

CHRONIC PAIN

What is known about the Aetiology?

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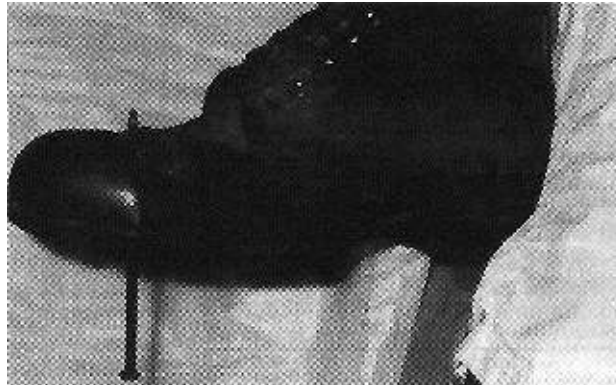
Definition of pain

IASP, 1979

Pain is an unpleasant sensory & emotional experience, associated with actual or potential tissue damage, or described in terms of such damage

“Pain” & “Injury” not synonyms

A builder aged 29 came to the accident and emergency department having jumped down on to a 15 cm nail. As the smallest movement of the nail was painful he was sedated with fentanyl and midazolam. The nail was then pulled out from below. When his boot was removed a miraculous cure appeared to have taken place. Despite entering proximal to the steel toecap the nail had penetrated between the toes: the foot was entirely uninjured.--J P FISHER, senior house officer, D T HASSAN, senior registrar, N O'CONNOR, registrar, accident and emergency department, Leicester Royal Infirmary.

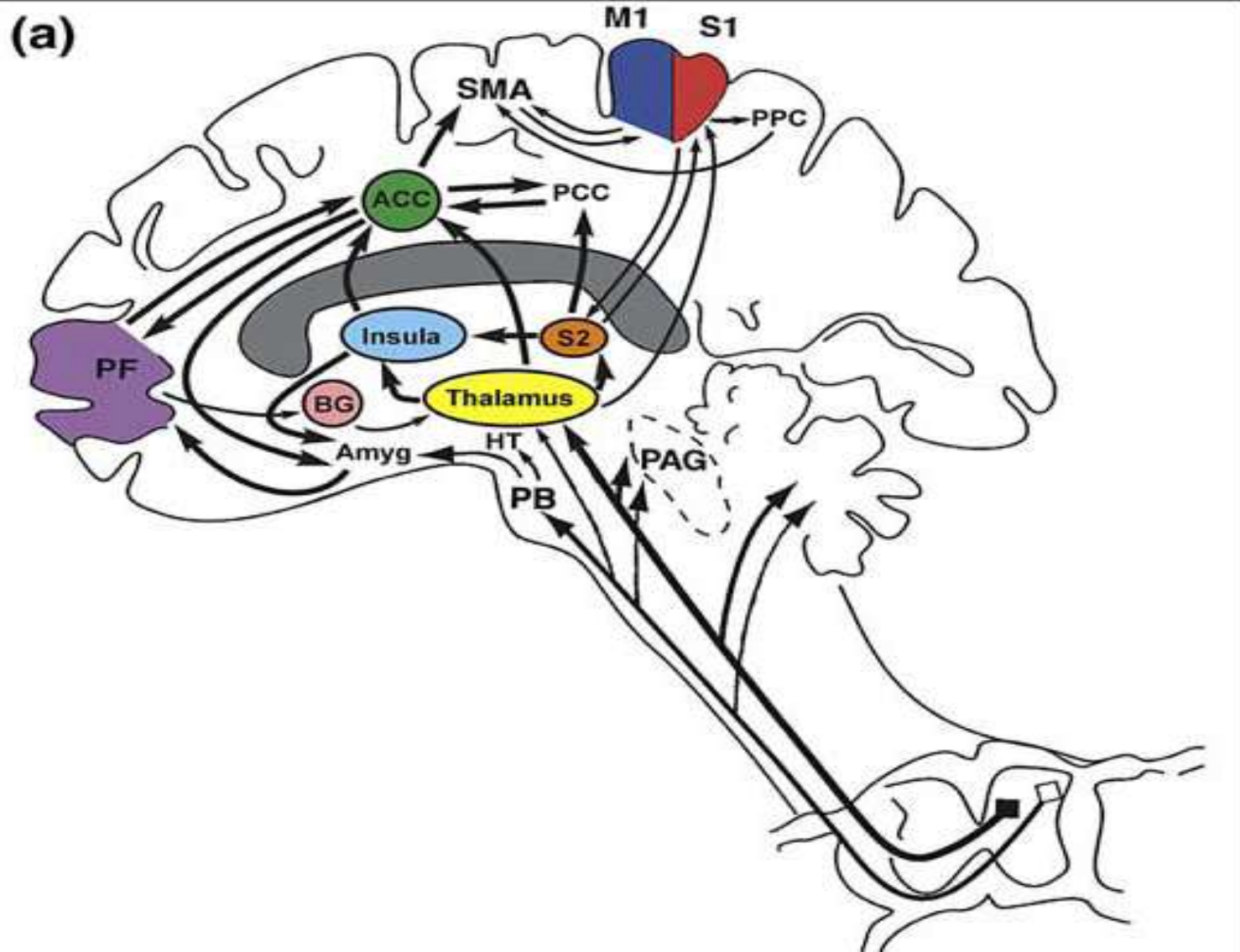


Fisher, J P et al. BMJ 1995;310:70

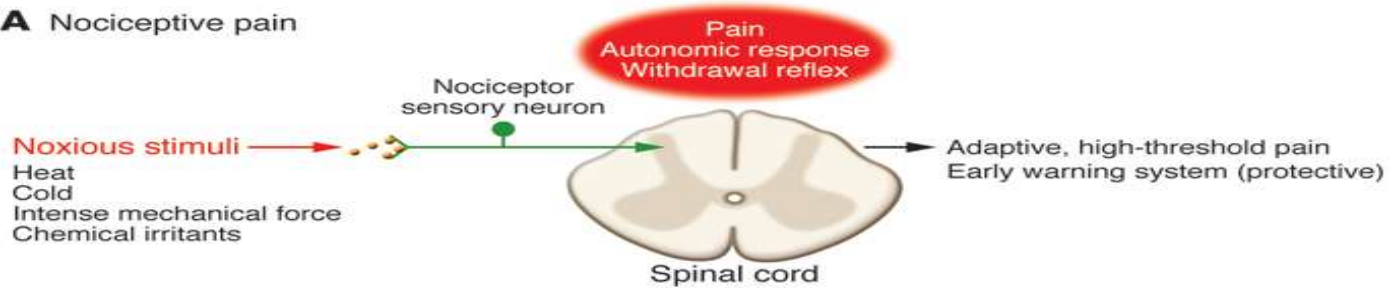


Somatic Deamplification. Reprinted from *Associated Press*, World Wide Photos
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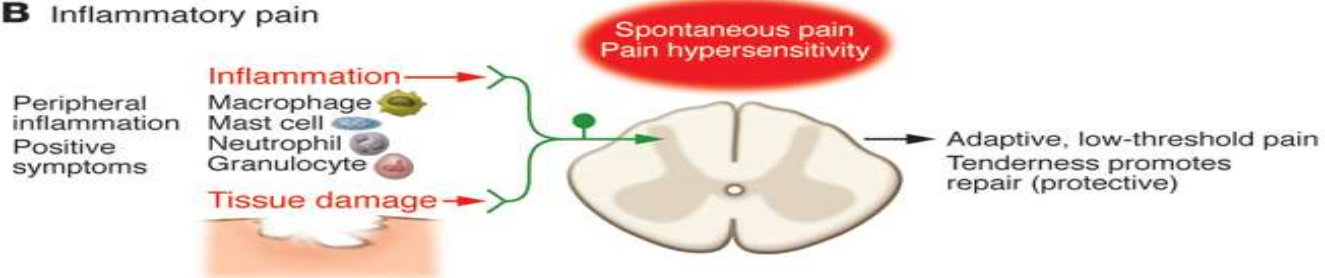
Sensory/discriminative, affective/motivational, and cognitive/evaluative involvement in pain perception



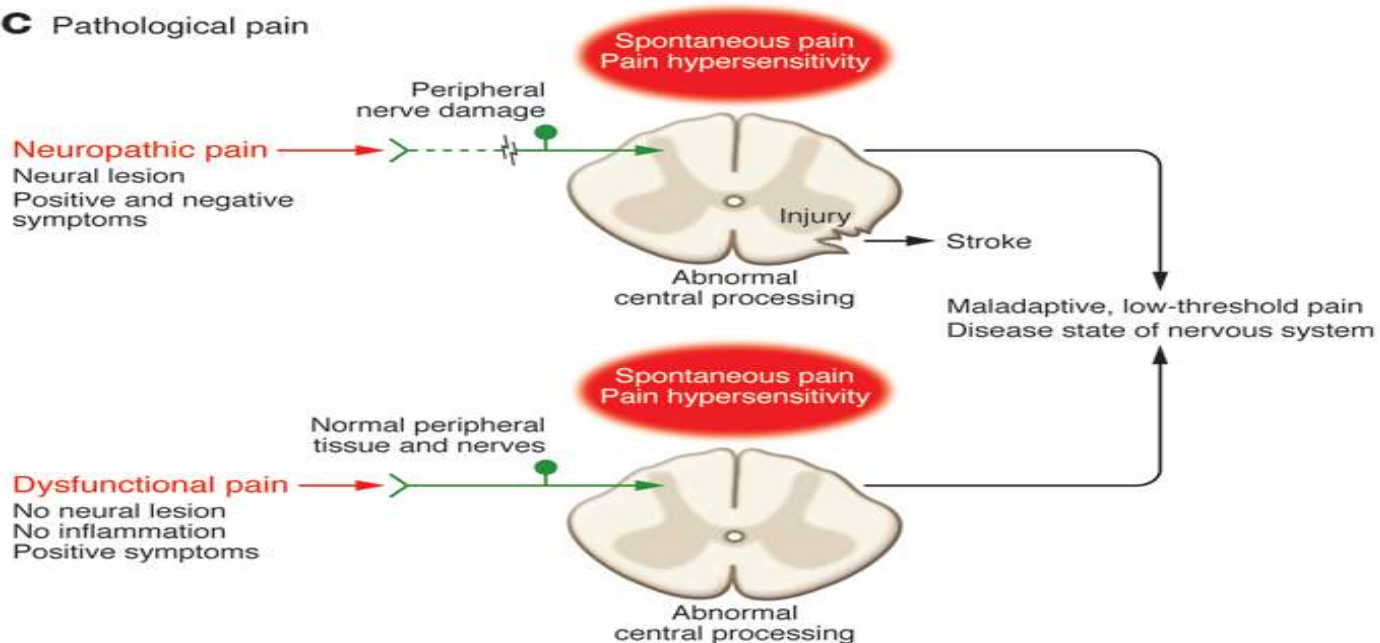
A Nociceptive pain



B Inflammatory pain

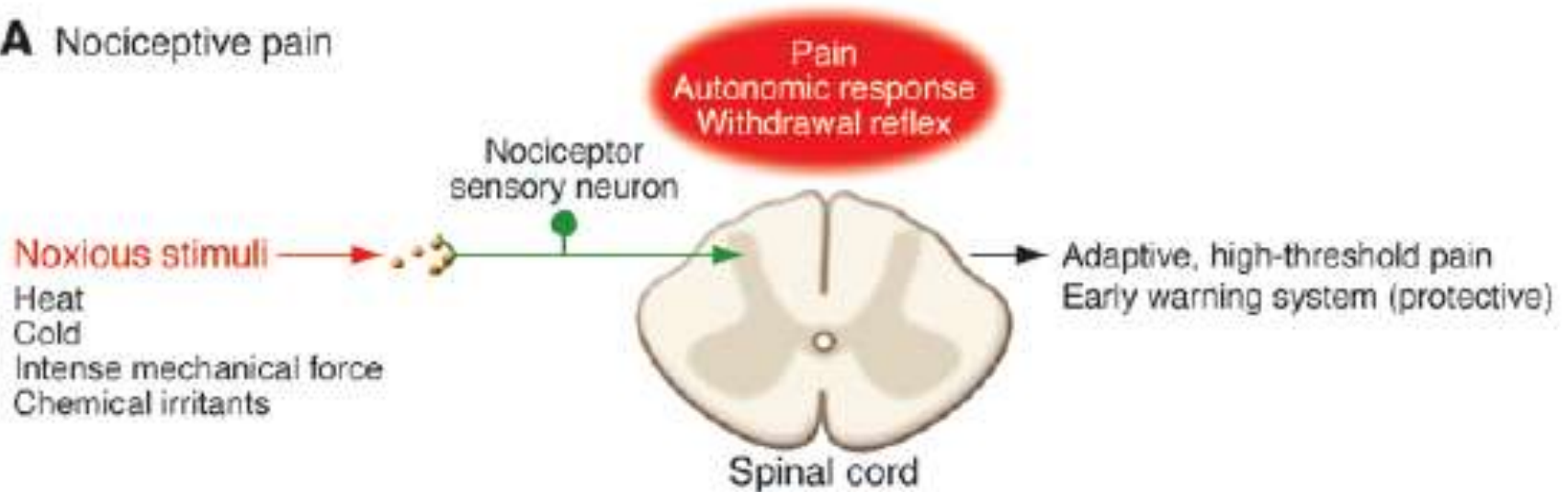


C Pathological pain



Nociceptive Pain

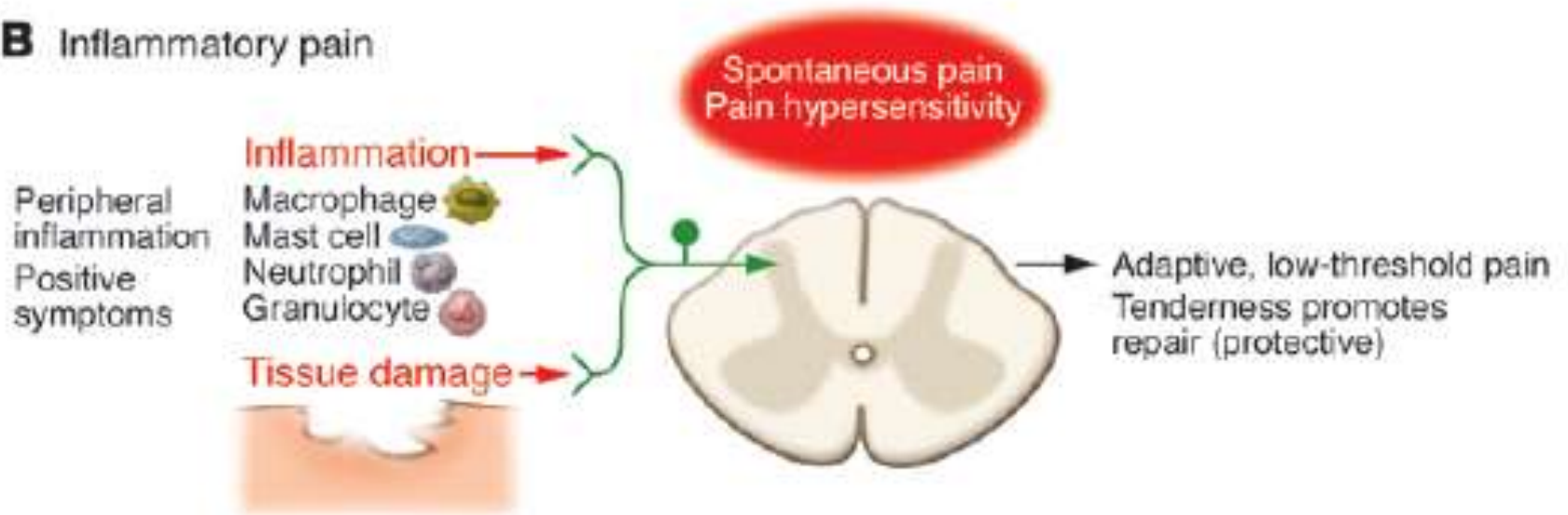
A Nociceptive pain



Function: early warning of a potentially damaging stimulus → avoidance of stimulus (& injury)

Inflammatory Pain

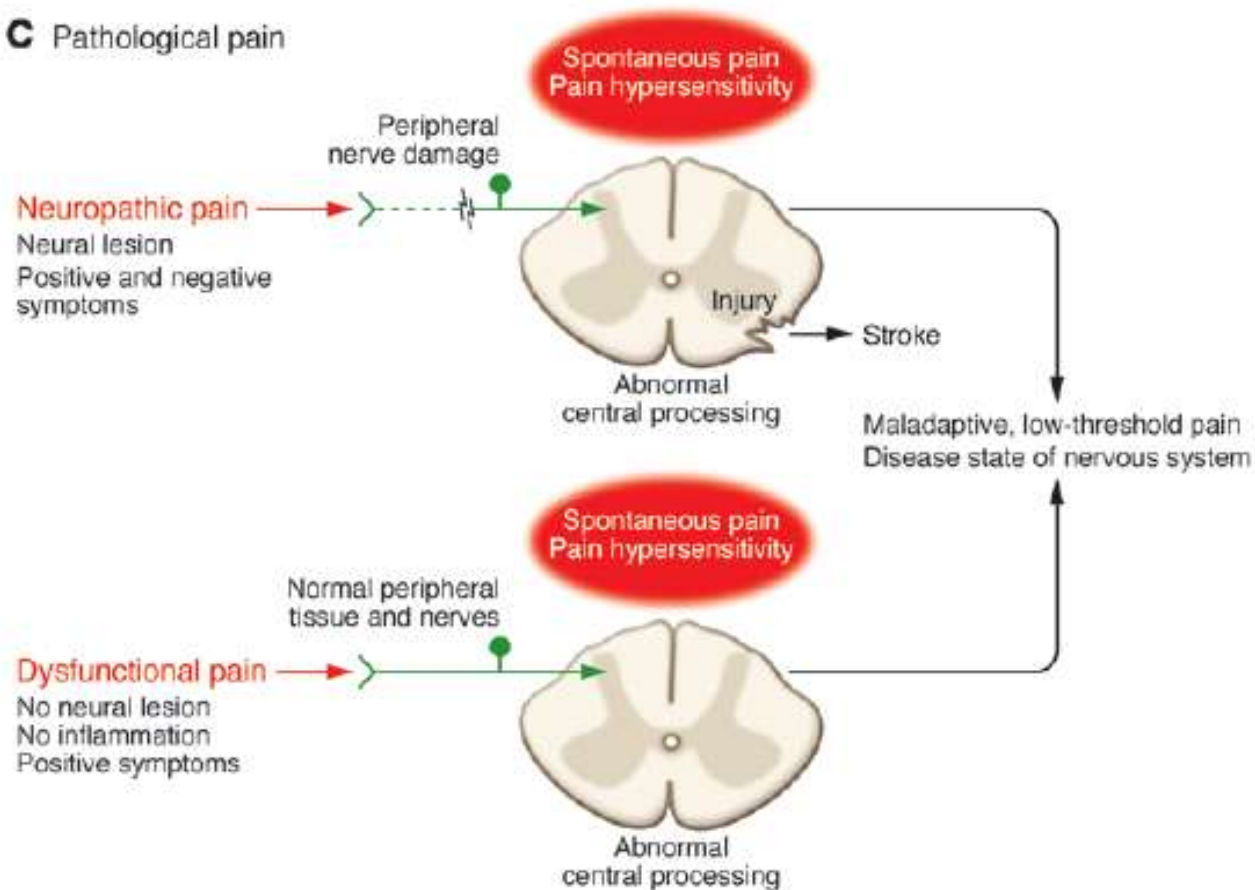
B Inflammatory pain



Function: (no longer protection, but) promote / permit healing

Pathological Pain

C Pathological pain



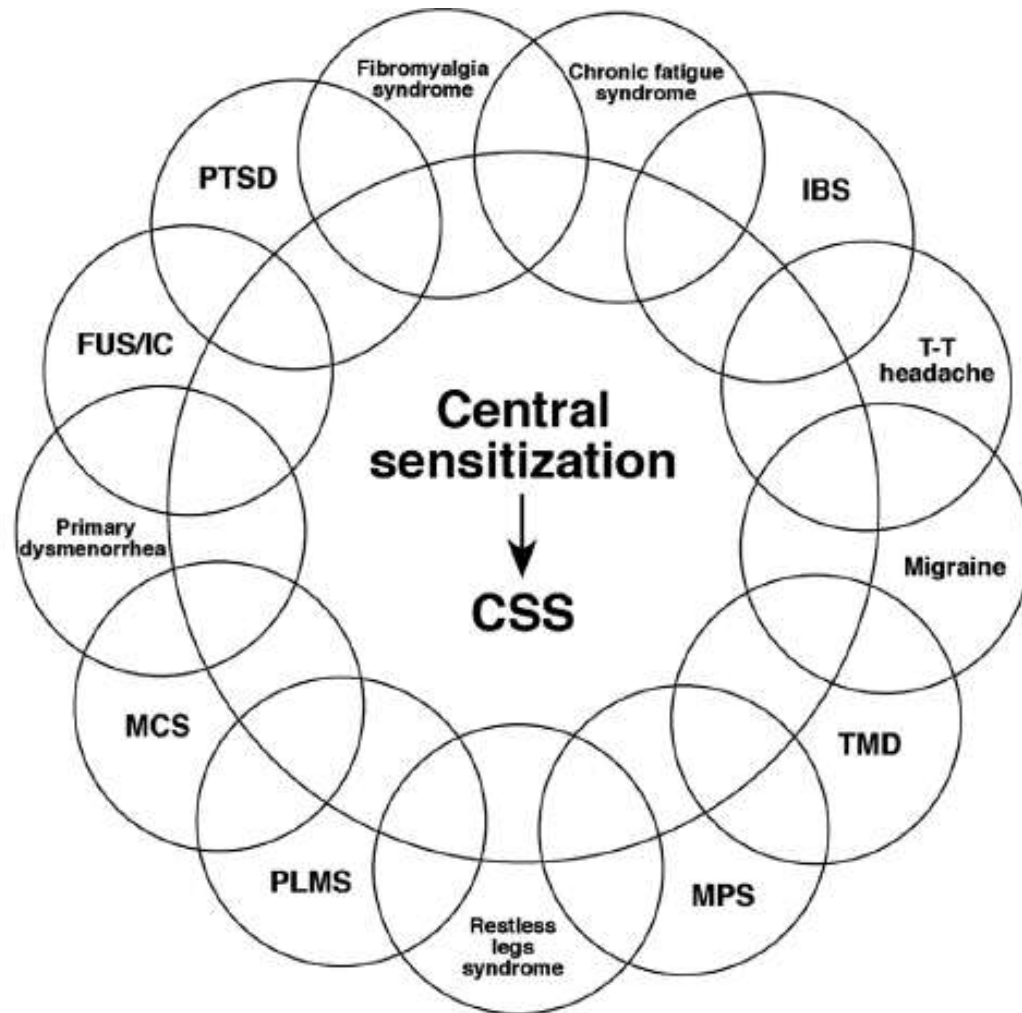
No **Function** – dysfunctional/maladaptive pain

“Finally, there is the pain that is not protective, but maladaptive, resulting from abnormal functioning of the nervous system. This *pathological pain (Figure 1C)*, which is not a symptom of some disorder but rather a disease state of the nervous system, can occur after damage to the nervous system (neuropathic pain), but also in conditions in which there is no such damage or inflammation (dysfunctional pain). ... include fibromyalgia, irritable bowel syndrome, tension type headache ... interstitial cystitis, and other syndromes in which there exists substantial pain, but no noxious stimulus and no, or minimal, peripheral inflammatory pathology. The clinical pain syndrome with the greatest unmet need, pathological pain is largely the consequence of amplified sensory signals in the central nervous system, and is a low-threshold pain. By analogy, if pain were a fire alarm, the nociceptive type would be activated appropriately only by the presence of intense heat, inflammatory pain would be activated by warm temperatures, and pathological pain would be a false alarm caused by malfunction of the system itself. The net effect in all 3 cases is the sensation we call pain ... the processes that drive each are quite different.” (Woolf, C: *J Clin Invest*, 11.10; 3742-44)

“Similar changes take place in the spinal cord and brain ... these changes are responsible for facilitating the responses to peripheral inputs — a phenomenon known as central sensitization — so that the threshold for generating pain falls and its duration, amplitude, and spatial distribution increase. In essence, this represents an uncoupling of nociceptive pain from its absolute need for noxious stimuli. A big difference between inflammatory and pathological pain is that the former represents hypersensitivity in reaction to a defined peripheral pathology, whereas the latter is the result of altered neural processing. ... Intriguingly, it seems clear that susceptibility to pain hypersensitivity and conversion from acute to chronic pain has a large heritable component, and we now need to define exactly who is at risk”. (Woolf, C: *J Clin Invest*, 11.10; 3742-44)

Central Sensitivity Syndromes

(Missing– Non-Cardiac Chest Pain; PNES)

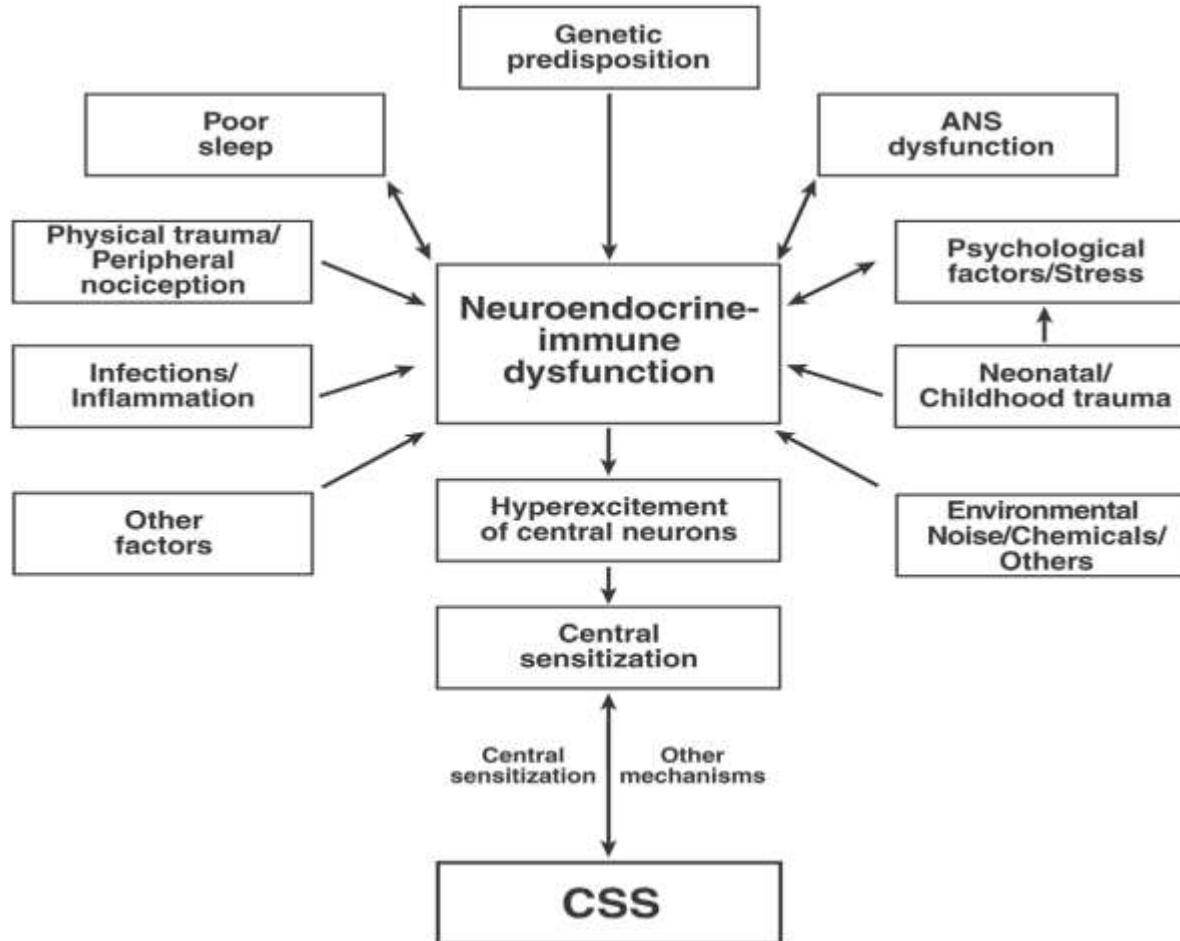


(Yunus: Semin Arth Rheum, June 2007, page 341)

Functional symptoms & syndromes in medical specialties

<u>Gastroenterology:</u>	Irritable bowel syndrome
<u>Respiratory:</u>	Chronic cough; Brittle asthma (some)
<u>Rheumatology:</u>	Fibromyalgia, Chronic back pain (some)
<u>Gynaecology:</u>	Chronic pelvic pain; Dysmenorrhea (some)
<u>Allergy:</u>	Multiple chemical sensitivity syndrome
<u>Cardiology:</u>	Noncardiac chest pain, palpitations (some)
<u>Infectious diseases:</u>	Postviral chronic fatigue syndrome
<u>ENT:</u>	Globus, functional dysphonia
<u>Neurology:</u>	PNES, functional weakness, sensory symptoms
<u>Psychiatry:</u>	Depression, anxiety

Simplified Suggested Biopsychosocial Mechanisms for CS & CSS



(Yunus: Semin Arth Rheum, June 2007, page 347)

A range of potential aetiologic factors in patients with functional symptoms

Neurologic Clinics, Feb 2009, page 4

Factors	Biologic	Psychological	Social
<u>Factors acting at all stages</u>	Organic Disease	Emotional disorder Personality disorder	Socioeconomic deprivation / Adverse life events
History of previous functional symptoms			
<u>Predisposing</u>	Genetic factors affecting personality Biologic vulnerabilities in nervous system?	Perception of childhood experience as adverse Personality traits Poor attachment / coping style	Childhood neglect/abuse Poor family functioning Symptom modeling (via media or personal contact)
<u>Precipitating</u>	Abnormal physiologic event or state (eg, hyperventilation, sleep deprivation) Physical injury/pain	Perception of life event as negative, unexpected Acute dissociative episode/ panic attack	
<u>Perpetuating</u>	Plasticity in CNS motor & sensory (incl pain) pathways Deconditioning Neuroendocrine & immunologic abnormalities, similar to those seen in depression & anxiety	Illness beliefs (patient & family) Perception of symptoms as caused by disease/damage/ without the scope of selfhelp Not feeling believed Avoidance of symptom provocation	Presence of welfare system Social benefits of being ill Availability of compensation Stigma of mental illness from society & medical profession Ongoing medical investigations & uncertainty

“CFS : understanding a complex illness”

(Nature Reviews Neuroscience, September 2011; 539-44)

- “We do not know the cause of CFS, for the same reason we do not know the cause of many neurologic diseases: we have not yet been clever enough to figure it out.” (A.L. Komaroff)
- “There are many similar disorders (of) which we do not know the cause” (S. Wessely)

CFS

Prins, JB et al: Review; *Lancet*, 2006; 367: 346–55

Predisposing Factors

- Personality: neuroticism & introversion
- Inactivity in childhood, & after IMN
- Genetics: Twin studies → familial predisposition

Precipitating Factors (Acute physical or psychological stress):

- 75% CFS patients report infectious trigger: a cold, flulike illness, IMN, Lyme
- “Serious injuries, surgery, pregnancy, or labour, which are reported as the onset of CFS by patients, have not been studied systematically.”
- “Psychological stress as a trigger of CFS has also been studied. Serious life events, such as the loss of a loved one or a job, and other stressful situations have been found to precipitate the disorder”.

CFS

Prins, JB et al: Review; *Lancet*, 2006; 367: 346–55

Perpetuating Factors

- “Psychological processes ... involved in the perpetuation of complaints in patients with CFS. ... ideas or cognitions of patients about complaints, behavioural factors such as persistent avoidance of activities associated with an increase in symptoms. A strong belief in a physical cause of the illness, a strong focus on bodily sensations, and a poor sense of control over complaints contribute.”
- “Inactivity of patients with CFS is caused by perceptions and expectations rather than by physical fitness. In CFS, discrepancies between perceived & actual cognitive performance” (& sleep) “have been found.”
- “social processes ... solicitous behaviour to lack of social support. Illness perceptions & illness behaviour can be reinforced by people in the patient’s environment, such as a partner or family. Practitioners can contribute ... unnecessary medical diagnostic procedures, by persistently suggesting psychological causes, or by not acknowledging CFS as a diagnosis ... Apart from the many disadvantages, long-lasting illness can also have more desirable consequences, such as care, attention, disengagement, or even financial benefits, which might also be considered perpetuating factors”

Aetiology of Psychogenic Non-Epileptic Seizures

Biopsychosocial Model

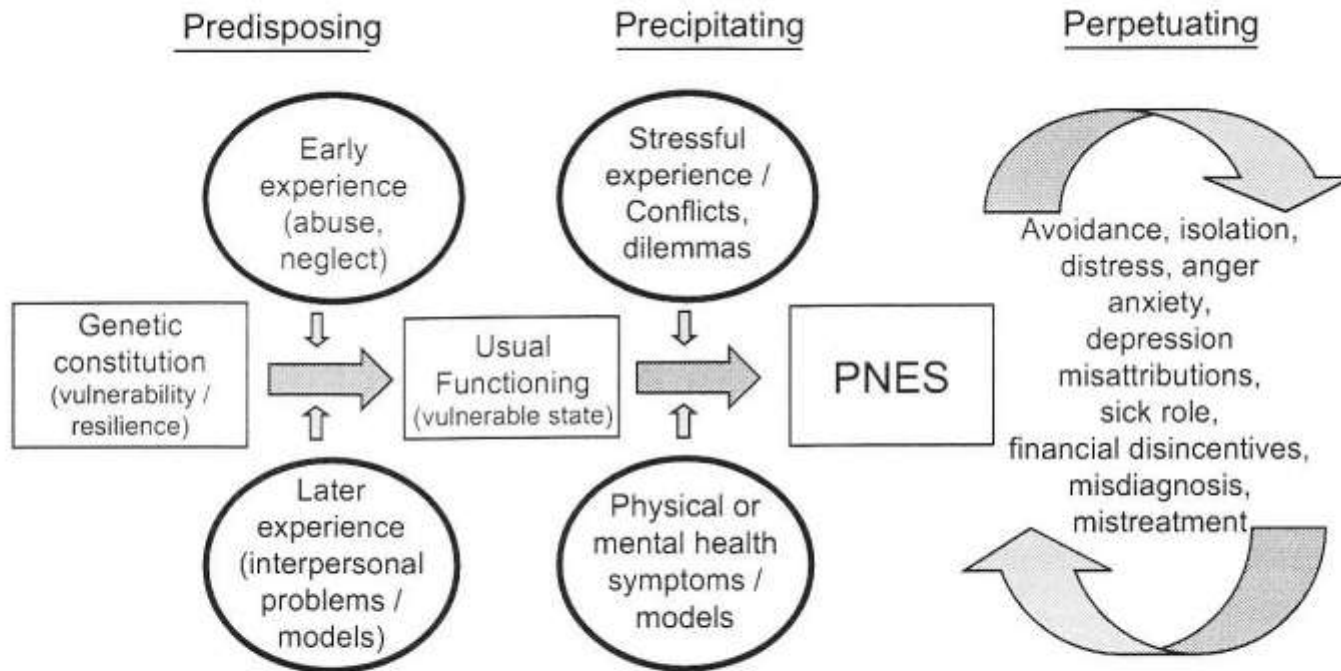


Fig. 1. Etiology of psychogenic nonepileptic seizures: a multifactorial model.

Aetiology of Addiction – BPS model

- “Many factors—genetic, neurobiological, and social—affect addiction. The new ASAM (American Society of Addiction Medicine) definition also describes addiction as a primary disease (not merely the result of emotional or psychiatric problems), and a chronic disease needing treatment over a lifetime. (“Addiction: a complex disorder”: Editorial, *Lancet*, 27.8.11)

BSP model applies even to medical diseases: Obesity

- Strong genetic and neurobiological bases to obesity (Proietto, J: *MJA*, 1.8.11; 144-146)
- This week's *Lancet* (27.8.11) is a special issue on the global obesity epidemic, focussing on the social (economic, political, social class, etc) factors in the obesity epidemic.

What causes chronic pain?

- “Complex Regional Pain Syndrome occurs, in part, as a departure from the orderly and predictable response of an extremity to a traumatic or surgical insult. The exact pathophysiologic cause is not well defined. A transient dystrophic response with pain, hypersensitivity, and altered autonomic function (abnormal physiology) to injury or trauma is normal. However, an abnormal prolongation of this response, and inability of the patient to modulate or control the pain cycle, appears to be the best explanation of CRPS. A cascade of reversible and irreversible events may ensue.” (“CRPS of Upper extremity”. JHS(A), 9.11)

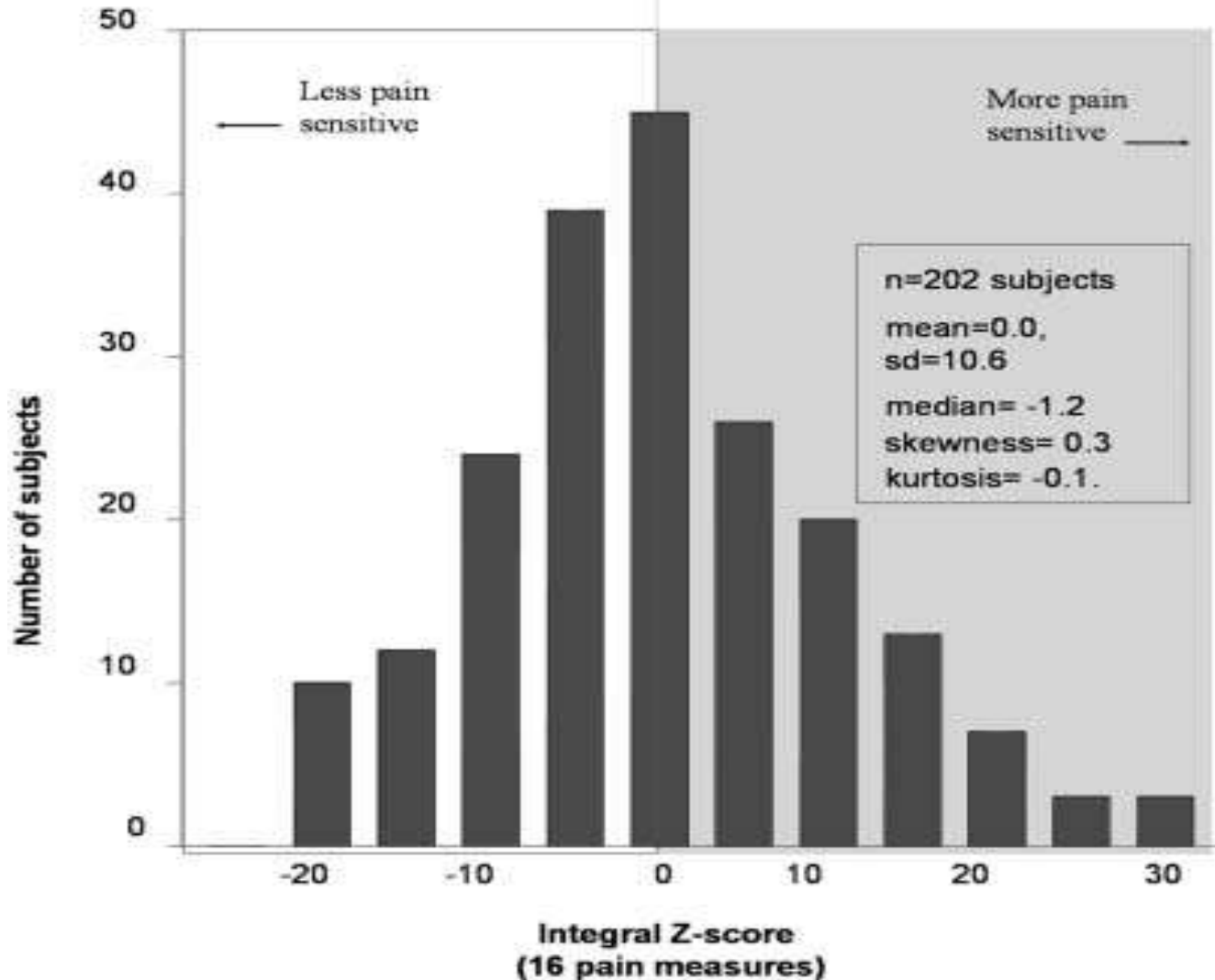
But not quite that simple:

- “Complex Regional Pain Syndrome (CRPS) usually develops after a noxious event, but spontaneous onsets have been described in 3–11% of the cases.”
- 537 CRPS patients were analyzed: 498 (93%) patients reported a known eliciting event; but 39 (7%) did not.

(de Rooij, AM et al: *Euro J Pain*: 14; 2010: 510–13)

Pain Genetics

Diatchenko et al: *Human Molecular Genetics*, 2005, Vol. 14, No. 1; pp 135–143



5 combinations of COMT haplotypes are strongly associated ($P=0.0004$) with variation in the sensitivity to experimental pain. Even a single haplotype diminishes, by as much as 2.3 times, the risk of developing TMJD

Pain Genetics

Classic Twin Studies

- 98 female British twin pairs (51 MZ, 47 DZ) → 22 to 55 % heritability in various acute pain responses. “Sensitivity to a variety of experimental thermal, mechanical and chemical pain producing stimuli has a genetic contribution ... Since experimental pain sensitivity is known to be a predictor for pathological pain, our data imply that genetic factors have an important aetiological contribution towards clinical pain states.” (*Brain*; 2007, 130, 3041-49)
- 15,000 Danish twins (44% MZ, 56%DZ): Genetic susceptibility explained 40% of lumbar & neck pain: “Moderate to high genetic correlations indicated a common genetic basis for many spinal pain syndromes.” (*Arthritis Care Research*; Vol. 61, October 15, 2009, pp 1343–51)
- 147 MZ & 153 DZ male Finnish twin pairs (N = 600 subjects). 30-46% heritability estimates for chronic back pain (*Pain*, 131, 2007: 272–80)

Pain Genetics

Twin Studies

- > 10,000 Finnish twins: 51% heritability of FMS symptoms. “The symptoms known to be associated with fibromyalgia seem to have a strong genetic background.” (*Euro J Pain*, 13; 2009: 744–50)
- 991 MZ & 1074 DZ British twin pairs: heritability of MSP at multiple sites = 46% (*Rheumatology*, Sept 2010)

Pain Genetics

Family studies

- 533 relatives of 78 FMS pts, & 272 relatives of 40 RA pts: OR 8.5: FMS in relatives of FMS pts vs RA [95% CI 2.8–26, $P = 0.0002$)
- FM co-aggregated significantly with major mood disorder: OR 1.8: major mood disorder in a relative of a FMS pt vs relative of a RA pt = (95% CI 1.1–2.9, $P = 0.013$).
- “FM and reduced pressure pain thresholds aggregate in families, and FM coaggregates with major mood disorder in families ... mood disorders and FM may share some of these inherited factors”
- Arnold, LM et al: *Arthritis Rheumatism*, Vol. 50, No. 3, March 2004, pp 944–52

Pain Genetics

Family studies

- Familial CRPS: 31 Dutch CRPS families were identified with 2 or more affected relatives: including 2 families with 5, 4 with 4, 8 with 3, and 17 with 2 affected relatives. (de Rooij, AM: *Euro J Pain*; 13; 2009: 171–77)

Pain Genetics

Individual human risk for chronic NP

- Traumatic double amputees in Sierra Leone: stump & phantom pain observed in only a fraction of patients. But a very high bilateral concordance: when they occurred in one arm, they almost always also occurred in the other.
- CABG → 2 iatrogenic wounds (sternotomy; saphenectomy). In > 1000 pts → 12% chronic chest pain, 9% chronic leg pain; 18% at both sites (total 39%). If there was no increased risk, expect 1.1% to have CP in both sites (vs 18%; $P < 0:001$).
- “It is clear that, like the double amputees noted above, if you developed chronic pain at one site, you are much more likely than predicted by chance alone to develop it also at the second site. These data therefore constitute evidence that certain patients are pre-disposed to developing chronic pain after nerve injury.” (Devor, M: *Pain*, 108 (2004) 199–202)

Pain Genetics

Genetics of FM – review (Pharmacogenomics, 2007; 8(1), 67–74)

- “The exposure of a genetically predisposed individual to a host of environmental stressors is presumed to lead to the development of FMS. Fibromyalgia overlaps with several related syndromes, collectively compromising the spectrum of the functional somatic disorder. FMS is characterized by a strong familial aggregation. Recent evidence suggests a role for polymorphisms of genes in the serotonergic, dopaminergic and catecholaminergic systems in the etiopathogenesis of FMS. These polymorphisms are not specific for FMS, and are similarly associated with additional comorbid conditions. The mode of inheritance in FMS is unknown, but it is most probably polygenic.”

Some specific ion channel pain sensitivity genes

- KCNS1: High risk allele (val, vs isoleucine) prevalent: 20% val:val homozygous, 50% heterozygous. Val:val → increased acute pain sensitivity, & RR 2-3 CLBP & other chronic pains. (Costigan, N et al: *Brain*, Sept 2010: 133; 2519–2527)
- CACNA2D3 (a2d3) a SNP → reduced heat pain sensitivity & CLBP. (Neely, GG et al: *Cell*; 143, 628–638, Nov 12, 2010)

A specific monoamine pain sensitivity gene

- Female carriers of the COMT 158 Met→Val SNP allele were 4.9-fold more likely to have OA hip or knee pain (95% CI 1.6–14.8, P 0.005). (Meurs, JBJ et al: Arth Rheum, Feb 2009, 628-629).

Some other risk factors for CP

- **Physical & sexual abuse** (*Arthritis Care & Research*, Vol. 63, 6: June 2011, 808–820; *JAMA*, August 5 2009, Vol 302, No. 5: 550-561)
- **Lower socio-economic class** (*Ann Rheum Dis*; 2009;68:1591–1595; *Euro J Pain*; 15; 2011: 103–109)
- **Lower school PE grade in adolescence predicts chronic soft tissue MSP 30 yr later** (*Pain*; 150:2010; 414–419)
- **Frequent primary school complaints of aches & pains (OR=6.75) predicted permanent work disability 40 years later** (*Br J Psychiatry* 2009; 194, 220–223)

The role of trauma in CP

- RCT of epidural vs non-epidural in labour - 369 randomised; 306 F/U 26/12 later.
- No differences in onset or duration of LBP, spinal mobility or in disability.
- (BMJ, 17 August 2002)

Minor trauma & serious LBP

- 200 asymptomatic working adults followed 6/12ly for 5 years.
- no association of minor trauma to LBP: risk each 6/12 of serious LBP episode was 2.1% unassociated with minor trauma, vs 2.4% following minor trauma ($P = 0.59$).
- (*Serious trauma = pain $\geq 6/10$ for $\geq 1/52$, & work disabled*)

(*Spine* 2006, Vol 31, No. 25, pp 2942–2949)

Trauma & CWP

- >2000 asymptomatic adults checked at baseline (incl psychological health, sleep issues, health behaviour), & followed for 4 yr
- 11.6% had developed CWP over the 4 yr
- > 1/3 total population self-reported at least 1 traumatic event over the 4 yr → OR 1.34 to report CWP (#, RTA, work injuries; not surgery or childbirth).
- But fully attenuated after controlling for confounders (OR 1.01)
- RTA only – OR 1.84 → OR 1.50 after controlling (95% CI 0.89–2.52)
- *Arthritis Care & Research* Vol. 63, No. 5, May 2011, 696–701

“Previous work has shown that patients with CWP often attribute symptom onset to a precipitating physically traumatic event; and, although some studies have reported associations between such events and the onset of CWP, they have been unable to adequately adjust for pre-trauma psychological health, which may confound any observed relationship. The current study provides some support for the hypothesis of an “at risk” phenotype, where individuals characterized by poorer health and psychological variables may be predisposed to develop CWP following a traumatic trigger event ... We have also shown that involvement in an RTA specifically does appear to confer a modest increase in the likelihood of symptom onset over the short to medium term, although in general this effect is removed after adjusting for potential confounding factors. Future research should examine what it is about involvement in an RTA, or about one’s reaction to an RTA, that confers this increase in the risk of CWP onset, which does not seem to occur with other traumatic events.”