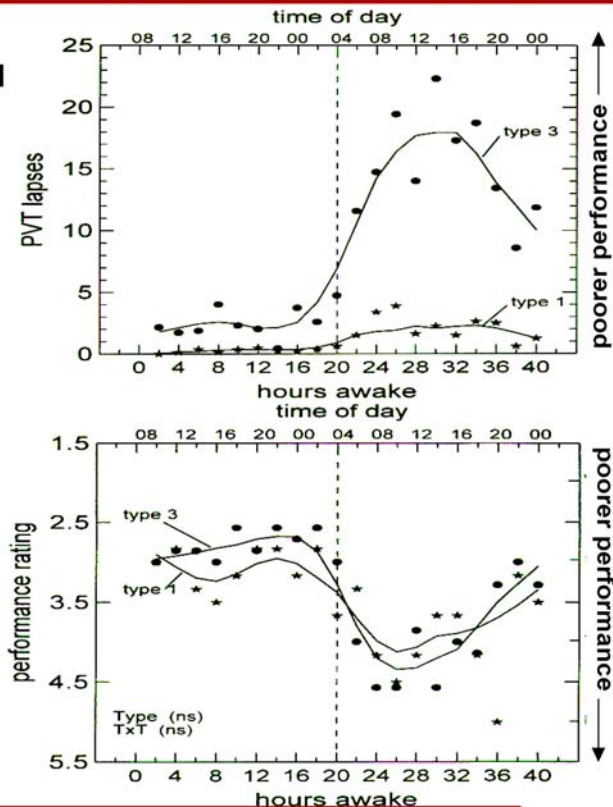
Dawson D, Reid K. Fatigue, alcohol and performance impairment. *Nature* 1997;388(6639):235.

Differential vulnerability to cognitive effects of sleep loss

There are substantial individual differences in cognitive response to sleep loss. Some people (type 3 responses) are severely affected, while others (type 1 responses) are less affected.

Despite large individual differences in cognitive responses to sleep loss, subjects appear to be unaware of their differential responses (type 1 = type 3 responses)

Dinges et al. (2000)

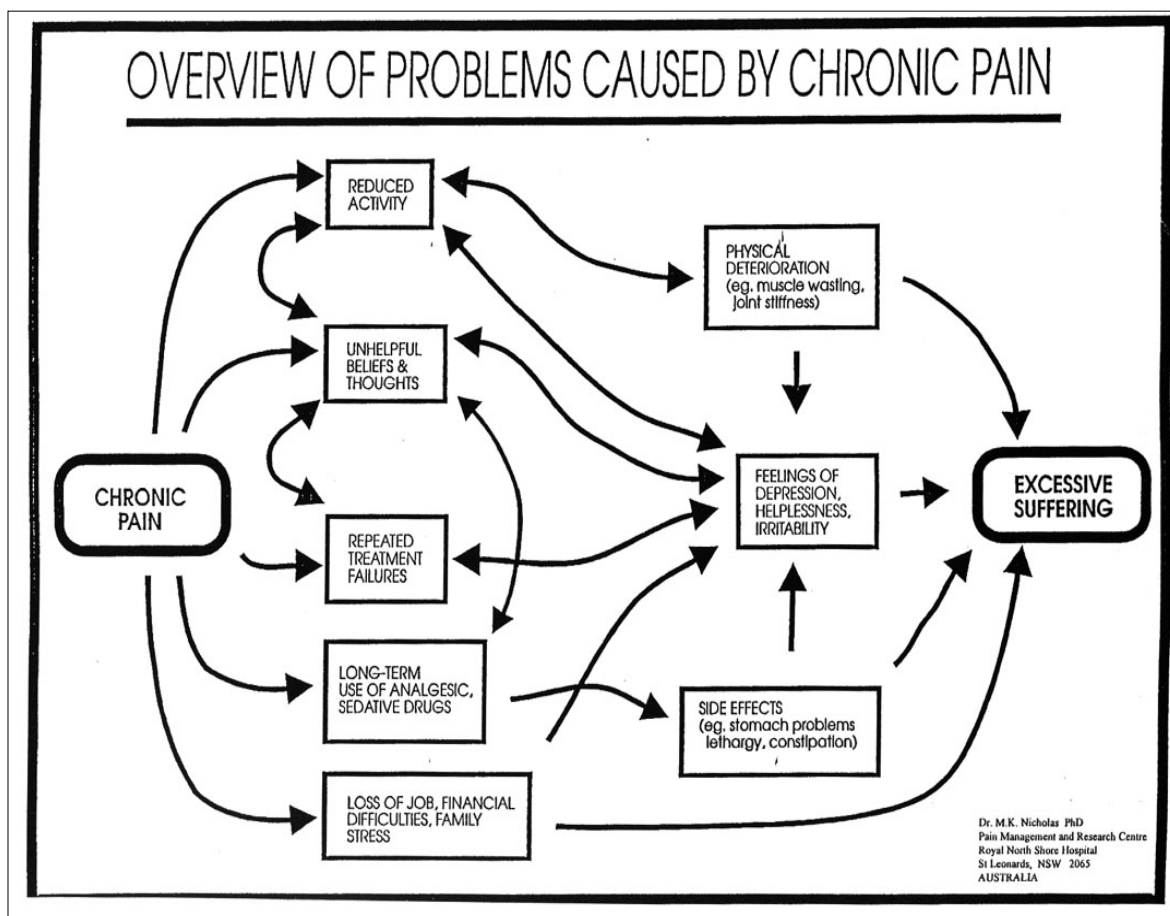


Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Van Dongen et al, Sleep, 1:27(3):423-33, 2004*

- ➔ "Neurobehavioral deficits from sleep loss varied significantly among individuals and were stable within individuals. Interindividual differences in neurobehavioral responses to sleep deprivation were not merely a consequence of variations in sleep history. Rather, they involved trait-like differential vulnerability to impairment from sleep loss, for which neurobiologic correlates have yet to be discovered."
- ➔ These seem to parallel interindividual diff's in vulnerability to pain (and anxiety, depression, PTSD, etc...)
- ➔ The relationships & Interactions have not been studied

Sleep Disturbance and Hyperalgesia

- The effect of sleep deprivation on pain. Kundermann et al (2004). (Review). *Pain Res & Mgmt*, 9(1):25-32
 - ▶ Experimental human and animal studies on the effects... sleep deprivation produces hyperalgesic changes. Furthermore, sleep deprivation can counteract analgesic effects of pharmacological treatments involving opioidergic and serotonergic mechanisms of action....
- Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers. Kundermann et al (2004). *Psychosom Med*, 66(6):932-7
 - ▶ ...pain thresholds tended to decrease also during sleep deprivation, whereas the warmth and cold detection thresholds remained unaffected. Pain complaints were not induced by sleep deprivation.... findings suggest that sleep deprivation produces hyperalgesic changes that cannot be explained by nonspecific alterations in somatosensory functions.





Pain 79 (1999) 105–111

PAIN

Review Article

The cortical representation of pain

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Received 22 June 1998; accepted 31 August 1998

Central representation of pain: PET studies (4 centres; 11 studies)

Contralateral	%
anterior cingulate cortex	82
thalamus	50-70
insula	64
S2 cortex	45
sensorimotor cortex (S1/M1)	45
lenticulate nucleus	40-50
posterior parietal cortex	36
lateral prefrontal cortex	36
premotor cortex	27
Ipsilateral	
thalamus	30
Midline	
cerebellum	75
dorsal midbrain PAG	50

Casey KL (1997) IASP 8th World Congress

Anterior Cingulate Cortex

- **Most common activation site in pain studies (caudal ACC)**
- **Major target of opioids (rostral ACC) ***
- **Extensive connections - limbic and autonomic**
- **Contains NS and WDR neurons; neurons have very large receptive fields**
- **Intensity coding; Integration of affect, Cognition and Response Selection; Social Behaviour**
- **Pain & Unpleasantness likely encoded in caudal region**
- **Deep Brain Stim: Reperfusion of ACC correlated with Pain Relief**
- ***high placebo responders activated same area as opioids**

Chronic Back Pain & Prefrontal, Thalamic Gray Matter

- *J of Neurosci, 24(46):10410-10415; Chronic Back Pain Is Associated with Decreased Prefrontal & Thalamic Gray Matter Density. Apkarian et al (2004)*
- **Patients with CBP showed 5-11% less neocortical gray matter volume than control subjects.... magnitude of this decrease is equivalent to the gray matter volume lost in 10-20 years of normal aging.... was related to pain duration, indicating a 1.3 cm³ loss of gray matter for every year of chronic pain.... compared with matched controls using voxel-based morphometry and nonparametric statistics.... reduced in bilateral dorsolateral prefrontal cortex and right thalamus... strongly related to pain characteristics in a pattern distinct for neuropathic and non-neuropathic CBP.... imply that CBP is accompanied by brain atrophy and suggest that the pathophysiology of chronic pain includes thalamocortical processes.**

Updating Canon's 1929 "Fight - Flight" Response

Ethological & Human Research

Bracha et al: Psychosomatics 45:448-449, October 2004; Gray, 1988

■ "Flight or Fight" Not Fight or Flight

▶ 1. Freeze Response: *hypervigilance*

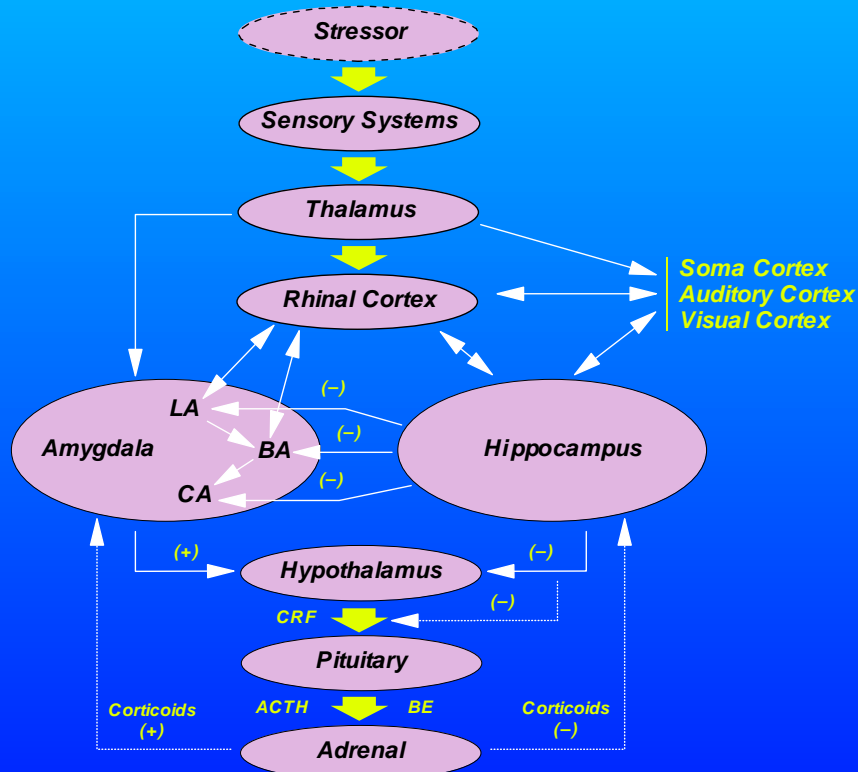
– "stop, look & listen"; avoid detection

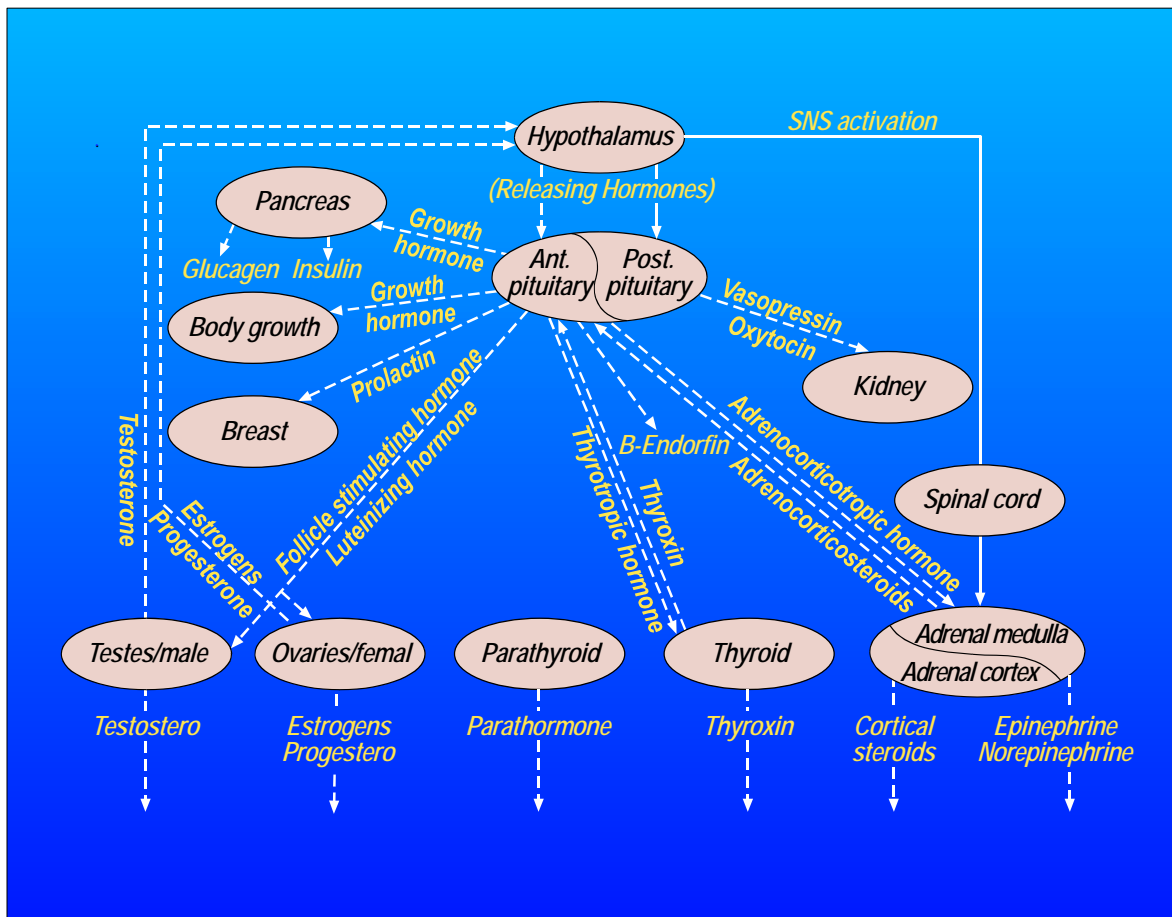
▶ 2. Attempt to Flee

▶ 3. Attempt to Fight

▶ 4. Fright Response: *Tonic immobility*

– "playing dead"; cf rape, violence victims





Stress, Glucocorticoids & Memory

- **Neurogenesis**
 - ▶ increases with learning
 - ▶ decreases with stress
- **Glucocorticoids**
 - ▶ increase amygdala functions
 - ▶ impair hippocampus functions
 - ▶ impair explicit learning/memory
 - ▶ impair adaptive response to stress
 - ▶ produces depression, futility, learned helplessness

HPA Axis: Anxiety, Pain, Depression

- **Anxiety & Pain**
 - ▶ Amygdala alert!
 - ▶ serotonin, norepi.
 - ▶ vigilance, arousal
- **Benzodiazapines**
 - ▶ enhance gaba, prefrontal & hippocampul functions
 - ▶ Reduce serotonin, norepi. release
- **Depression**
 - ▶ glucocorticoids
 - ▶ impair hippocamp.
 - ▶ impair learning & adaptive responses
- **SSRI's**
 - ▶ increased calcium
 - ▶ enhanced protein synth
 - ▶ enhanced learning
 - ▶ enhanced hippoc. neurogenesis

Perceived Controllability & Pain Response

- *J of Neurosci, 24(32):7199-7203; Perceived Controllability Modulates the Neural Response to Pain. Salomons et al (2004)*
- Previous studies indicate that perceived controllability affects pain tolerance, learning and motivation, and the ability to cope with intractable pain, suggesting that it has profound effects on neural pain processing. Using fMRI...we found that pain that was perceived to be controllable resulted in attenuated activation in the three neural areas most consistently linked with pain processing: the anterior cingulate, insular, and secondary somatosensory cortices. This suggests that activation at these sites is modulated by cognitive variables, such as perceived controllability, and that pain imaging studies may therefore overestimate the degree to which these responses are stimulus driven and generalizable across cognitive contexts.

Pain Catastrophization

- **A negative cognitive response to, or anticipation of, pain**
 - ▶ **Magnification** - “I am afraid that the pain will get worse”
 - ▶ **Rumination** - “I can’t seem to keep it out of my mind”
 - ▶ **Helplessness** - “There’s nothing I can do to reduce the intensity of the pain”
- **Most robust psychosocial variable in the literature**
- **Higher catastrophizing predicts:**
 - ▶ **higher pain intensity ratings, incl. post-op pain, lower tolerance of painful procedures, higher analgesic use**
 - ▶ **poorer physical functioning and greater disability**
 - ▶ **more reports of pain interference in daily activities**
 - ▶ **reduced ability to work & less general activity**
 - ▶ **higher psychological distress & psychosocial dysfunction**
- **Catastrophizing is a better predictor than disease severity, pain levels, age, sex, depression, anxiety**
 - *Sullivan et al (2001) Clin J Pain, 17: 52-64*

Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain.*

2004 Apr;127(Pt 4):835-43. Gracely et al.

- **Method:** characterizations of pain as awful, horrible and unbearable, and brain responses to blunt pressure assessed by functional MRI... with removal of depressive symptomatology effect.
- **Conclusion:** Pain catastrophizing, independent of depression, is significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to amygdala) and motor control.
- These results support the hypothesis that catastrophizing influences pain perception through altering attention and anticipation, and heightening emotional responses to pain. Activation associated with catastrophizing in motor areas of the brain may reflect expressive responses to pain that are associated with greater pain catastrophizing

Learned Helplessness

- **Cell Proliferation in Adult Hippocampus is Decreased by Inescapable Stress: Reversal by Fluoxetine Treatment.** Malberg et al., *Neuropsychopharmacology* 28, 2003, 1562-1571
- **Functional neuroanatomy of learned helplessness,** Bauer et al. *NeuroImage* (in press).
- **Inescapable shock induces resistance to the effects of dexamethasone** O'Connor et al., *Psychoneuroendocrinology*, 28, 4, 2003, 481-500.
- **Characterization and functional significance of glucocorticoid receptors in patients with major depression: modulation by antidepressant treatment**
- **Calfa et al.,** *Psychoneuroendocrinology*, 28, 5, 2003, 687-701.
- **TBI: depression, neurogenesis and medication management...** Perna et al., *JHTR*, 18, 2, 201-.
- **Altered protein kinase a in brain of learned helpless rats: effects of acute and repeated stress.** Dwivedi et al., *Biological Psychiatry* (In Press).
- **Depression: a case of neuronal life and death?** Duman. *Biological Psychiatry* (In Press)

Learned Helplessness *(continued)*

- **Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment.** Vythilingam et al., *Biological Psychiatry* (In Press).
- **Stress models of depression,** Vollmayr and Henn, *Clinical Neuroscience Research*, 3, 4-5, 2003, 245-251.
- **A biopsychosocial model of pain and depression in rheumatoid arthritis: a 12-month longitudinal study.** Covic et al., *Rheumatology*, In Press
- **Stress increases dynorphin immunoreactivity in limbic brain regions and dynorphin antagonism produces antidepressant-like effects.** Ishida et al., *J Neurochem*. 2004 Sep;90(5):1258-68.
- **Brain systems underlying susceptibility to helplessness and depression.** Shumake and Gonzalez-Lima, *Behav Cogn Neurosci Rev*. 2003 Sep;2(3):198-221.

Kinesiophobia/ Cogniphobia

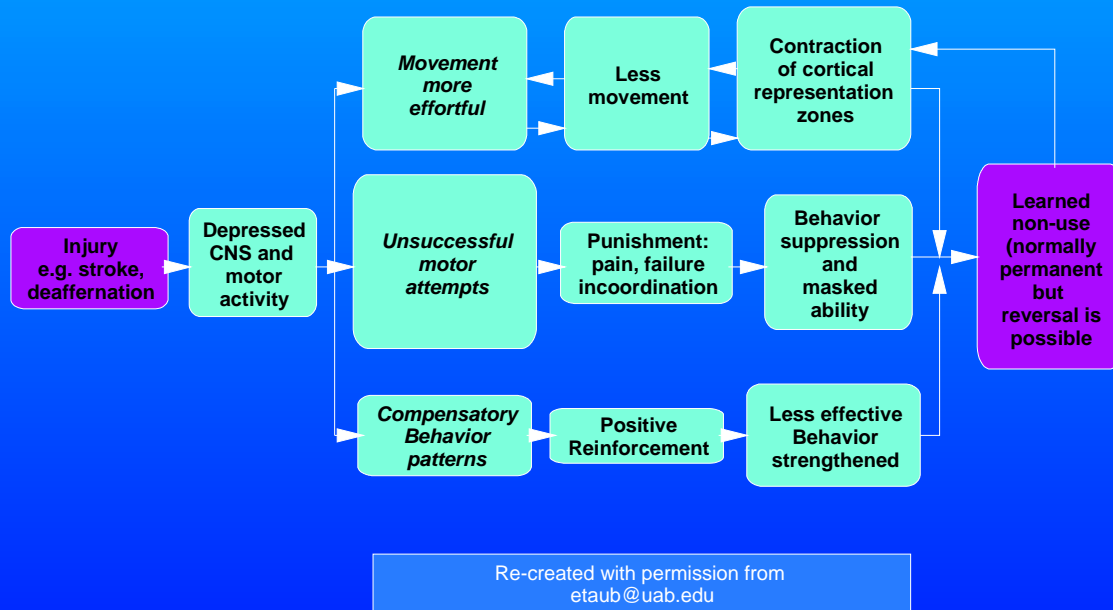
Fear of pain is more disabling than pain itself

- Derived in response to observations by health care treatment specialists of significant avoidance responses in the treatment of chronic back pain
- Defined as the unreasonable or irrational fear of pain and painful reinjury upon physical movement.
- Cogniphobia subsequently proposed as an unreasonable or irrational fear of headache pain or painful reinjury upon cognitive exertion. Phobic responses to pain (or pain phobias), as unhealthy pain maintaining habits, are a major contributor to pain related disability. Cutoff score of 37 discriminates clinically significant levels of avoidance conditioned pain related disability (ACPRD).

Cogniphobia (*continued*)

- **C-Scale Sample Items:** ...make the cause of my head pain worse if I concentrate too much; ...HA telling me that I have something dangerously wrong; ...at risk for the rest of my life; ...being careful not to concentrate too hard or too long is the safest thing I can do ...not safe for a person with a condition like mine to engage in too much thinking and concentrating; No one should ever concentrate on difficult mental tasks when s/he is in pain
- **ACPRD is treatable and can be eliminated through combination therapies:**
 - ▶ **Reeducation**
 - ▶ **Graduated exposure, cognitive reinterpretation and systematic desensitization, and**
 - ▶ **Promotion of adaptive attitudes and treatment participation /cooperation.**

Model of Learned Non-Use



Central Desensitization Options

Countering Central Sensitization

- ☐ **Desensitizing Central Nervous System (CNS) Medications**
 - ☐ Anti-epileptic drugs, Tizanidine HCL, Amytal)
- ☐ **Desensitizing Peripheral Nervous System (PNS) Med's**
 - ☐ muscle relaxants; homeopathics?)
- ☐ **Desensitizing CNS Psychophysiologic Procedures**
 - ☐ EEG Biofeedback or EEG Driven Stimulation (EDS)
 - ☐ CranioElectrotherapy Stimulation (CES)
 - ☐ Sensory Desensitization / Reprocessing Psychotherapy
 - ☐ Adjunctive AudioVisual Stimulation (AVE)
 - ☐ Transcranial Magnetic Stimulation (TMS)
 - ☐ Anterior Cingulate Gyrus Stimulation
- ☐ **Desensitizing PNS Psychophysiologic Procedures**
 - ☐ EMG, EMG, Temp. Biofeedback; Relaxation, TENS, VNS, Massage, Palliative Modalities, Heat/Cold, etc.

Central Desensitization Options

(continued)

- ☐ **Desensitizing Behavioral Activity Procedures**
 - ☐ Graduated Exposure / graduated activity programs / Pacing
 - ☐ Exposure Desensitization Interventions, systematic desensitization, etc.; Pacing
- ☐ **Desensitizing Psychotherapeutic Procedures**
 - ☐ Emotional desensitization of catastrophic reaction to injury and pain and other fears and trauma;
 - ☐ Splinting of emotional reactions; calming the catastrophic reaction;
 - ☐ Emotional reaction systematic desensitization;
 - ☐ Sensory desensitization / reprocessing psychotherapy

HPA, Neuroendocrine Factors & Stress

- **J Psychosom Res. 2002 Oct;53(4):865-71.**
Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. Tsigos C, Chrousos GP.
- **CRH antagonists may be useful in human pathologic states, such as melancholic depression and chronic anxiety, associated with chronic hyperactivity of the stress system, along with predictable behavioral, neuroendocrine, metabolic and immune changes, based on the interrelations outlined above. Conversely, potentiators of CRH secretion/action may be useful to treat atypical depression, postpartum depression and the fibromyalgia/chronic fatigue syndromes, all characterized by low HPA axis and LC/NE activity, fatigue, depressive symptomatology, hyperalgesia and increased immune/inflammatory responses to stimuli.**

"Subjective Health Complaints"

- J Psychosom Res. 2004 Apr;56(4):445-8. Subjective health complaints, sensitization & sustained cognitive activation (stress). Eriksen HR (cf "unexplained medical symptoms").
- Most common: musculoskeletal pain, GI, and "pseudoneurology" (tiredness, sleep problems, fatigue, and mood changes).... common in the general population, but reach a level that requires care and assistance.
- Suggestion: Based on normal physiological processes...which have become intolerable. Cases without somatic disease, or with minimal somatic findings, including: burnout, epidemic fatigue, multiple chemical sensitivity, chronic musculoskeletal pain, chronic low back pain, chronic fatigue syndrome, and fibromyalgia.... particularly common in cases of poor coping and high levels of helplessness and hopelessness.
- CONCLUSION: The psychobiological mechanisms for this is suggested to be sensitization in neural loops maintained by sustained attention and arousal.

Treatments for Posttraumatic Headache

- | | |
|--|-----------------------------------|
| ■ Patient education | ■ Social / assertiveness training |
| ■ Biofeedback -
Psychophysiologic
Self Control | ■ Imagery and hypnosis |
| ■ Cognitive behavioral | ■ Relaxation training |
| ■ Operant treatment | ■ Habit reversal |
| ■ Medication
management | ■ Neurophysiologic TX |
| | ■ Combination Tx's |
| | — CBT & Biofeed. |
| | — Medical & Behav. |

RECOMMENDATIONS FOR ASSESSMENT

- **Chronic pain & associated symptoms are a source of performance variance on NP Tests**
- **Consider postponing assessment where pain and related symptoms (esp sleep disturbance, depression) have not been adequately or aggressively treated**
- **Consider altered test procedures to promote optimal performance & minimize discomfort and distress**
 - Comfortable seating/positioning, use accustomed esthetics, cushions, heating/ice pads, optimized ergonomics, frequent breaks, frequent position changes, modified lighting, etc.
- **Assess (or refer) chronic pain and its concomitants: when complaints cause significant everyday interference, poor pain adaptation; atypical cognitive profiles**
- **Mood, emotional-personality, & pain-specific measures should always be employed. Significant emotional distress, negative pain related beliefs, and inconsistent lifestyle interference should increase caution in attributing performance decrements to brain dysfunction**

RECOMMENDATIONS *(continued)*

- **Assessing presence & severity of pain throughout testing for estimating possible performance effects. More importantly, assess cumulative effects of coping with chronic pain and associated symptoms. Supplement interview with symptom checklists and independent corroborated report assessing associated complaints of chronic pain. Specifically assess associated complaints (e.g., sustained, attention-demanding, timed test at end of a session to identify fatigue-related deficits)**
- **Consider pain medication effects in interpreting test results for persons who rely upon them for pain management (esp given prn use). Restricting use during testing may be inadequate as effects of unmodulated chronic pain may be worse for some aspects of cognitive functioning than induced opiate analgesia.**
- **Always assess response bias to identify exaggeration, estimate pain effects on performance, avoidance, etc. Employ instruments that address motivation, primary and secondary gains and losses.**

Applying General Medical Ethics to Clinical and Forensic Services

Based on the primary ethical principle of **Respect for Others**, four core bioethical principles (*Beauchamp & Childress, 1994*):

Autonomy: *Self-determination re: healthcare-related decisions*

Non-maleficence: *Doing no harm*

Beneficence: *Patient welfare promotion*

Justice: *Equitable distribution of the burdens & benefits of care*

Applying Medical Ethics (cont.)

Changes in Relevant Ethical Standards: A.P.A. 2002

New Principle D (Justice)

- Expands & focuses emphasis on individual professional responsibility & efforts to ensure our processes, procedures & services are just (i.e. not biased), equitable & fair in terms of access and benefit)
- More stringently enjoins taking active precautions to ensure that potential biases (& limitations of competence, expertise and measures) do not lead to or condone unjust practices.
- Applies to neuropsychologists conducting work in increasingly restrictive environments where dwindling reimbursement adds strong financial incentives for forensic work, and where these incentives inherently conflict with objectivity.

Applying Medical Ethics (*cont.*)

Changes in Relevant Ethical Standards: 2002

9.02, 9.06 (*Assessment Procedures, Interpretation*)

- **Tightening of procedures, Increased Accountability, Transparency**
 - More specifically call for use of reliable and valid instruments for the specific pop. (9.02b) being examined
 - More specifically describe strengths & limitations when these have not been established.
 - More specifically consider various situational, personal, cultural, other factors & characteristics of persons that might affect inferences or reduce accuracy of interpretations (9.06)
 - More specifically document any potential limitations, not just examiners concerns
 - Combines standards for forensic and clinical assessment

Conclusion

- **Pain Assessment & Treatment is complicated, challenging.** Pain can have a more disabling effect across a wider range of functions than brain or many other types of injuries.
- **In addition to absence of clear & objective measures, pervasive misconceptions dominate medical and psychological practice.**
- **Familiarity with many important issues and the current knowledge base in the specialty field of pain management is required to effectively Assess and Treat chronic pain**
- **The standards for specialty knowledge and training for treating pain parallel those for treating brain injury**
- **Available options for Neuropsychologists: referral to a someone with specialty competence; consult when referrals cannot be made; acquire knowledge, supervision and training as indicated.**

HANDOUTS & REFERENCES

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• TALKS: SLIDE SHOWS section

THE END

That's all Folks!!

