



# Postoperative Pain: Nature vs Nurture

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# A tale of two patients

## TAH

- 39 yrs 72kg
- **GA:** Propofol, desflurane, relaxant, paracetamol, paracoxib, fentanyl (2ug/kg+2ug/kg/hr) [=1.21ng/ml]
- **PACU** pain **10/10**
  - 15 mg morphine iv
- **Day1** PCA 40mg morphine
  - Rest pain **4/10**

## TAH

- 52yrs 73kg
- **GA:** Propofol, desflurane, relaxant, paracetamol, paracoxib, fentanyl (2ug/kg+2ug/kg/hr) [=0.95ng/ml]
- **PACU** pain **0/10**
  - 0 mg morphine iv
- **Day1** PCA 12mg morphine
  - Rest pain **2/10**

**Can we  
predict  
this?**

# In search of the Holy Grail of personalised medicine...



# Methods of pre-operative pain prediction

- Demographics
  - Type of surgery, age, gender, redheads...
- Psychological
  - Anxiety-depression
  - Catastrophising
- Pain Physiology (Quantitative sensory testing)
  - Individual endogenous pain control systems
  - Response to exogenous opioids
    - Cold/heat
    - Electricity
    - Pressure
  - *Pain & fentanyl dose-response*

# Prediction of severe pain (VAS>7) in PACU

Reduced and extended (final) model to predict preoperatively the occurrence of severe pain (VAS ≥ 8) within first hour at recovery room

	Reduced model		Extended (final) model		
	Regression coefficient (SE)		Regression coefficient (SE) <sup>a</sup>	OR <sup>a</sup>	p-Value
Female gender	0.36 (0.14)		0.22 (0.14)	1.24	0.12
Age (per year)	- 0.018 (0.0046)		- 0.016 (0.0047)	0.98	<0.001
Pre-op pain			0.14 (0.025)	1.15	<0.001
Type of surgery					
Ophthalmology					
Laparoscopy			0.38 (0.43)	1.46	0.37
Ear/nose/throat			0.50 (0.36)	1.80	0.10
Orthopedics			0.97 (0.35)	2.64	0.006
Abdominal surgery			1.57 (0.36)	3.56	<0.001
Other			0.48 (0.34)	1.62	0.17
Medium			0.23 (0.16)	1.26	0.15
AP/ASIS			0.053 (0.017)	1.05	0.002
AP/ASIS			- 0.080 (0.032)	0.92	0.01
Intercept			- 1.74 (0.46)		<0.001

Preop pain OR=1.2

Abdo OR=3.6

Anxiety OR=1.05

ROC=71%

Table 3. Outcome Variables, Predictors, Nonpredictors, and Correlation

Study	Outcome Variables	Predictors	Nonpredictors	Correlation	Contribution (%)
Gynecological and obstetrical surgery					
Hsu et al. <sup>28</sup>	AP, RA*	STAI-S, PPTc	—	RF = 0.37-0.39	27-38
Grant et al. <sup>29</sup>	AP	PPTc	STAI-S	RF = 0.48	46
Wilden-Smith et al. <sup>27</sup>	AP	EDT, EPT, ESTP	HPT	RF = 0.70-0.81	10-54
Pan et al. <sup>34</sup>	AP	HPT, HSTP, expectation, EP	Preoperative pain, STAI	RF	4-7
	RA†	HPT, preoperative pain, STAI	HSTP, expectation, BP	RF	20-28
Strulov et al. <sup>26</sup>	AP	HSTP (tonic), PCS	HPT, HSTP (phasic)	RF	22-27
Nielsen et al. <sup>25</sup>	AP	EPT	EDT	RF	14-17
Rudin et al. <sup>25</sup>	AP	HSTP, preoperative pain, STAI-T, vulnerability	WDT, HPT, HADS	RF	27-42
	RA‡	HSTP	WDT, HPT, STAI-T, vulnerability, HADS	RF	29-43
Abdominal surgery					
Aasvang et al. <sup>31</sup>	AP	Age	EDT, EPT, EPTc	RF	6
Bjergaard et al. <sup>28</sup>	AP	CPPTc, age, vulnerability, preop. biliary symptoms	—	RF	4-9
Thoracic surgery					
Yamitzky et al. <sup>28</sup>	CPP	DNIC	HPT, HSTP	OR	7
Weissman-Fogel et al. <sup>28</sup>	AP	MSTP, MTS	HPT, HSTP, HTS, MPT, STAI, PCS	OR	7
Knee surgery					
Werner et al. <sup>22</sup>	AP	HSTP	WDT, HPT, SHA	RF	32-42
Martinez et al. <sup>27</sup>	AP	Preoperative pain (dynamic)	CDT, CPT, WDT, HPT, HSTP, MPT	RF	38
	RA*	HSTP	CDT, CPT, WDT, HPT, MPT, preoperative pain (dynamic)	RF	40
Lundblad et al. <sup>26</sup>	CPP	Preoperative pain	EDT	OR = 6.48 (95% CI 1.32-31.98)	?
	EPT		EDT	OR = 9.19 (95% CI 1.89-52.57)	?

4%

to

40%

Preoperative prediction of severe postoperative pain

C.J. Kalkman Pain 105 (2003) 415-423

# Prediction of Postoperative Pain

## *A Systematic Review of Predictive Experimental Pain Studies*

Mads U. Werner Anesthesiology 2010; 112:1494 –1502

### **Predicting Postoperative Pain Based on Preoperative Pain Perception**

#### *Are We Doing Better Than the Weatherman?*

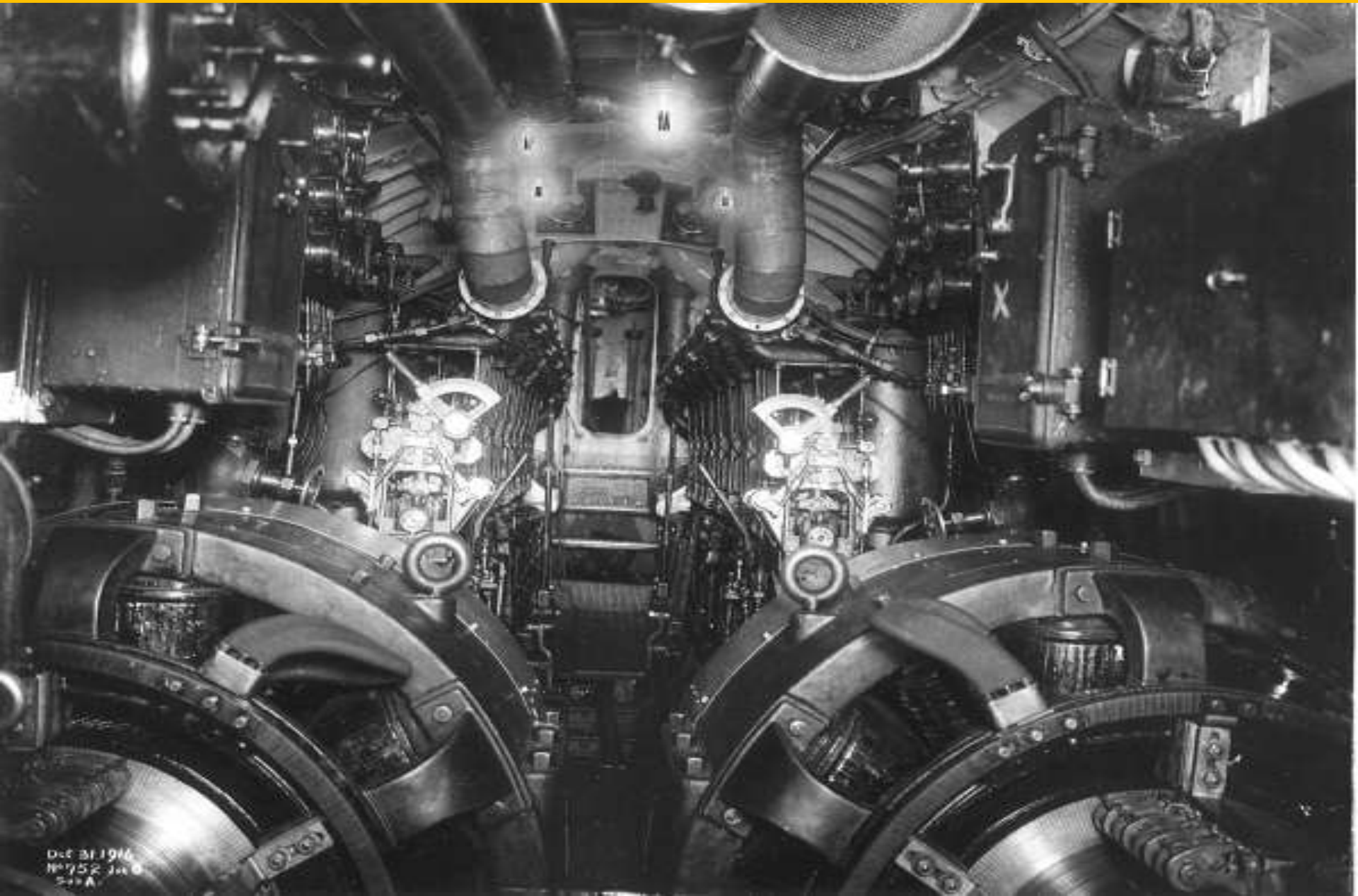
“Despite extensive resources used on *patient-controlled analgesia, spinal drug delivery methods, co-analgesics, multimodal analgesia, guidelines for acute pain management, and implementation of acute pain services*, the **results**, in terms of an improved outcome after major surgery, **seem unexpectedly modest.**”

# Failure to get the Holy Grail...

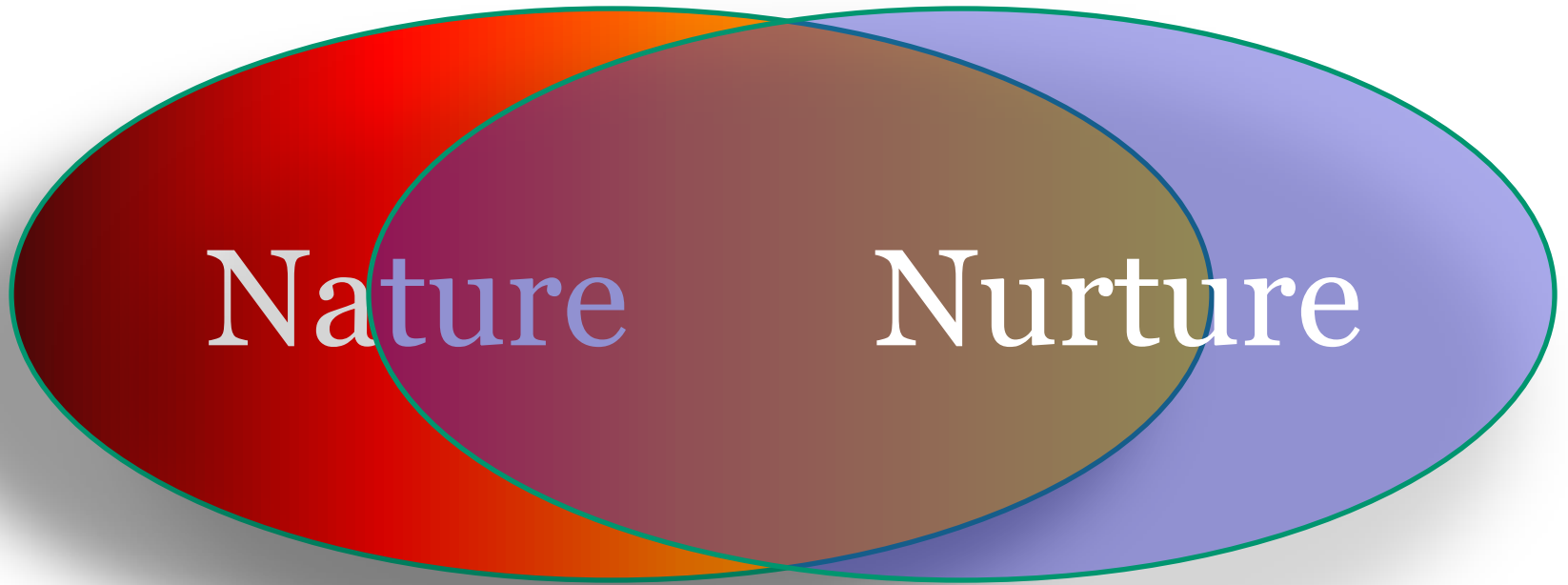


**Nature  
&  
Nurture**

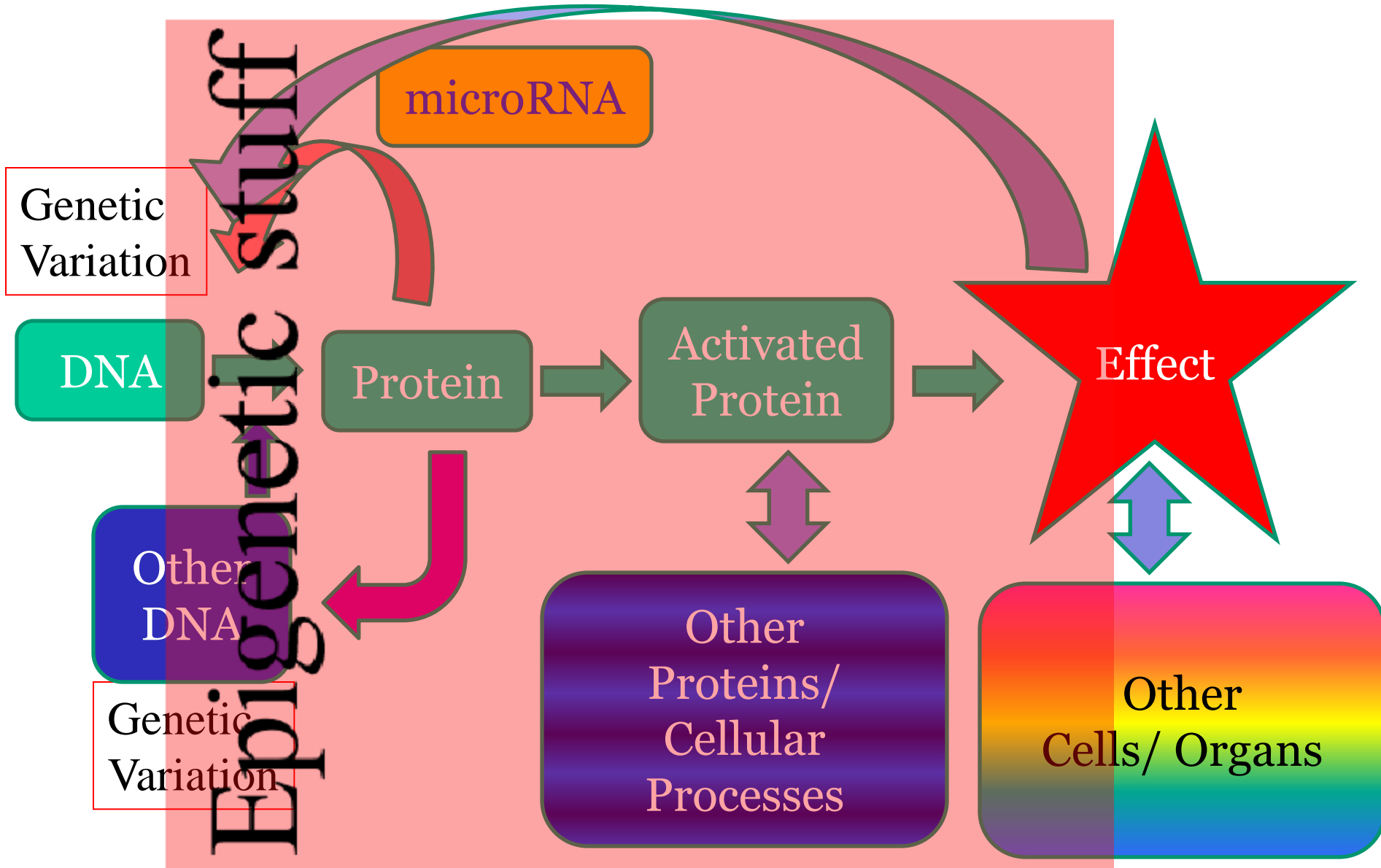
Lets look into the details of the machine



# Epigenesis



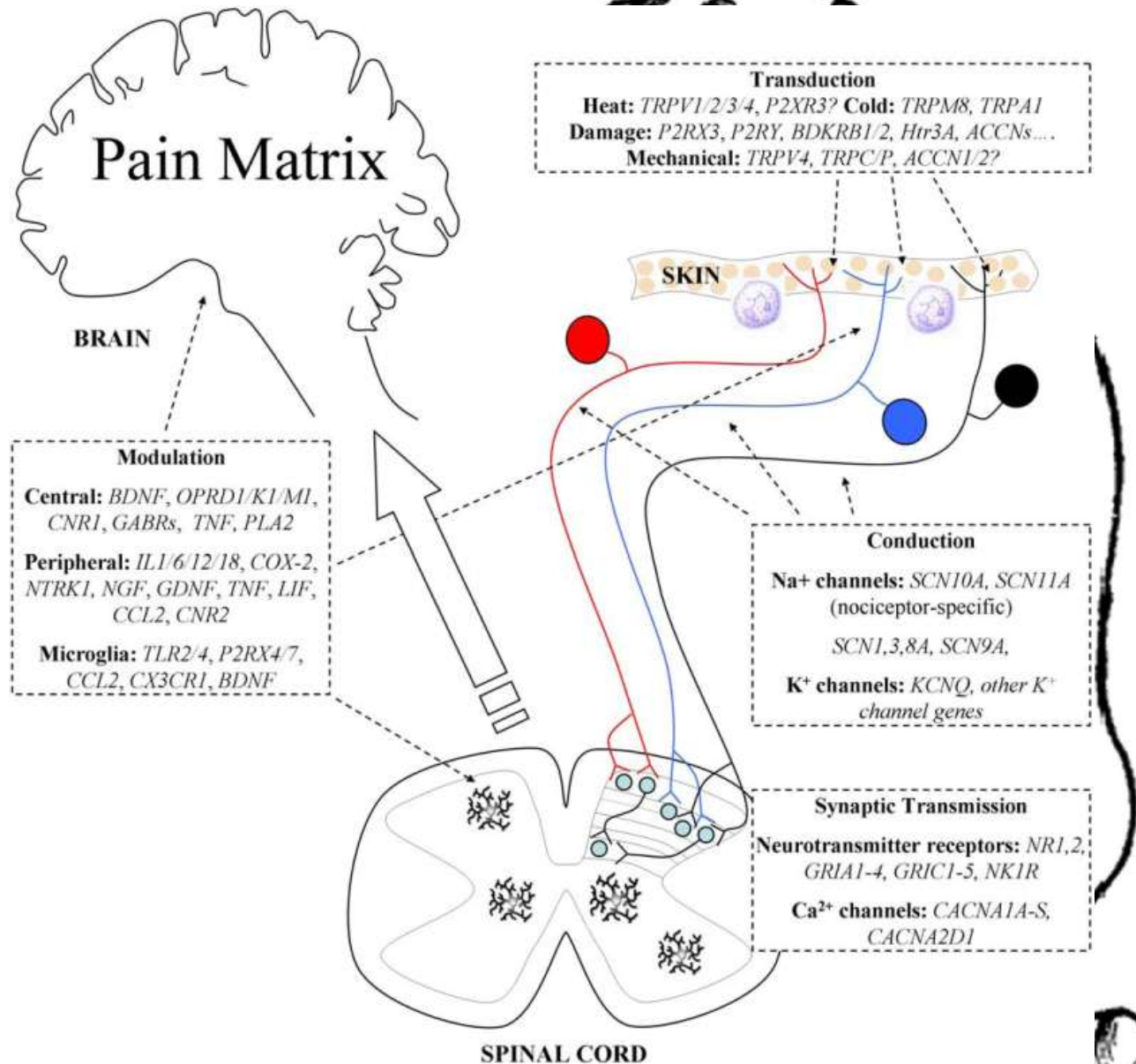
# Processes required for analgesia

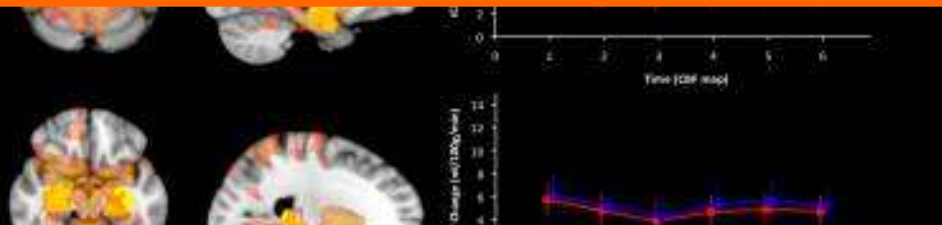
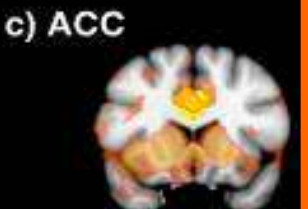
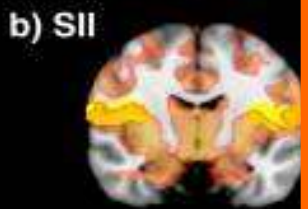


# Nature

= Genes

# The Pain Pathway



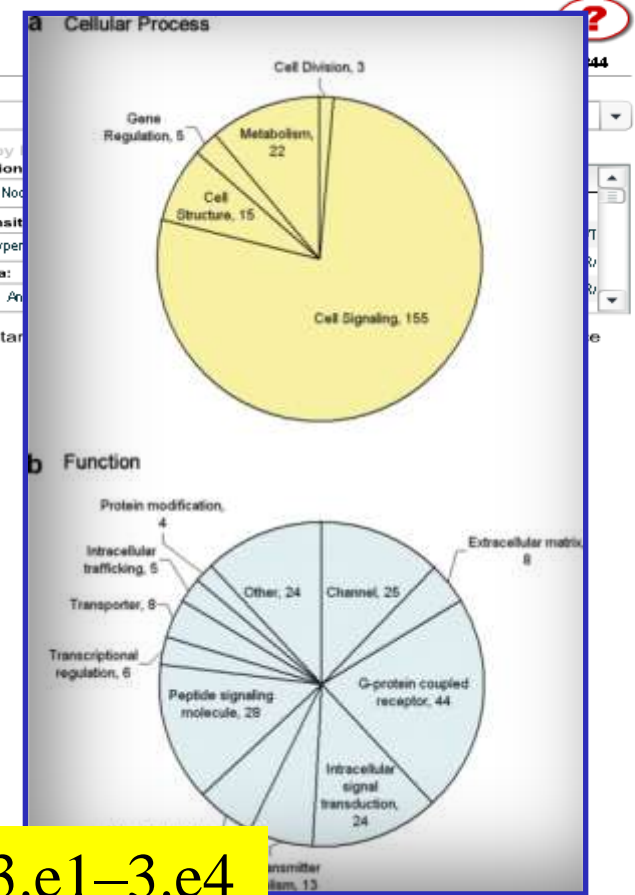
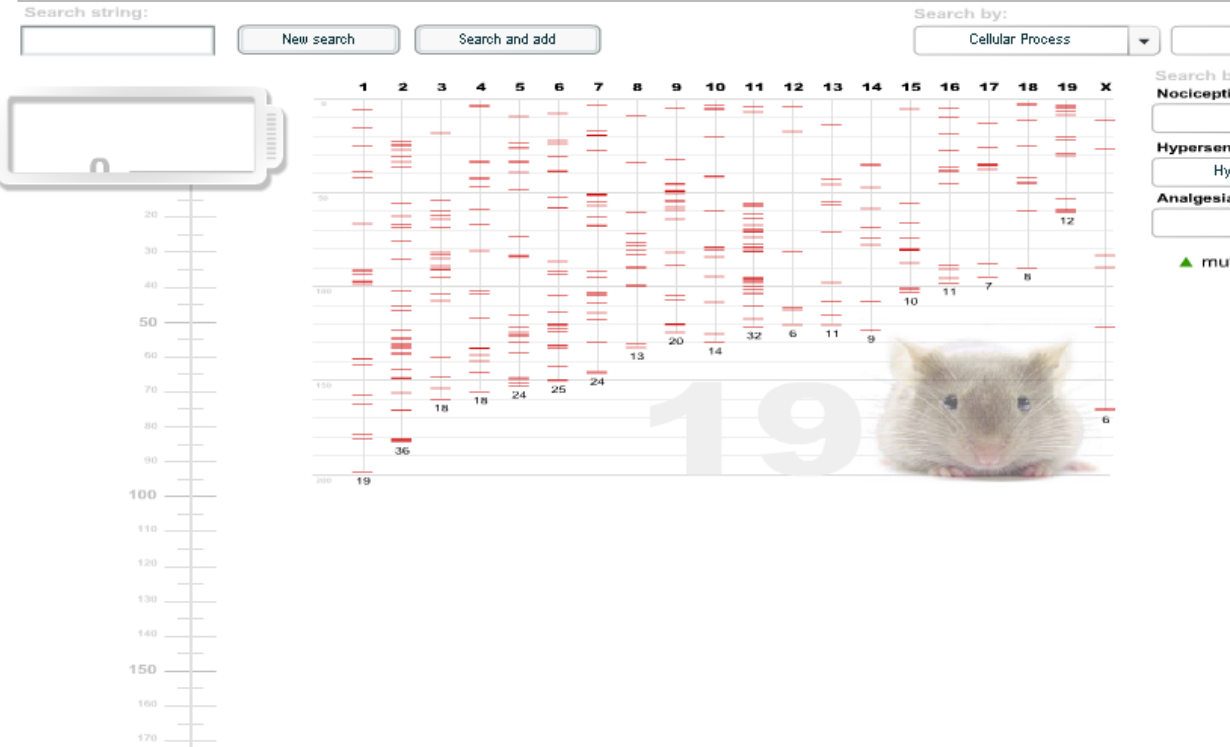


*Howard et al. Beyond Patient Reported Pain: Perfusion Magnetic Resonance Imaging Demonstrates Reproducible Cerebral Representation of Ongoing Post-Surgical Pain. PLoS One. 2011 Feb 23;6(2):e17096.*

**“Lets hurt some mice...”**

# The Mutant Mouse Database (~400SNPs)

## PainGenesdb Selector



Michael L. LaCroix-Fralish. Pain 131 (2007) 3.e1–3.e4

[http://paingeneticslab.ca/4105/06\\_02\\_pain\\_genetics\\_database.asp](http://paingeneticslab.ca/4105/06_02_pain_genetics_database.asp)

# What is the relative contribution of genetics to pain sensitivity?

***“Lets hurt some twins...”***

- 22%-55% Norbury
  - Heat, cold, acid, ATP
- 26% to 60% Neilsen

*Norbury (2007) Heritability of responses to painful stimuli in women: a classical twin study. Brain 130: 3041–3049.*

*Nielsen CS, (2007) Individual differences in pain sensitivity: Genetic and environmental contributions. Pain 136: 21–29.*

# Laws of genetics # 1

**Rare genes can have big effects...**

*Clinically useless, but scientifically important – the path to new drugs*

**Table 2.** Heritable Pain Conditions.

Syndrome	Gene Affected	Cell Loss	Phenotype	Reference
HSAN-1	Autosomal dominant mis-sense mutations in serine palmitoyltransferase long chain base subunit 1 (SPTLC1)	Apoptotic cell loss of sensory and other neurons	Pain and heat loss	[70]
HSAN-2	Mis-sense mutations in the protein kinase PRKWNK1	Developing sensory cell loss	Developing loss of all sensation	[71]
HSAN-3 (Familial dysautonomia)	Splicing deficit in IkbKAP protein	Failure in sensory neuron development	Pain-free phenotype	[72]
HSAN-4 (CIPA)	Loss of functional NGF receptor TrkA	Loss of most small diameter sensory neurons	Congenital insensitivity to pain	[1]
Mutilated foot rat	$\delta$ subunit of the (Cct4) gene	Loss of nociceptors	Ulceration and loss of pain sensitivity	[73]
Erythralgia	Point mutations in sodium channel Na <sub>v</sub> 1.7 – increased excitability	No cell loss	Chronic inflammation	[9]
Paroxysmal extreme pain (familial rectal pain)	Point mutations in Na <sub>v</sub> 1.7 - loss of inactivation	No cell loss	Mechanically induced extreme pain	[8]
Insensitivity to pain	Mis-sense mutations in Na <sub>v</sub> 1.7	No cell loss	Complete insensitivity to acute pain	[7]

# The Tale of 3 Sodium Channels

- $\text{Na}_v1.9$  (SCN11A)
  - controlled by inflammatory mediators and controls thresholds
- $\text{Na}_v1.8$  (SCN10A)
  - Specific for nociception/thresholds/cold
- $\text{Na}_v1.7$  (SCN9A)
  - Delayed inactivation = bursting
    - Loss-of-function mutants = normal (pain-free) human [but dead mice]
    - Gain-of-function mutants = erythromyalgia & acute paroxysmal pain

# Laws of genetics # 2

## Common genes have small effects...

- Pain sensitivity
  - COMT haplotypes and TM Pain
  - Chronic pain propensity (OPRM1, Beta-2)
- PD responses to analgesics
  - OPRM1
- Analgesic PK
  - P450 (CYP2D6, also CYP3A4/5, UDG)
    - Codeine & Tramadol
  - ABCB1 (ATP-binding cassette = drug efflux)

# OPRM1: A118G

- AA=5.9 vs GG=9.4 mg morphine

**Table 1 Recent studies of *OPRM1* gene SNPs and opiate neuraxial analgesia**

Study	SNP	Number of subjects	Study cohort	Opiate studied	Measured outcomes	Observed associations
Sia <i>et al.</i> [15*]	A118G	588	Chinese Singaporean women undergoing elective cesarean term delivery	Intrathecal morphine	1) Pain scores 2) 24 h postoperative IV morphine requirement 3) Nausea	Pain scores and IV morphine requirement lowest in AA group; postoperative nausea highest in AA group
Hayashida <i>et al.</i> [16]	A118G	138	Japanese men and women undergoing abdominal aortic surgery	Epidural fentanyl or morphine	24 h postoperative opioid requirement (systemic fentanyl equivalent)	The GG group required significantly more 24 h opiates than the AG and AA groups
Landau <i>et al.</i> [17]	A118G	224	Nulliparous women laboring at full term	Continuous spinal-epidural analgesia using intrathecal fentanyl	ED <sub>50</sub> related to intrathecal fentanyl dose with respect to labor analgesia	Reduced intrathecal fentanyl ED <sub>50</sub> in G allele carriers

Kosarac. Effect of genetic factors on opioid action. *Current Opinion in Anaesthesiology* 2009,22:476–482

## In Summary - Bad News...

- *“To date, almost every genetic association with common human nociception has been disputed...”*
- “The study of pain-related SNPs in the human has proved problematic, due to the tendency of different data sets to yield conflicting conclusions; **in many cases, a finding from one has been contradicted by those from others”**

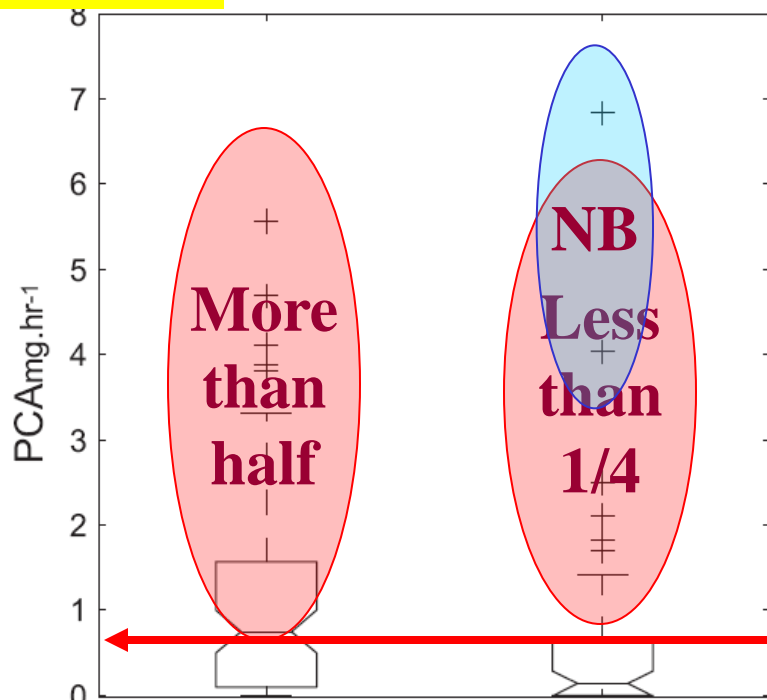
# ?? Solutions

1. Look at *other parts* of the DNA...
2. Look at *combinations* of common pain-related genes...
3. Look in more detail at *nurture*...

# Combos: the clinical usefulness?

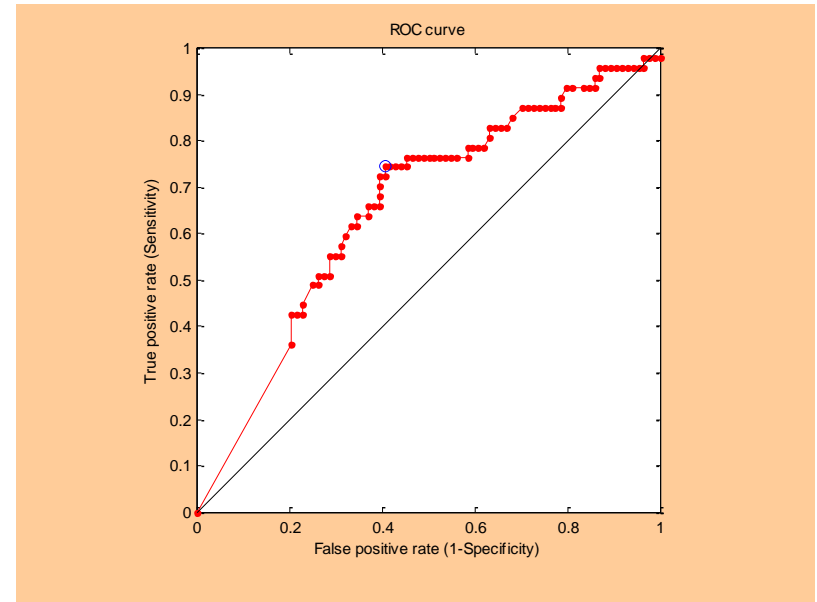
**P = 0.003**

*KCNJ6=G/G or ABCB1=C/C*



Don't have these genes

Do have this pain-protective genotype



**AUC-ROC = 68%** ( $P < 0.0001$ )

Sensitivity = 74% (PCA > 0.58mg/hr)

Specificity = 60%

NPV [Predict "Minimal-pain"] = 80%

PPV [Predict "Severe-pain"] = 50%

Misclassify = 35%

# Nurture

= Top Down

= Environment

# The Machinery of Nurture = Epigenesis

*...the environment  
makes the genes  
whisper or shout...*

# Epigenetics $\cong$ development

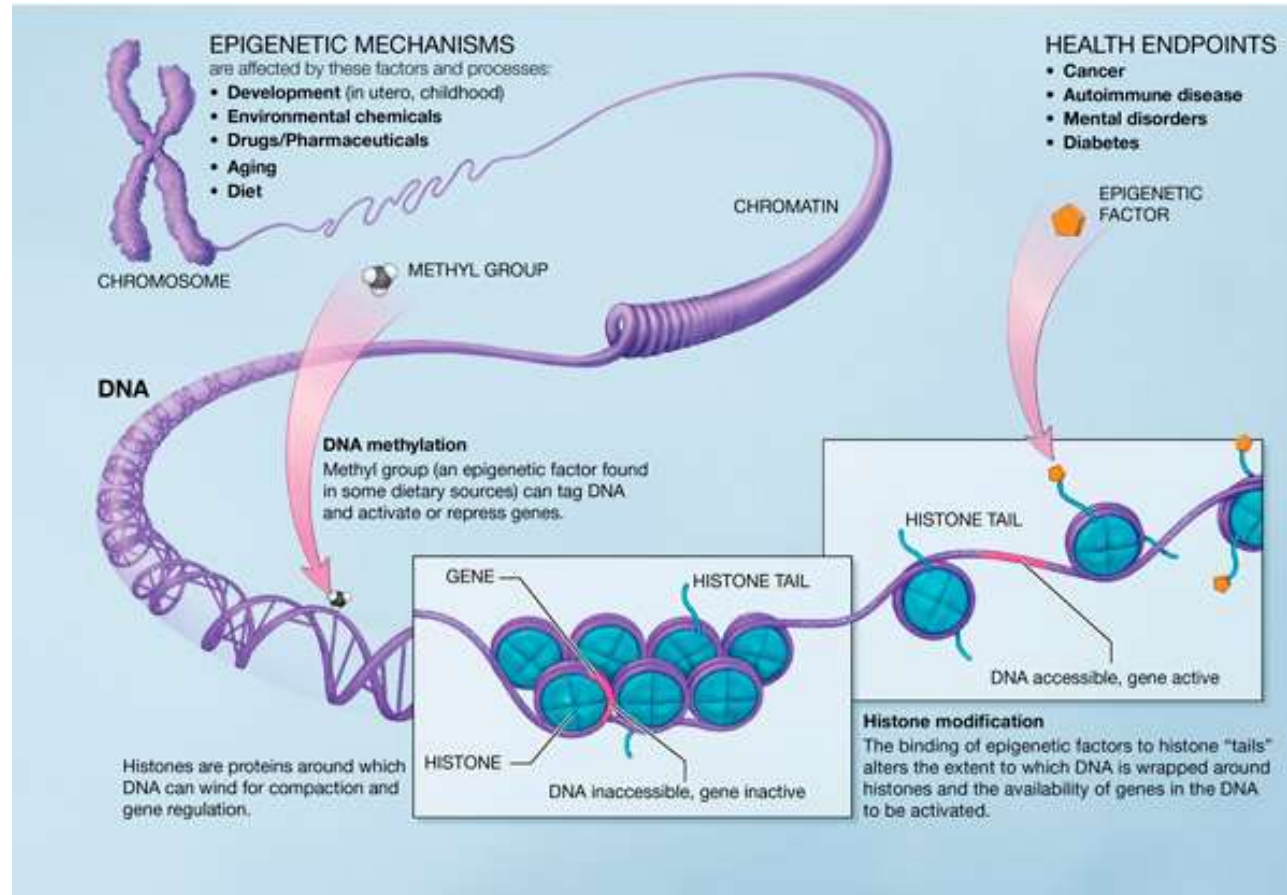
Royal jelly turns off DNA methylation

– stops young bees turning into a worker bees



# The Mechanisms of Epigenetics

- Histone acetylation = activates gene expression
- DNA-CpG methylation = silences genes
- RNAi



*Phenotypic plasticity and the epigenetics of human disease*

*Andrew P. Feinberg NATURE;447(24) 2007 doi:10.1038/nature05919*

*Review: Epigenetics in pain and analgesia: An imminent research field*

*Alexandra Doehring. European Journal of Pain 15 (2011) 11–16*

# Epigenetics and Pain: Studies #1

- Bladder Pain. "These genes act as transcriptional repressors, mediate gene silencing and inhibit cell differentiation by methylating the lysine residue 27 of histone H3 (H3K27me3). By contrast, inflammatory stimuli are strong inducers of the lysine (K)-specific demethylase 6B, an enzyme demethylating H3K27me3. In addition, the human polycomb group protein EZH2 (Enhancer of Zeste homolog 2) was shown to control CpG methylation by direct interaction with DNA methyltransferases"
- **PKPD**: HDAC1 and CYP3A4

# Epigenetics and Pain: Studies #2

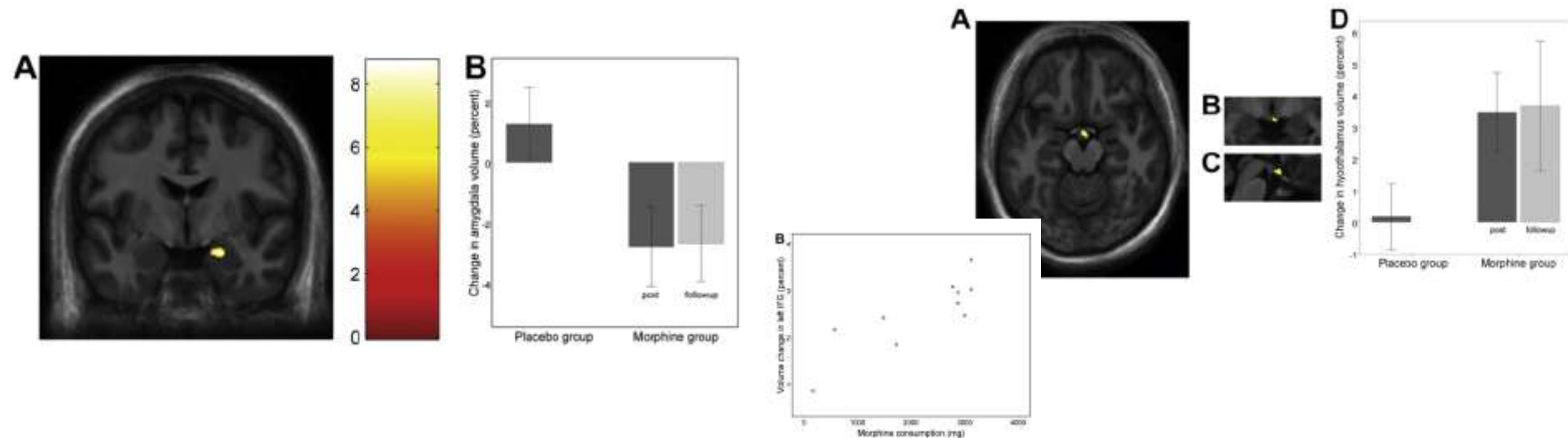
- Chronic opioids  $\uparrow$   $\mu$ -receptor gene methylation

Nielsen DA. Increased OPRM1 DNA methylation in lymphocytes of methadone-maintained former heroin addicts. *Neuropsychopharmacology* 2009;34(4):867-73.

- Prescription opioid analgesics rapidly change the human brain.

Younger JW *Pain*. 2011 Aug;152(8):1803-10.

**Right Amygdala 3%  $\downarrow$  ... Hypothalamus 4%  $\uparrow$**



# Possible epigenetic treatments

- Subarachnoid RNAi
  - Anti-NMDA
  - TRPV1 ..... *(5days-6 months analgesia)*
- Histone deacetylase inhibitors (HDACI) →  
↑expression of:
  - CYP3A4, mGlu2, &  $\mu$ -opioid receptors
  - Valproate
  - No tolerance

# Conclusions / Speculations

1. *Clinical/Psych testing  $\cong$  predicting rugby results.*
2. *Combinations of common pain-related genes might change the expected odds:*
  - *i.e. 25% severe pain  $\rightarrow$  70% severe pain*

**OR**

  - *i.e. 25% severe pain  $\rightarrow$  10% severe pain*
3. *Epigenetics... ? more important than genetics*
4. *What do we do with this information?*

Le Rêve

*Picasso*



# Epigenetics

*Phenotypic plasticity and the epigenetics of human disease*

*Andrew P. Feinberg NATURE;447(24) 2007 doi:10.1038/nature05919*

- “The modern definition of epigenetics is information heritable during cell division other than the DNA sequence itself.”
- Developmental processes are regulated largely by epigenetics, because different cell types maintain their fate during cell division even though their DNA sequences are essentially the same.