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# Prevention of chronic post-surgical pain. Is it possible?

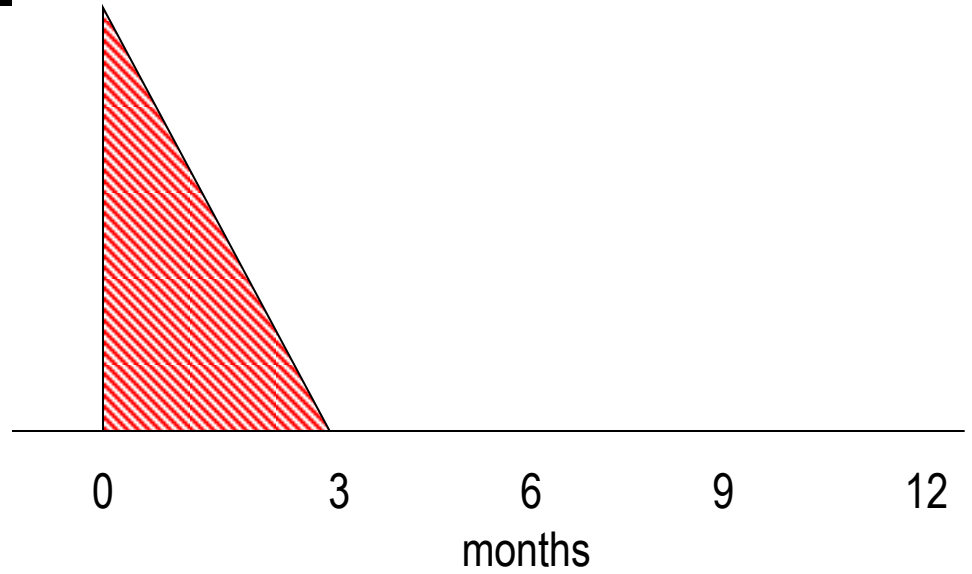
Dr Jane Quinlan

Consultant in anaesthesia and acute pain  
management

Oxford University Hospitals Trust

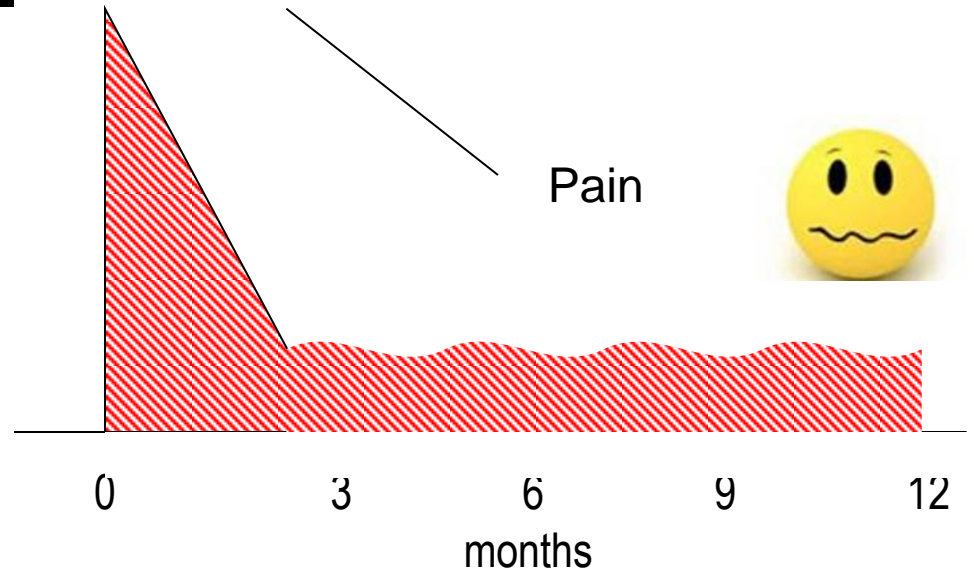


No pain





No pain



# Definition of CPSP

- The pain must develop after a surgical procedure
- The pain is of at least two months' duration
- Other causes for the pain have been excluded
- The possibility that the pain is from a pre-existing condition has been excluded.

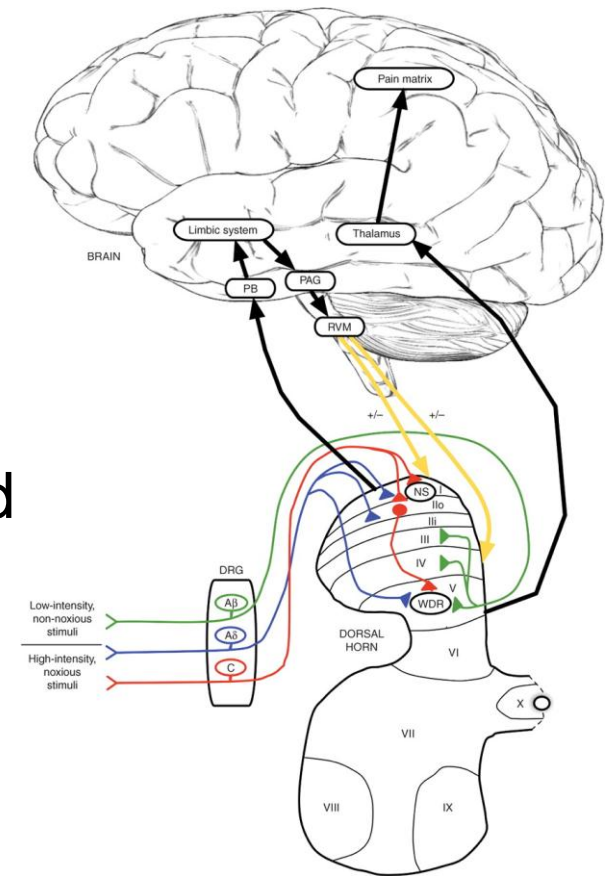
# Rat model

- Healthy subjects
- Exposed to standardised tissue injury
- Observe for progression from acute to chronic pain



# Central sensitisation

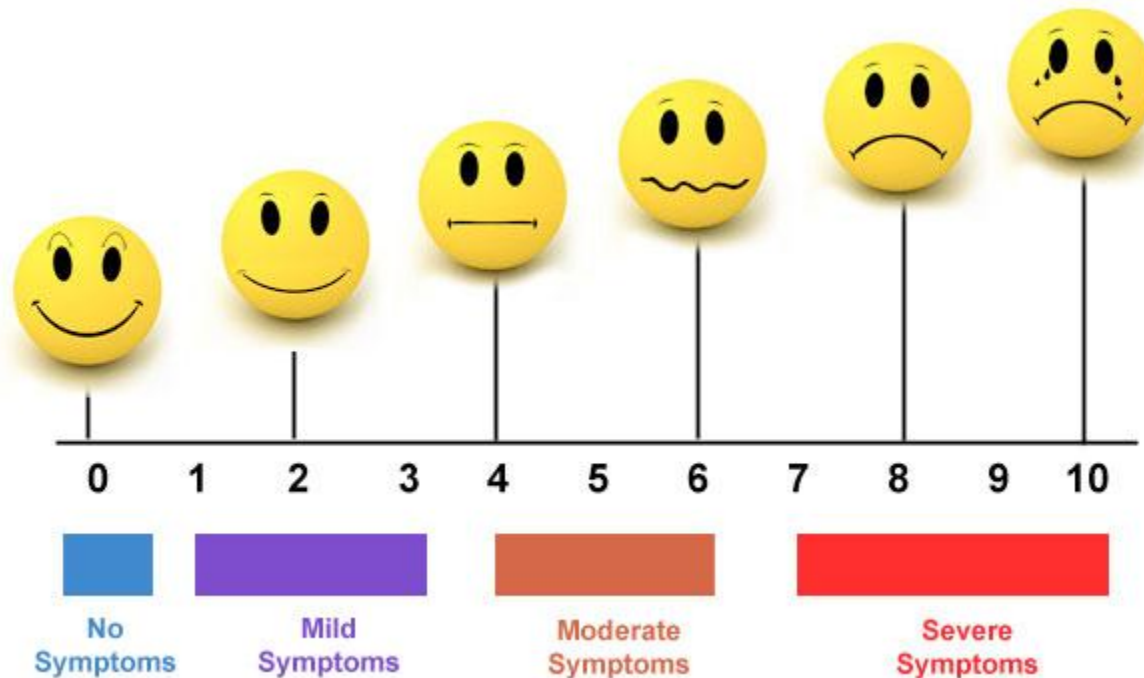
- Ongoing nociception produces peripheral nerve changes then central changes in the spinal cord
- Once these changes are established and the pain is “neuropathic”, then the risk of CPSP is increased



# Chronic post-surgical pain (CPSP)

Type of Operation	Incidence of Chronic Pain	No. of ops in UK in 2005-6	No. of ops in USA in 1994
Mastectomy	20-50%	18,000	131,000
Caesarean	6%	139,000	858,000
Amputation	50-80%	15,000	132,000
Cardiac Surgery	30-55%	29,000	501,000
Hernia repair	5-33%	75,000	689,000
Hip Replacement	12%	61,000	
Thoracotomy	5-65%		660,000

# What does pain at a year mean?



# Chronic pain clinic attendance

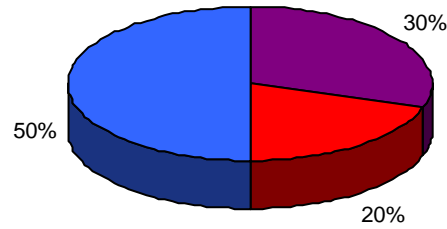
- 5130 patients in Scotland and northern England
- Surgery was responsible for the chronic pain in 22.5%
- Trauma was felt to have initiated chronic pain in 18.7%
- Of all clinic attendees:
  - Degenerative factors most common cause of pain
  - Surgery was second
  - Trauma third
- Distress, economic and societal impact

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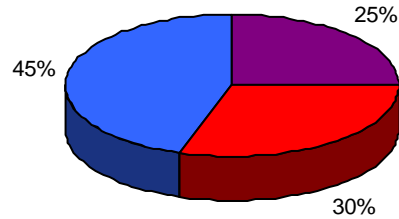
# Prevalence of persistent postsurgical pain – population study

- Tromsø, Norway
- 12 900 participants
- 2 041 had surgery in past 3 years
- 40.4% described persistent postsurgical pain
- 18.3% moderate to severe pain
- Association between pain and sensory abnormalities (hypo- or hyperaesthesia)

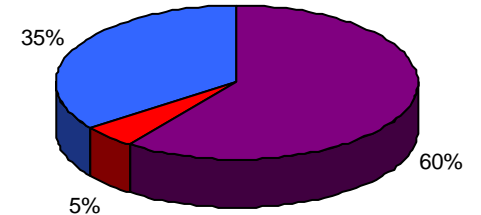
### Mastectomy



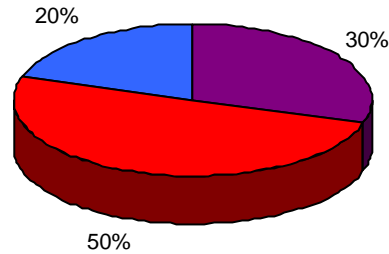
### Cardiac surgery



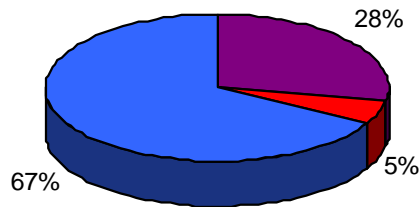
### Thoracotomy



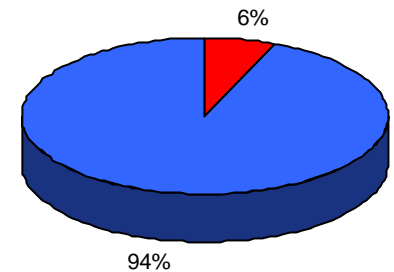
### Amputation



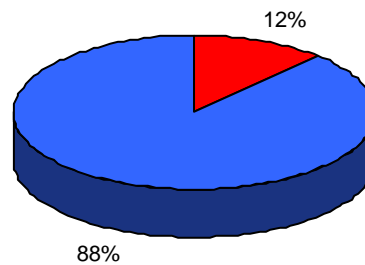
### Herniorraphy









### Caesarean section



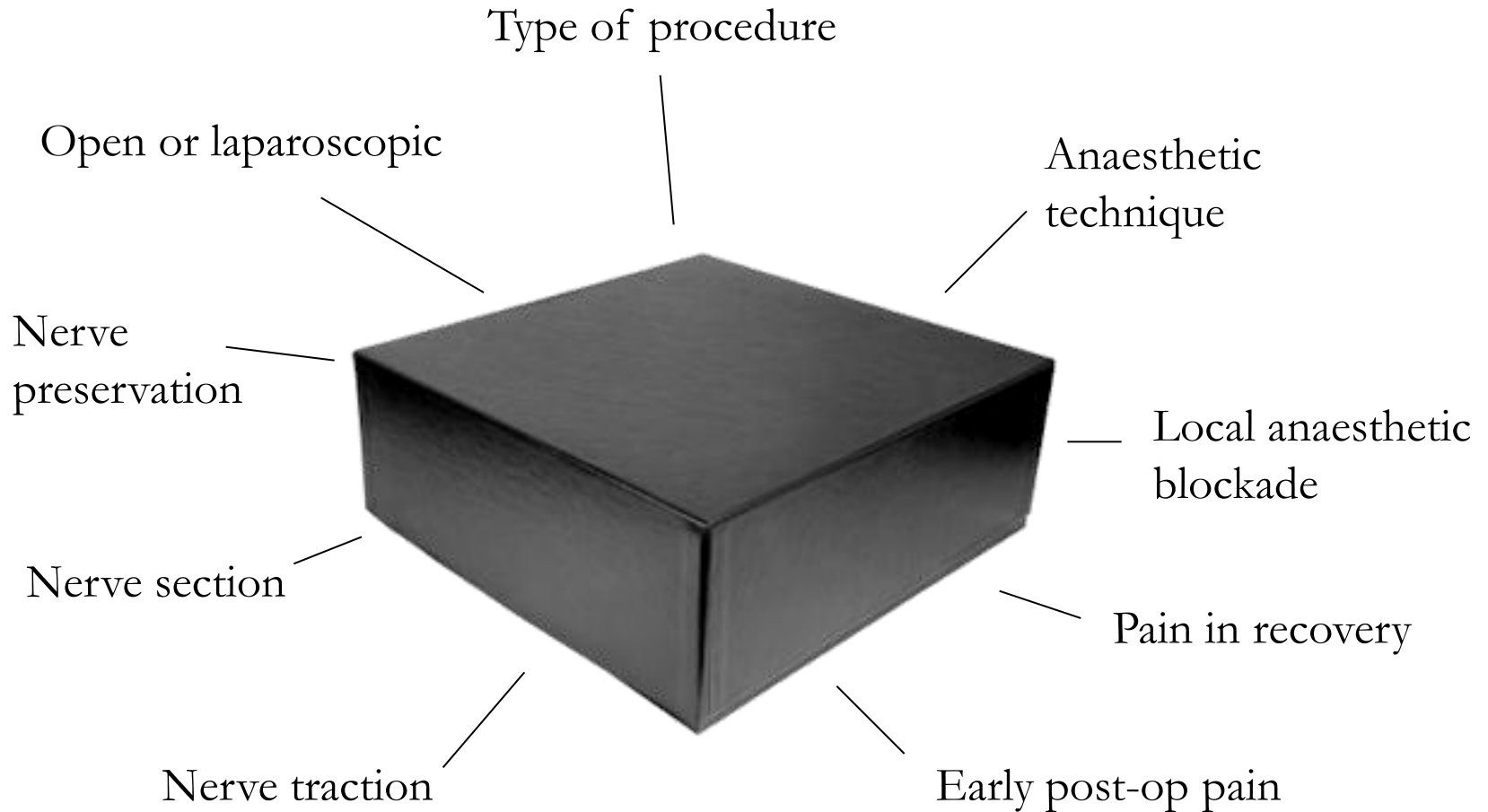
### Total hip replacement



Optimistic view:  Lowest reported incidence of CPSP  +  Pain-free in best case scenario

Pessimistic view:  +  Highest reported incidence of CPSP  Pain-free in worst case scenario

# Surgical black box



# Surgical technique



- Open vs laparoscopic
  - Hernia repair and thoracic surgery
- Foreign bodies
  - Mesh – chronic inflammation
- Nerve preservation techniques
  - More chronic pain if nerves not identified
  - No difference found between preservation or division
- Post-operative complications
  - Infection
  - Haematoma
  - Re-operation

# Anaesthetic technique



- Evidence for spinal being protective against CPSP
  - hysterectomy and caesarean section, as compared to general anaesthesia
- Some evidence of epidural analgesia after:
  - thoracotomy
  - colectomy
  - amputation
- Paravertebral blockade after mastectomy
- Other local anaesthetic infiltration may also be protective

Lavand'homme P, De Kock M, Waterloos H. *Anesthesiology* 2005;103:813–20.

Kairaluoma PM et al. *Anesth Analg* 2006;103:703–8.

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# Acute post-op pain

- Strong correlation between severity of acute post-op pain and CPSP
  - multiple studies
  - various surgical procedures

Kehlet H, Jensen TS, Woolf CJ. *Lancet* 2006; **367**(9522): 1618-25.

Macrae W, Bruce J. in Wilson PR, Watson PJ, Haythornthwaite JA, Jensen TS (eds) *Clinical Pain Management: Chronic Pain* 2008: 405-414.

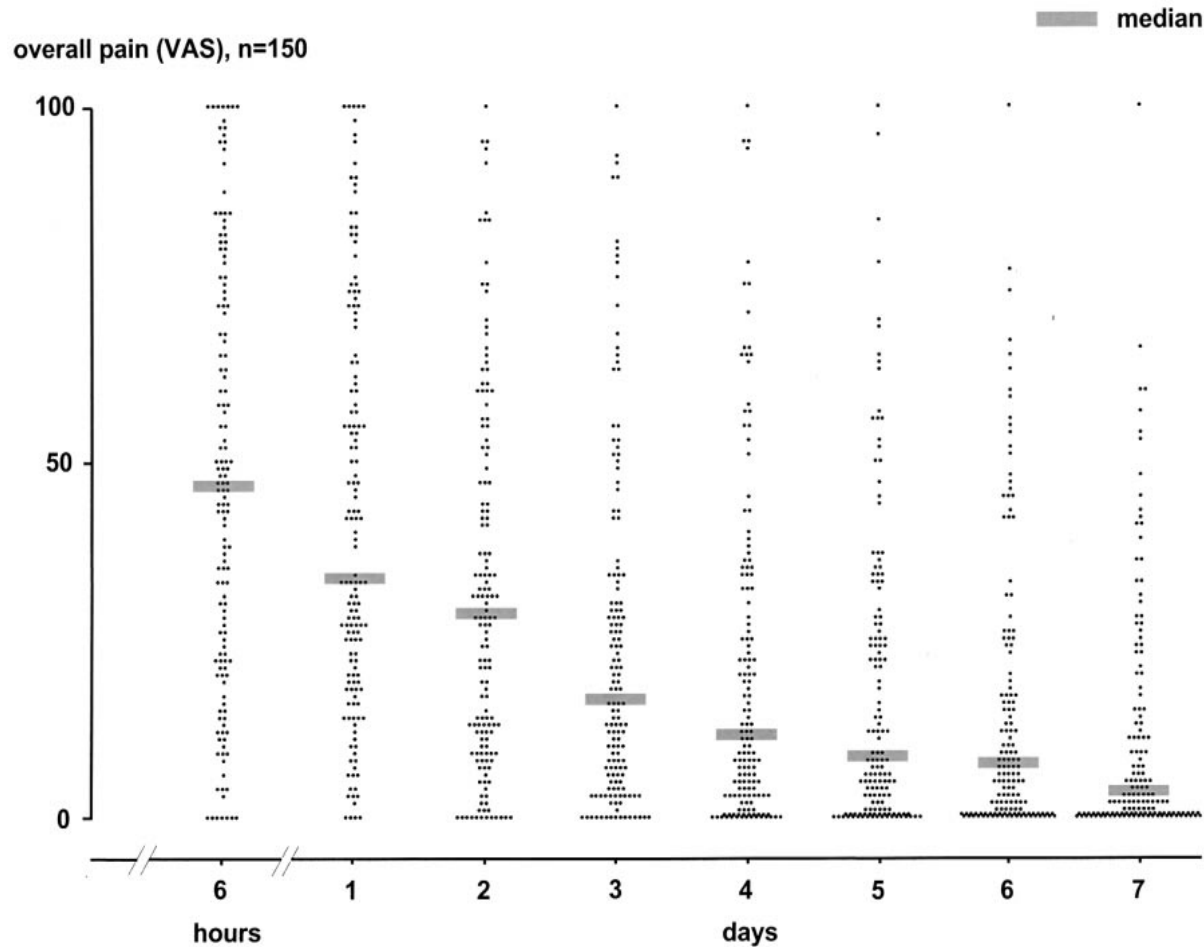
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# Sustained pain

- Median pain scores over 7 days more predictive than the max pain score
  - Possible reasons:
    - Sustained nociceptive input may produce central sensitisation
    - Or ongoing pre-op pain
    - Or may have severe acute pain because CPSP already developing
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# Pain in the first week after surgery



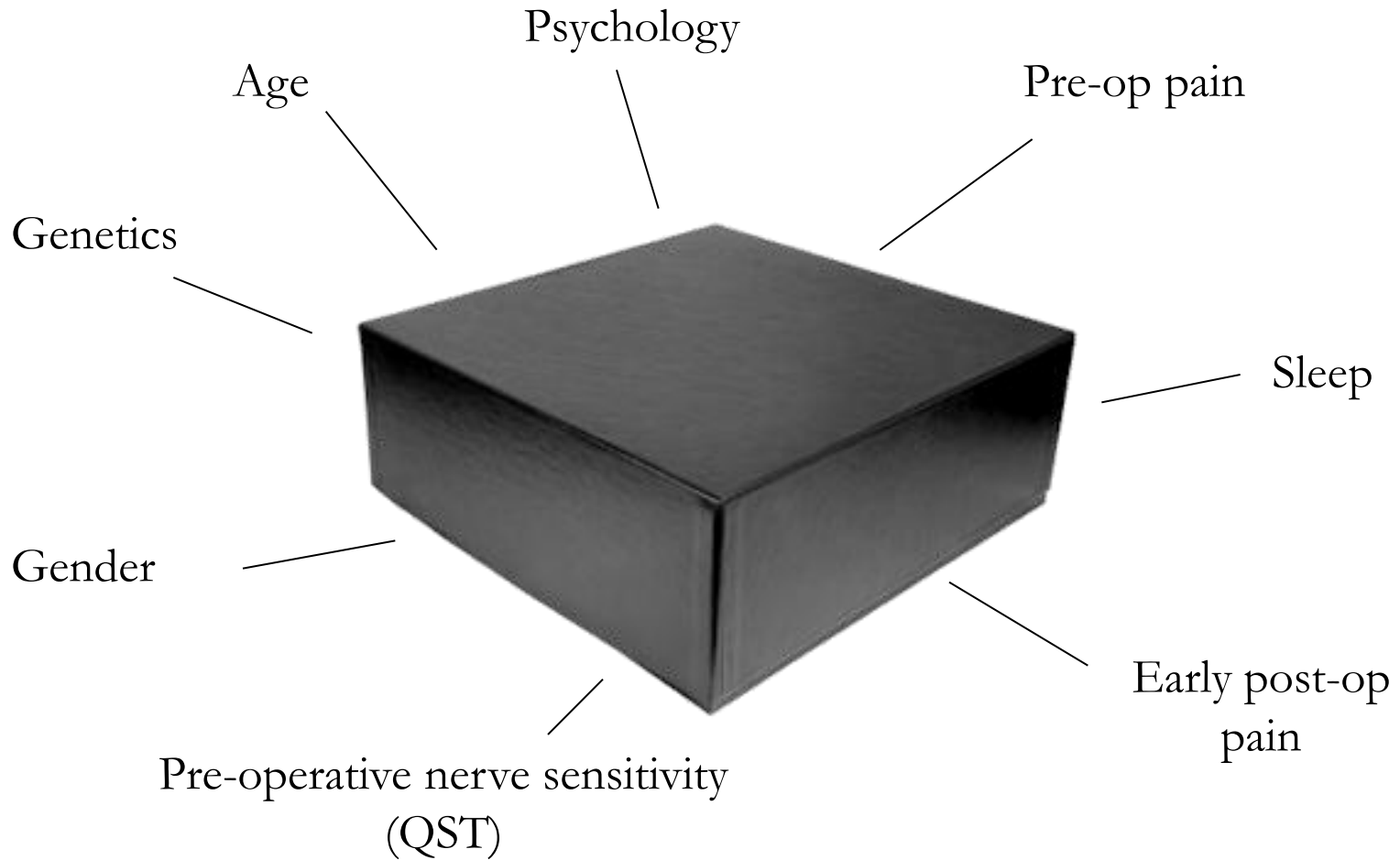
# Barriers to effective pain management at home

- 30-60% of patients:
  - moderate to severe pain in first 24 hours after discharge home following day surgery
- 25-30% continue to report pain at 7 days
- Insufficient prescribed drugs
- Prescribed but not taken:
  - Unclear (or no) instructions
  - Fear of addiction
  - Side effects (nausea, vomiting, constipation)

Watt-Watson J, Chung F, Chan VWS, McGillion M. *J Nursing Management* 2004;12:153–161

Townsend R, Cox F. *J Periop Pract* 2007;17(7):340-6

# Patient black box



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# Age

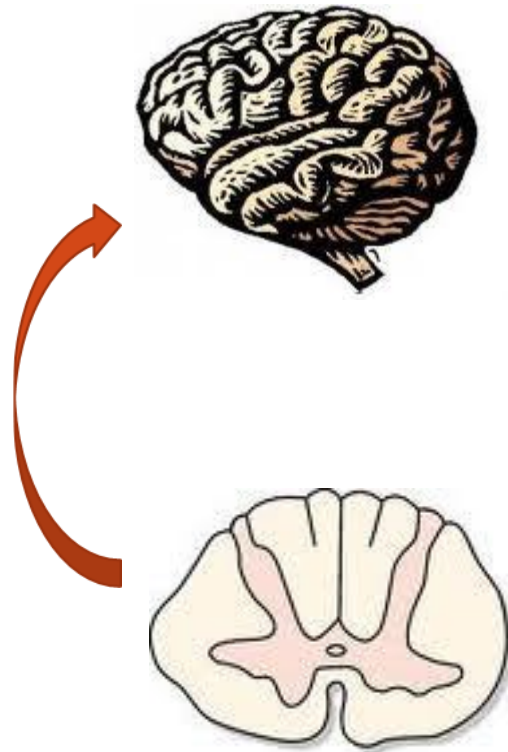
- Younger patients seem to have an increased risk of CPSP
    - Women undergoing breast cancer surgery: ↓probability of CPSP of 5% with each year increase in age
    - Similar to a study of hernia patients
    - Possibly due to a reduced peripheral nociceptive function with increased age
  
  - Children and adolescents have a decreased risk of CPSP
-

# Gender

- Women higher incidence of chronic pain
  - Neuropathic
  - Musculoskeletal
  - Abdo pain of unknown aetiology
  - Migraine (higher in boys pre-puberty)
- Acute post-operative pain:
  - Women have higher VAS ratings immediately post-op compared to men
  - Use less opioid via PCA
  - Possibly due to increased adverse effects
- Chronic post-surgical pain
  - Studies looking at CPSP have mixed results

Nociception:

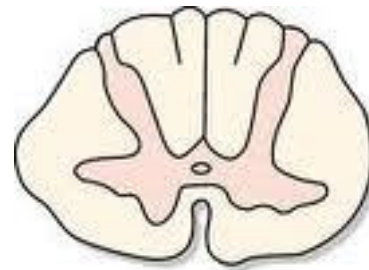
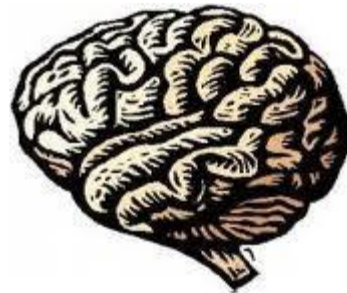
- Intensity
- Location
- Duration





Nociception:

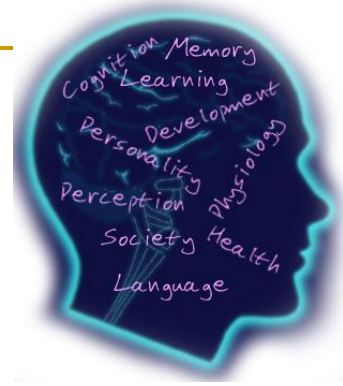
- Intensity
- Location
- Duration



*Interpretation:*

- *Anxiety*
- *Fear*
- *Catastrophizing*
- *Previous pain experiences*

# Psychology



- Depression
  - Severe CPSP correlated with severe pre-op depression
  - More likely to use antidepressants before surgery
- Psychological vulnerability
  - Factor both pre and post-op
- Late return to work
- Also:
  - Anxiety; catastrophizing; optimism / pessimism; locus of control; illness attitudes
- Psychological factors impact more on surgery for complex disorders

# Pre-operative pain

- Patients with CPSP after hernia repair
  - painful hernia pre-op
  - pre-existing chronic pain condition: headache, back pain, IBS
- Elective abdominal surgery
  - higher levels of pain immediately before surgery
  - presence of pain >6 months
- Severe pain immediately before lower limb amputation
  - predicts chronic pain in residual or phantom limb

Caumo W et al. *Acta Anaesthesiol Scand* 2002 **46**(10): 1265-1271.

Wright D et al. (2002). *Ann Surg* 2002; **235**(3): 333-7.

# Nerve sensitivity



- Quantitative sensory testing (QST)
  - Assesses skin  $A\beta$ ,  $A\delta$  and C fibre function with temperature, touch and vibration thresholds
  - Functional abnormalities have been found post-hernia repair
  - May predict severe acute post-op pain
- Descending noxious inhibitory control (DNIC)
  - Tests the effectiveness of the endogenous analgesia
  - Conditioning stimulus of hand in hot water
  - May be a better predictor of CPSP

# Genetic susceptibility



- Single nucleotide polymorphisms involved in pain processing
  - COMT
    - V158M – (methionine for valine) decreased morphine requirements
  - Mu-opioid receptor (OPRM1)
    - N40D – (asparagine for aspartate) – coded by A118G
    - GG patients have higher opioid requirements
  - SCN9A
    - the gene encoding the voltage-gated sodium channel Na(v)1.7
  - Cytochrome P450 enzymes
    - Metabolism of many analgesics

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Theory 1:

Perioperative nerve damage

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# Theory 1: perioperative nerve damage

- Pro:
  - thoracotomy
  - mastectomy
  - inguinal hernia repair



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# Theory 1: perioperative nerve damage

- Pro:
    - thoracotomy
    - mastectomy
    - inguinal hernia repair
  
  - Con:
    - vasectomy
-

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# Theory 2: Pre-existing pain

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# Theory 2: Pre-existing pain

- Pro:
  - Limb amputation



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# Theory 2: Pre-existing pain

- Pro:
  - Limb amputation
  
- Con:
  - Hip replacement



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# Theory 3: patient factors

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# Theory 3: patient factors

- Pro:
    - Women
    - Younger age
    - Anxiety
    - Depression
    - Sleep disturbance
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# Theory 3: psychology

- Con:
  - Caesarean section
    - Incidence of CPSP <10%



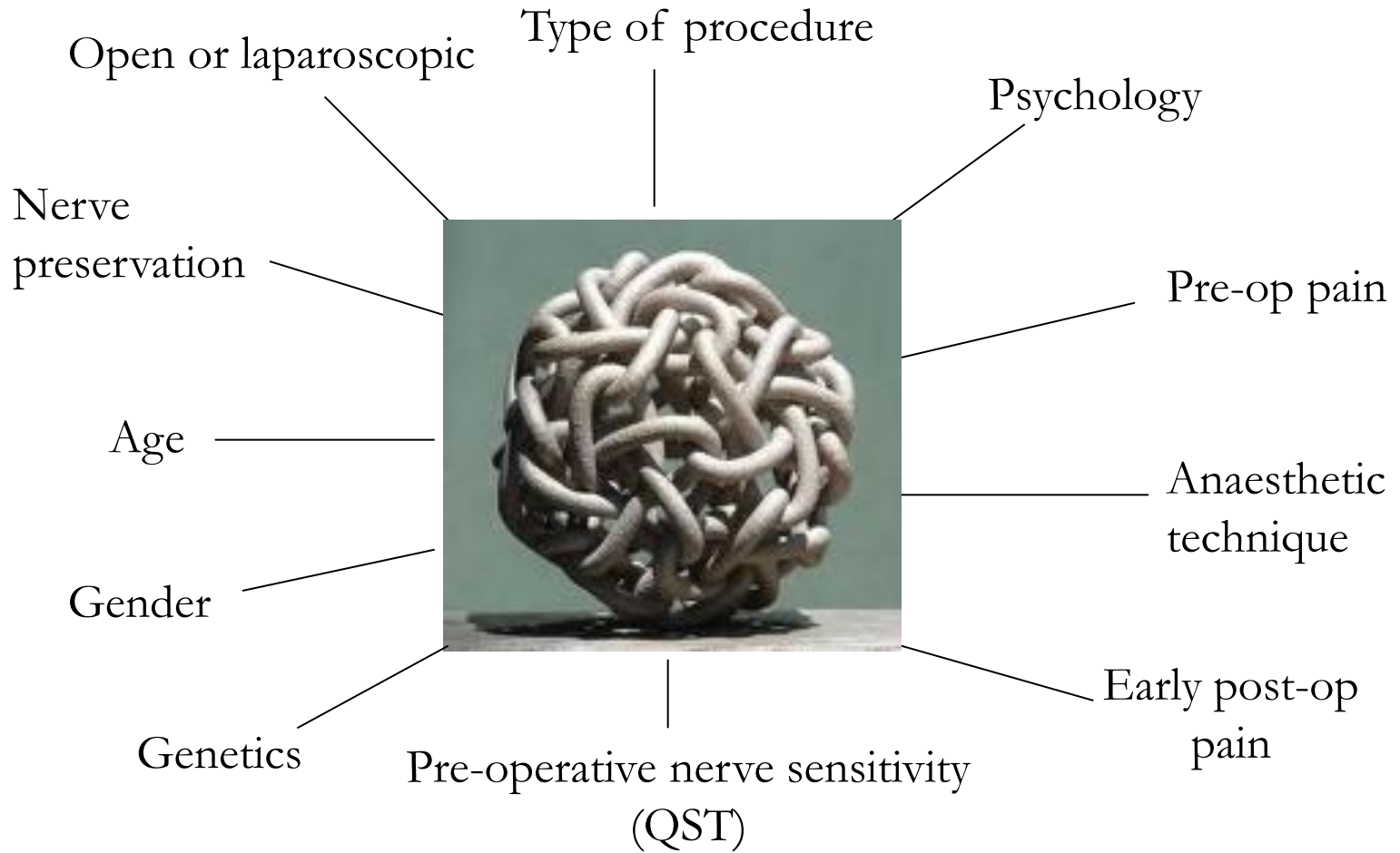
# Theory 4: Loss...



# Theory 4: ...versus gain



# Gordian knot



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# Alexander the Great



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# Identifying vulnerable phenotypes



# Gabapentinoids

- Recent meta-analyses showed a huge variety of gabapentin/pregabalin prescribing:
  - Pre-op alone, pre-op and one post- op, pre-op and for 4 subsequent days
  - Few effects except sedation and dizziness
  - Opioid-sparing effect immediately post-op
- Long term studies – mixed benefit
  - No clear benefit for gabapentin and THA
  - Some benefit for pregabalin and TKA
  - Some benefit one month after abdominal hysterectomy

•Sen et al. A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. *Anesth Analg* 2009;109(5):1645-50

•Ho KY, Gan TJ, Habib AS. *Pain* 2006;126(1-3):91-101

•Tiippana EM, Hamunen K, Kontinen VK, Kalso E. *Anesth Analg* 2007;104(6):1545-56

•Clarke H et al. *Acta Anaesthesiol Scand* 2009;53(8):1073-83

# Clonidine

- Intrathecal clonidine vs bupivacaine (+GA) for colonic surgery
  - ↓morphine post-op
  - ↓area of 2<sup>o</sup> hyperalgesia around wound
  - ↓pain at 6 months

# Ketamine

- Ketamine + morphine in PCA
  - benefits in morphine-sparing immediately post-op in thoracotomy
  - benefit in orthopaedic or abdominal surgery less clear
  - No long term evidence
- Ketamine bolus + infusion for THA
  - had morphine-sparing effect early post-op
  - facilitated rehabilitation at 1 month
  - decreased chronic pain up to 6 months later
- Epidural ketamine no benefit on long-term pain after thoracotomy

Carstensen M, Møller AM. Br J Anaesth 2010;104(4):401-6.

Remérand F et al. Anesth Analg 2009;109(6):1963-71.

Ryu HG et al. Clin J Pain 2011;27(4):304-8.

# Other drugs

## ■ Nitrous oxide

- ❑ NMDA antagonist
- ❑ 640 patients followed up for median 4.5 years
- ❑ 7% patients in N<sub>2</sub>O group described pain
- ❑ 14.8% patients in N<sub>2</sub>O-free group

## ■ Intravenous lidocaine

- ❑ 36 patients undergoing breast surgery
- ❑ Bolus 1.5mg/kg, infusion of 1.5mg/kg/hr for surgery + 1 hr after skin closure
- ❑ 2 patients (11.8%) pain @ 3/12 vs 9 (47.4%)

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# Drugs for all?

“if a preventive measure exposes many people to a small risk, then the harm it does may readily . . . outweigh the benefits, since these are received by relatively few.”

# Psychology

- Pain anxiety as a target for CBT
  - Useful in HIV patients
- Catastrophizing
  - A strong predictor of CPSP
  - Amenable to treatment

Huggins JL, Bonn-Miller MO, Oser ML, Sorrell JT, Trafton JA Behaviour Research and Therapy 2012; 50:72-78

Khan RS et al. Am J Surg 2011;201:122-131

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# Preventative strategies

- Avoid surgery...
  - Consider wisdom of operation if high risk of CPSP with no strong indication:
    - Vasectomy
    - Cosmetic breast surgery
    - Pain-free hernia
  - Particularly if predictive factor present
    - Visceral hypersensitivity conditions
      - IBS, interstitial cystitis
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# Conclusion

- Good quality post-op analgesia for all
    - LA blocks as appropriate
    - Extend analgesia into first 7 days
  - Extra interventions more likely to be of benefit if targeted at vulnerable patients
    - Anxiety, pre-op chronic pain, type of surgery
  - Psychological and pharmacological interventions may be of use but insufficient data as yet
    - Which drug, at what dose, for how long?
-

# Future directions: genetics?



# Acknowledgments

- Dr Katie Warnaby
- Prof Irene Tracey
  
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- Funding for OxPPOPS caesarean section:  
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Obstetric Anaesthetists' Association



OxPPOPS

Oxford Persisting  
Post-Operative Pain Study



Oxford Biomedical Research Centre

Oxford Radcliffe Hospitals   
NHS Trust



  
National Institute for  
Health Research

