

The Roles of Early Pain Experience, Sex Hormones and Aging on Endogenous Pain Modulation Deficits

Plenary session 201 May 29th 2008, 10:00 am
Lifespan factors that play a role in predisposition to chronic pain
CPS, Victoria May 27-30 2008

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Disclosure

Received honoraria, consultation fees or research grants from the following companies:

Janssen Ortho, Astra Zeneca, Pfizer, Purdue, Valeant, Merck Frosst



Objectives

Review how factors such as :

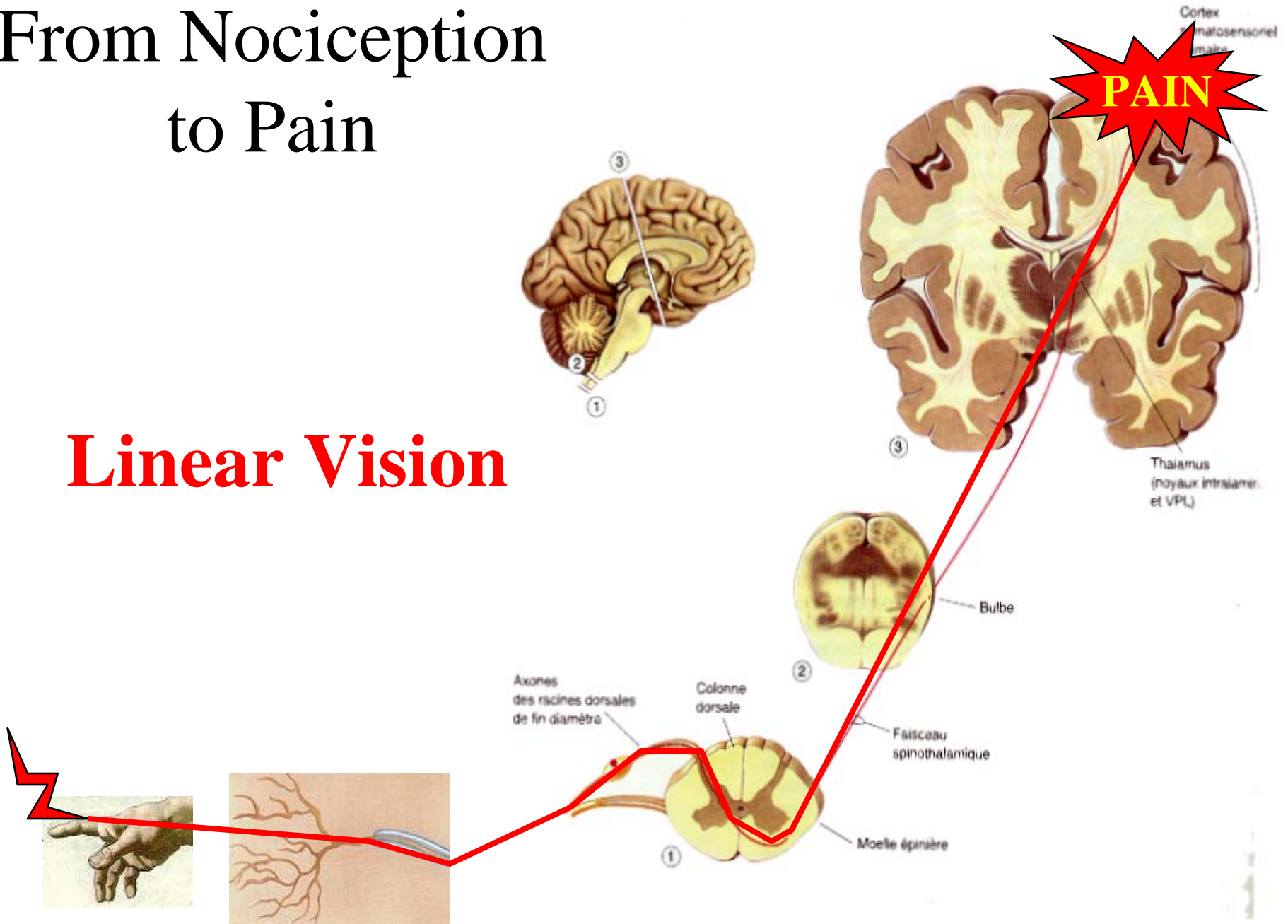
- Genetic
- Cognitive factors
- Early pain experience
- Sex hormones
- Aging

affect **endogenous pain modulation mechanisms** and may lead to a predisposition for neurogenic chronic pain conditions.



From Nociception to Pain

Linear Vision

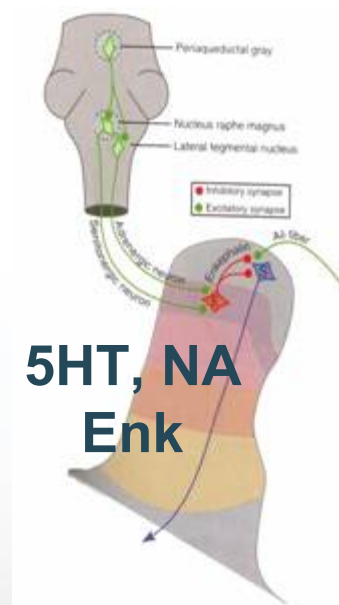
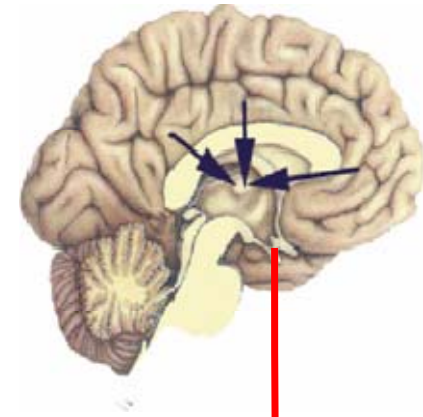


Endogenous Pain Modulation

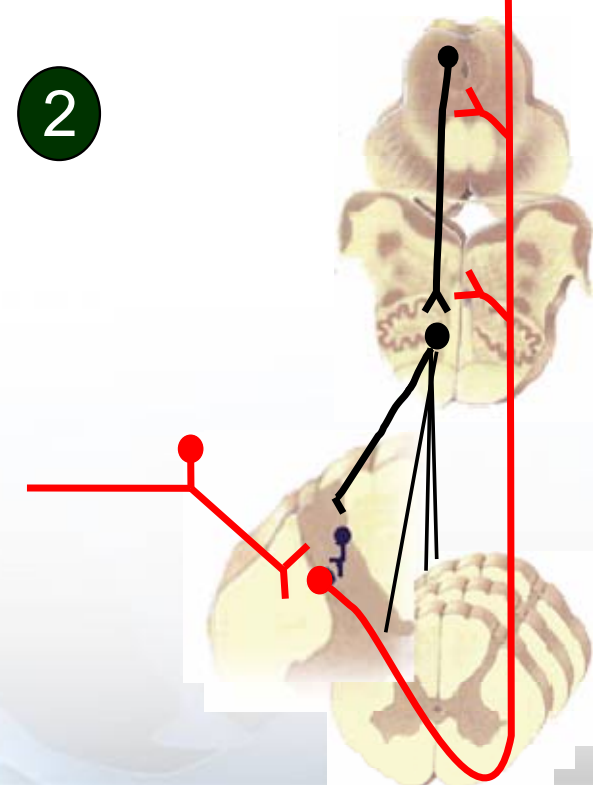
Descending System

Diffuse
Noxious
Inhibitory
Control

Phasic and Tonic !



2





Pain xx (2005) 1–8

PAIN

www.elsevier.com/locate/pain

Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition

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DNIC : Temporal Summation

Before

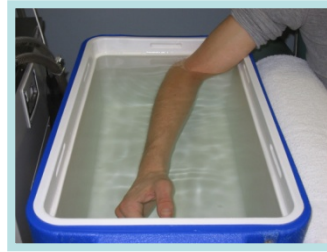


**Conditioning
DNIC**

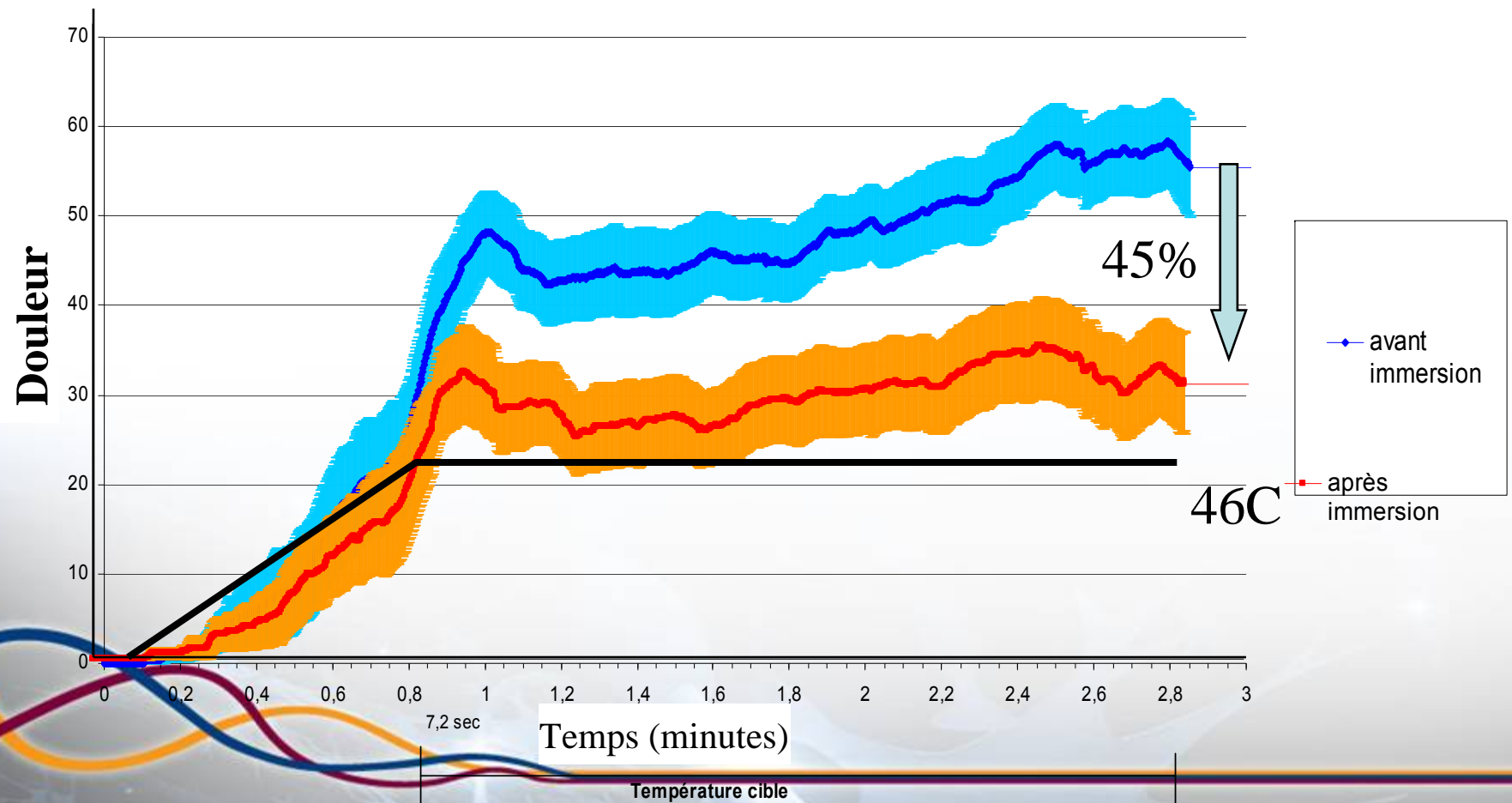


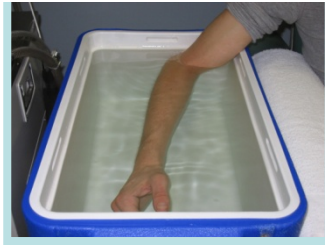
After



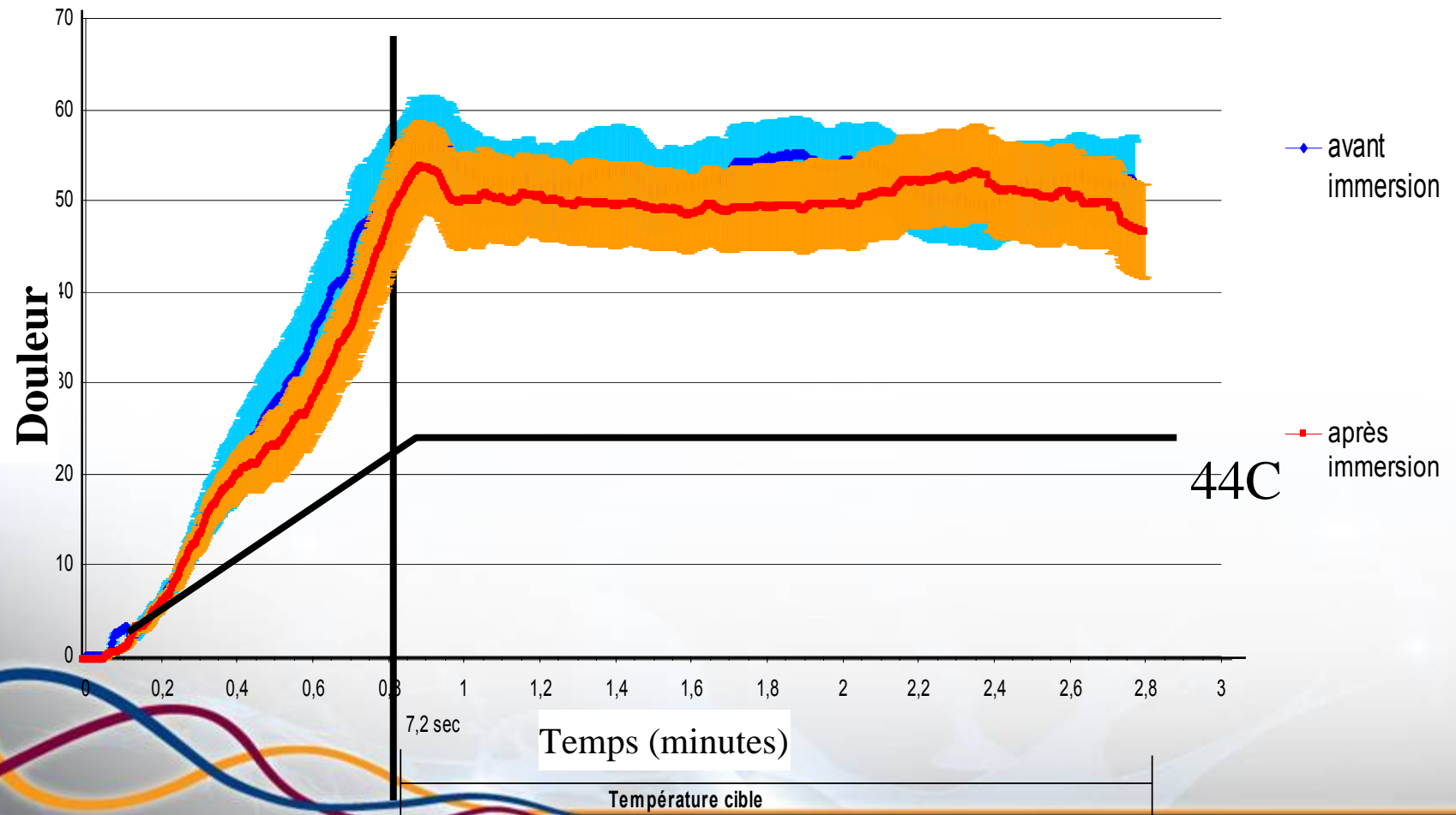


DNIC in Healthy Subjects





DNIC in Fibromyalgia



Dysfunction of DNIC :

Is it a generalized effect of all chronic pain conditions ?

- Deficits of DNIC in Tension-Type Headache (Pielsticker, PAIN 2005)
- Deficits of DNIC in IBS (Wilder-Smith,C.H., GUT 2004)
- ...
- No deficit of DNIC in Low Back Pain (Julien et al., PAIN 2005)

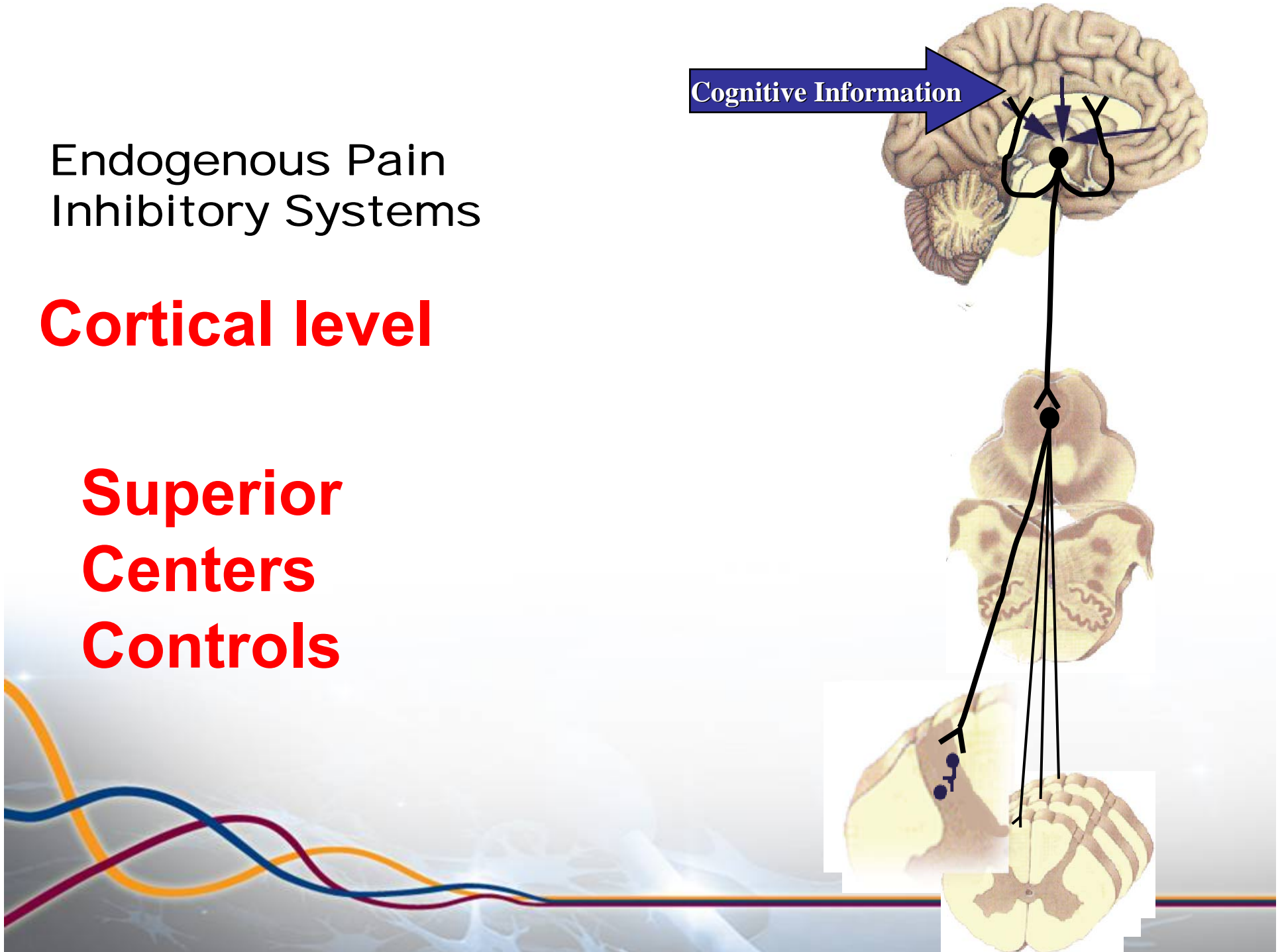


Endogenous Pain Inhibitory Systems

Cortical level

Superior Centers Controls

Cognitive Information





Descending analgesia – When the spine echoes what the brain expects

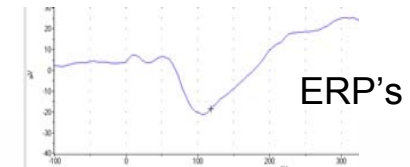
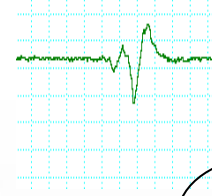
Philippe Goffaux ^a, William John Redmond ^a, Pierre Rainville ^b, Serge Marchand ^{a,*}

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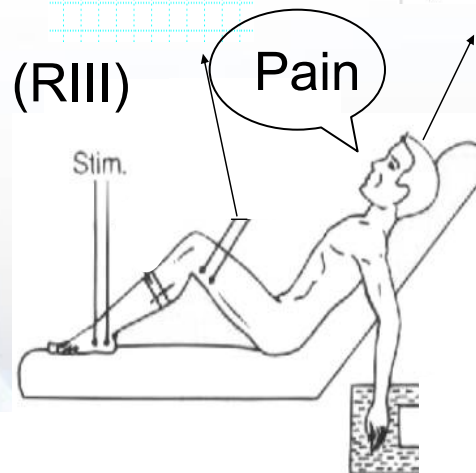
Received 21 June 2006; received in revised form 12 November 2006; accepted 21 November 2006

What happen to DNIC if we are expecting hyperalgesia rather than analgesia ?



Nociceptive reflex (RIII)

Pain



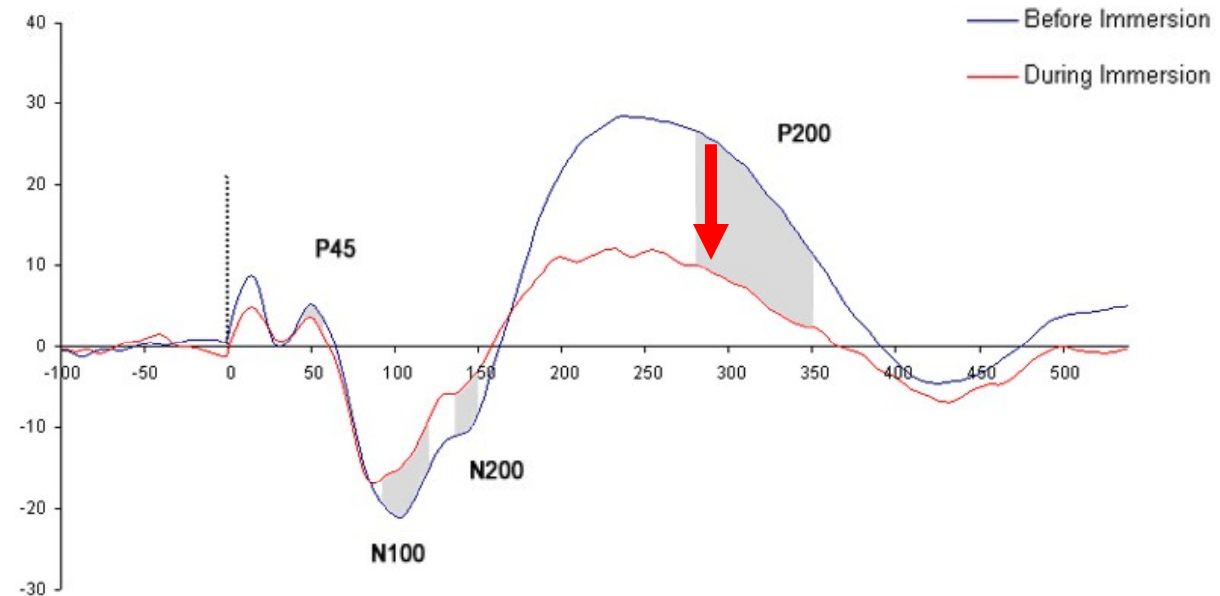
Cold water bath
used to trigger DNIC
activity

Expectation mediated Cerebrospinal modulation of the analgesia

Expecting Analgesia = 77% pain reduction after DNIC

RIII Reflex

Somatosensory Evoked Potential

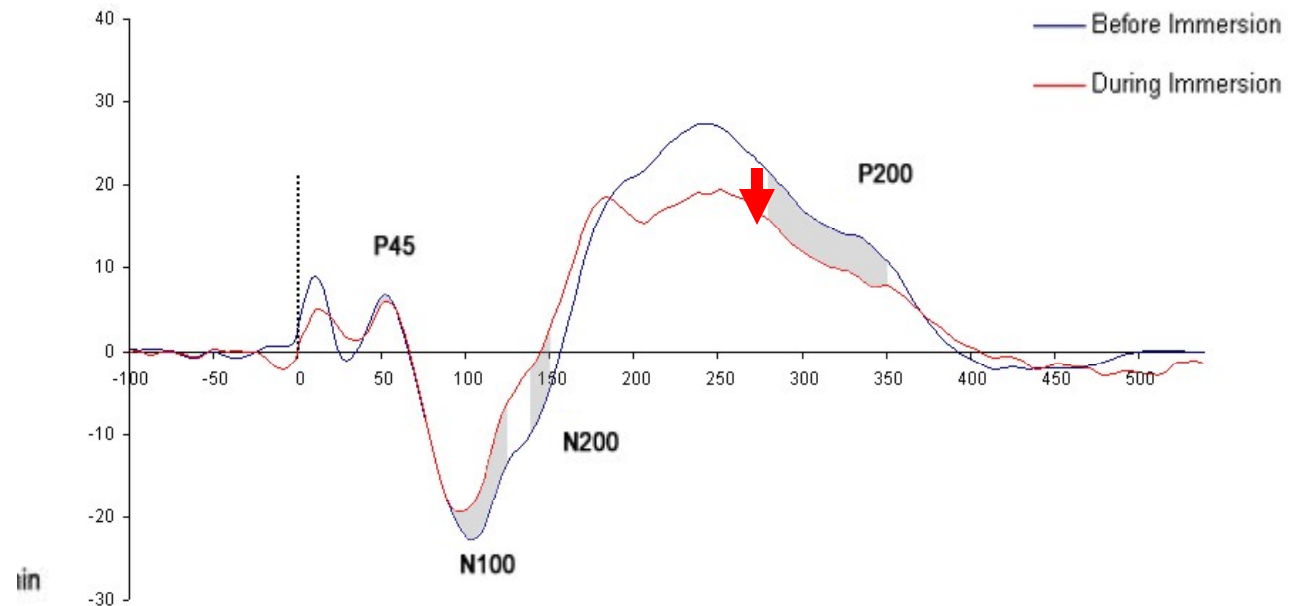


Expectation mediated Cerebrospinal modulation of the analgesia

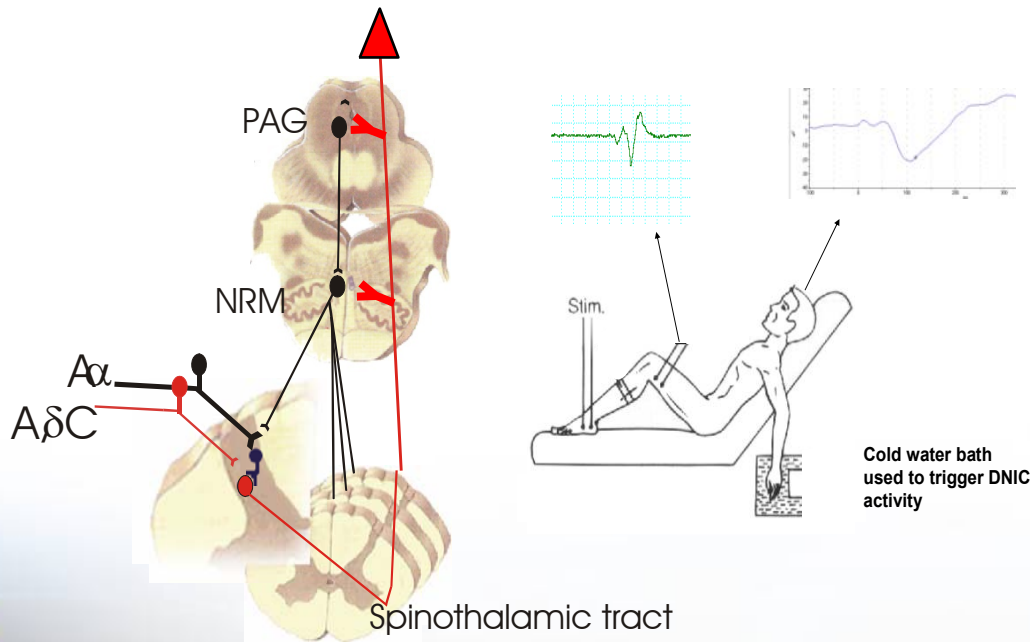
Expecting Hyperalgesia = no pain reduction after DNIC

RIII Reflex

Somatosensory Evoked Potential



The Role of Expectation on DNIC in Fibromyalgic Patients

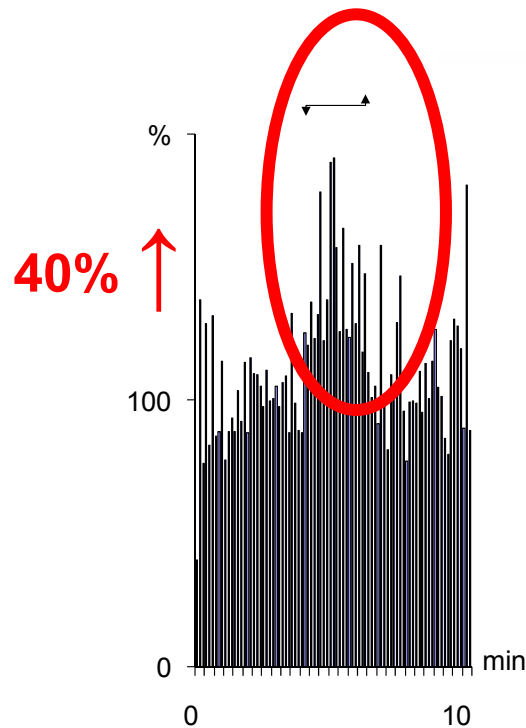


The role of expectation on DNIC in FM

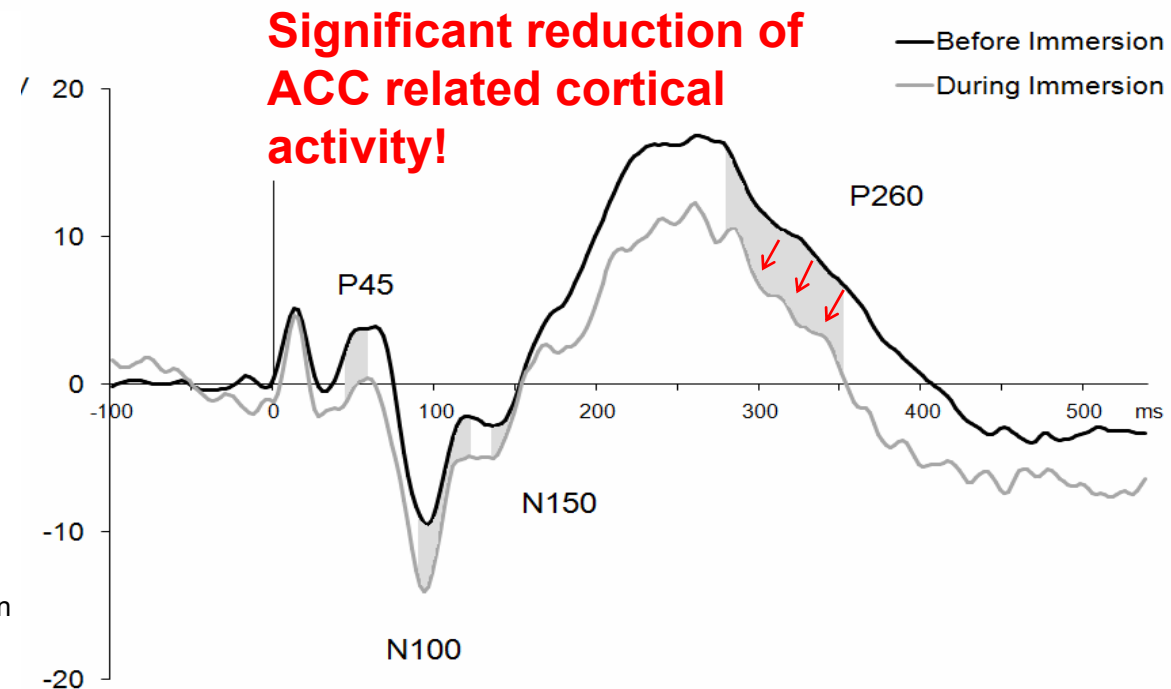
Expecting Analgesia

DNIC: 24% Decrease in Pain

Triggering a significant DNIC analgesia !



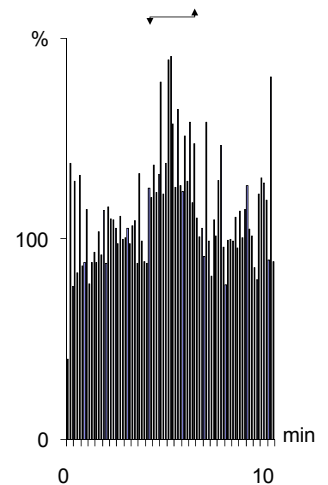
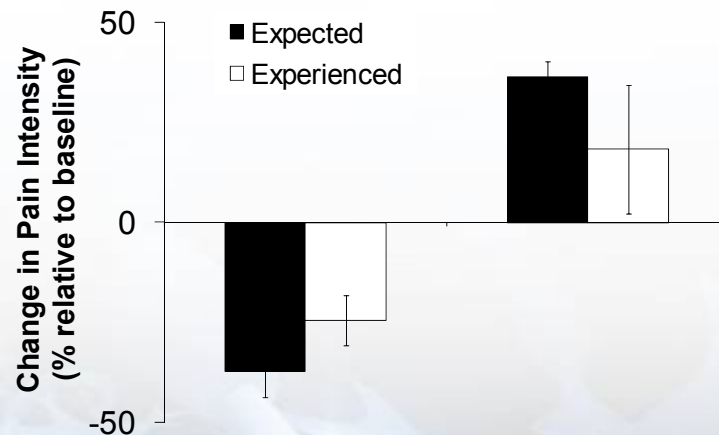
No reduction of the spinal activity !?!



Significant reduction of ACC related cortical activity!

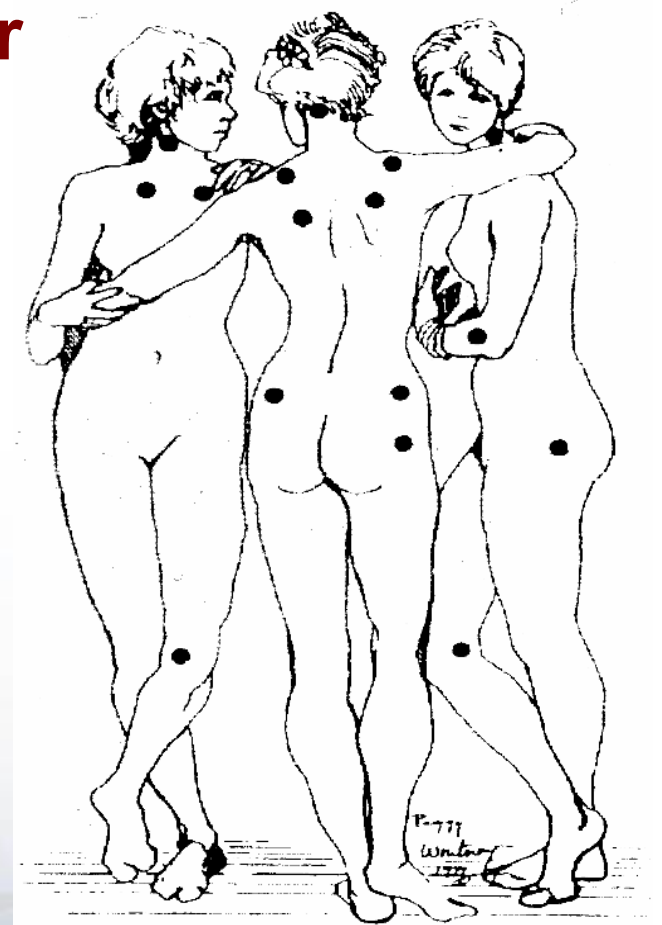
Conclusion

- FM patients are capable of expectancy-induced analgesia.
- Unlike healthy subjects, this does not depend on the recruitment of descending inhibitory projections.
- Neurogenic rather than Psychogenic !



Events triggering Widespread Chronic Pain !

Several patients reports developing fibromyalgia following a physical or psychological stress !

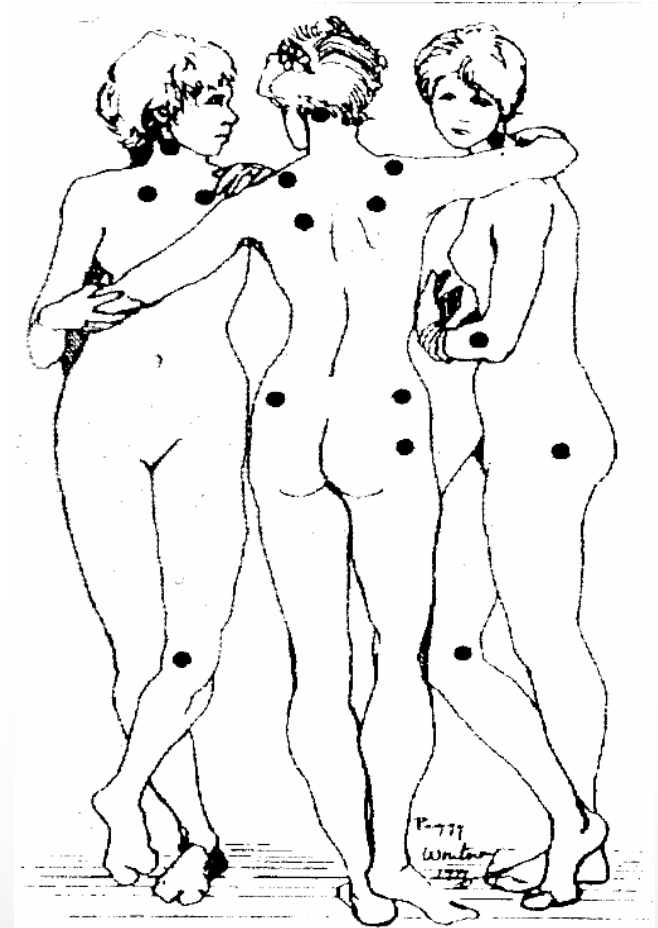


Being born prematurely and long-term effect on pain

- 2x more sensitivity points in adolescent (now 14) born pre-term compared to full-term
- Preterm = 6/18 Sensitivity points
- Full-term = 3/18

Not FM but perhaps at risk!

Buskila *et al.*, (2003)





Available online at www.sciencedirect.com



European Journal of Pain xxx (2008) xxx–xxx



www.EuropeanJournalPain.com

Preterm births: Can neonatal pain alter the development of endogenous gating systems?

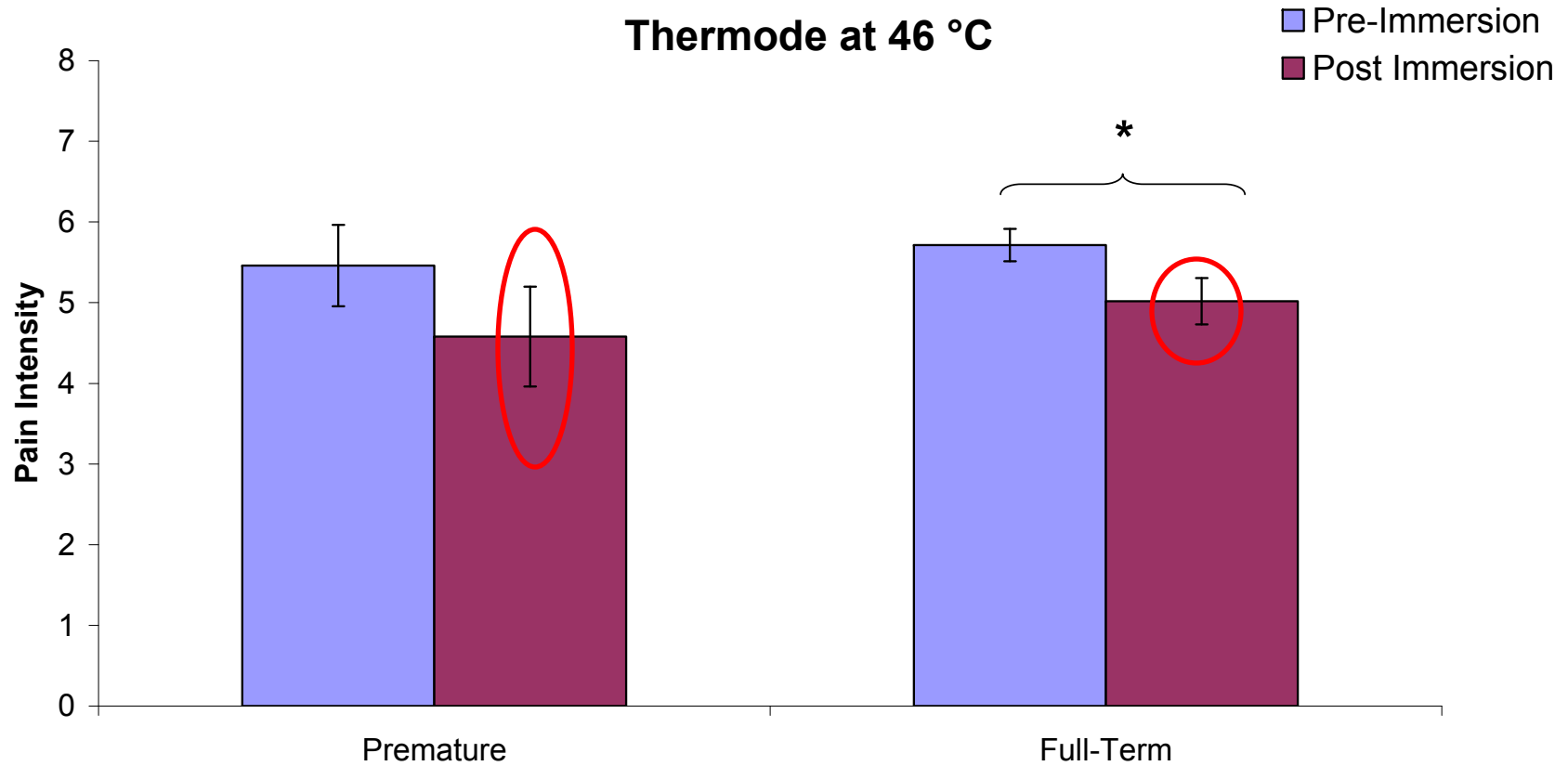
Philippe Goffaux, Sylvie Lafrenaye, Mélanie Morin, Hugues Patural, Geneviève Demers, Serge Marchand *

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- **Evaluation of the sensitivity to pain and the functional integrity of DNIC in pre-puberty children (7-10 yo) born prematurely vs. full term**

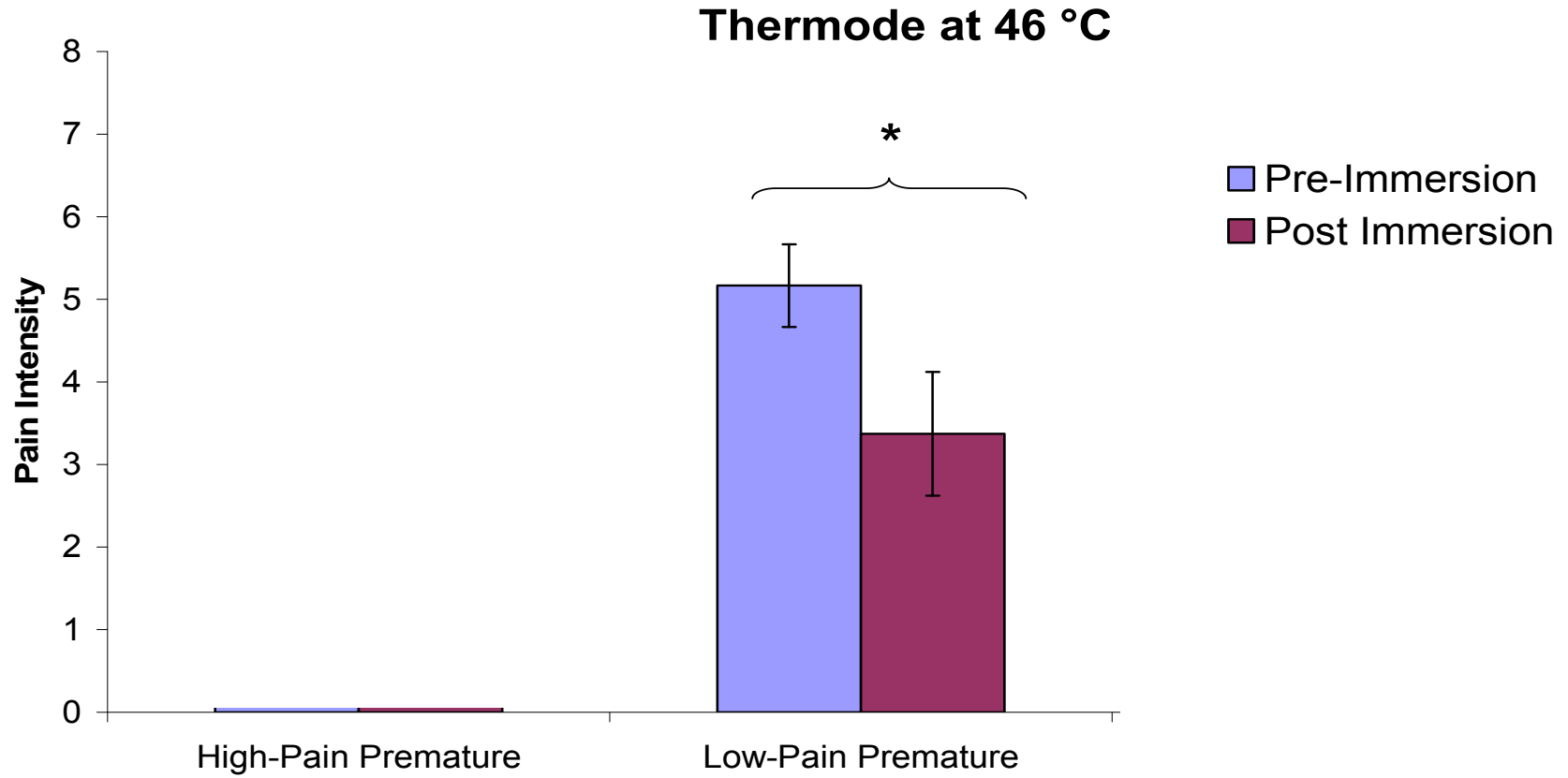
Being born prematurely versus full-term on DNIC



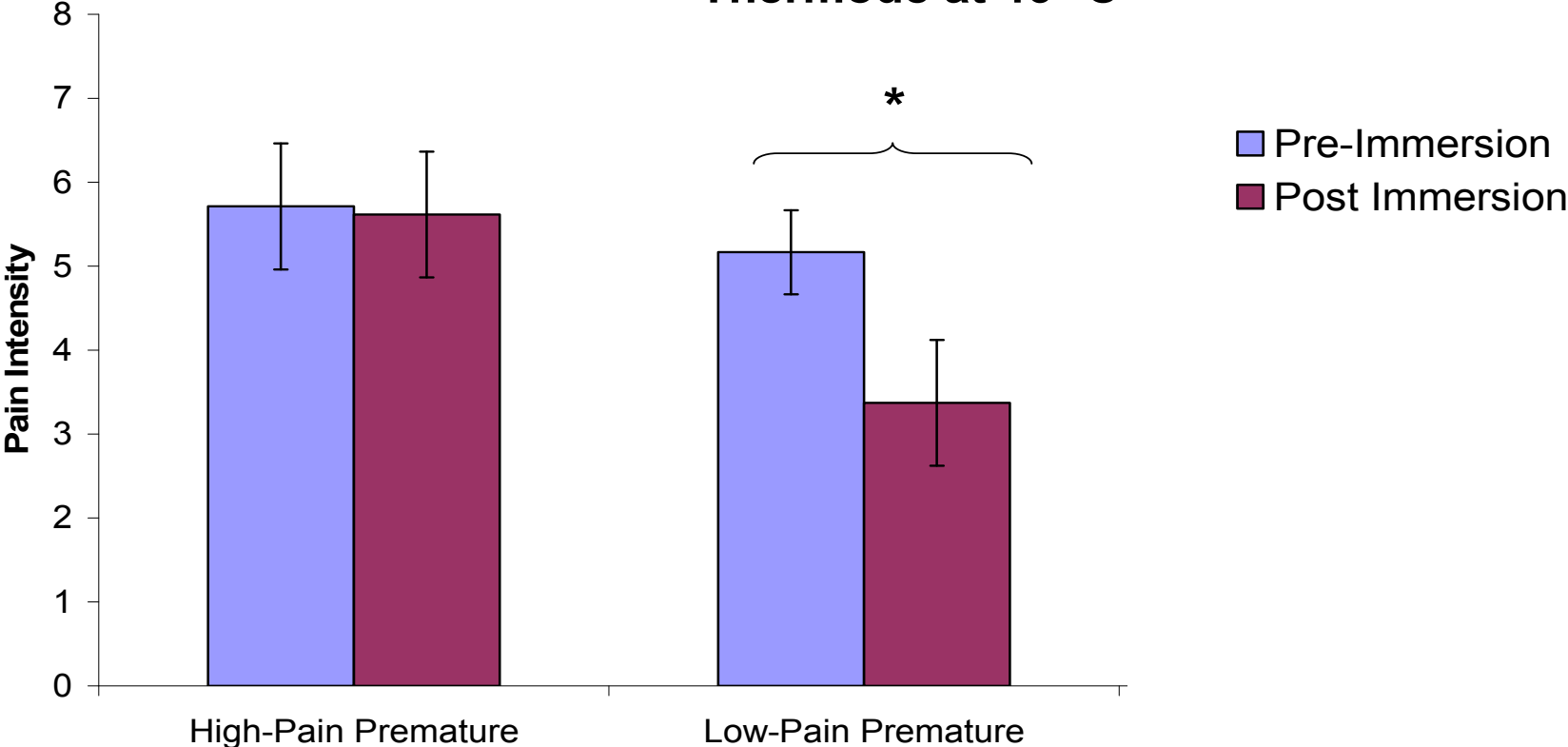
Many painful procedures

Few painful procedures

Childrens born prematurely



Thermode at 46 °C



Conclusion

DNIC appears ineffective, but only in children born prematurely **with a large number of painful interventions in the first month after birth.**

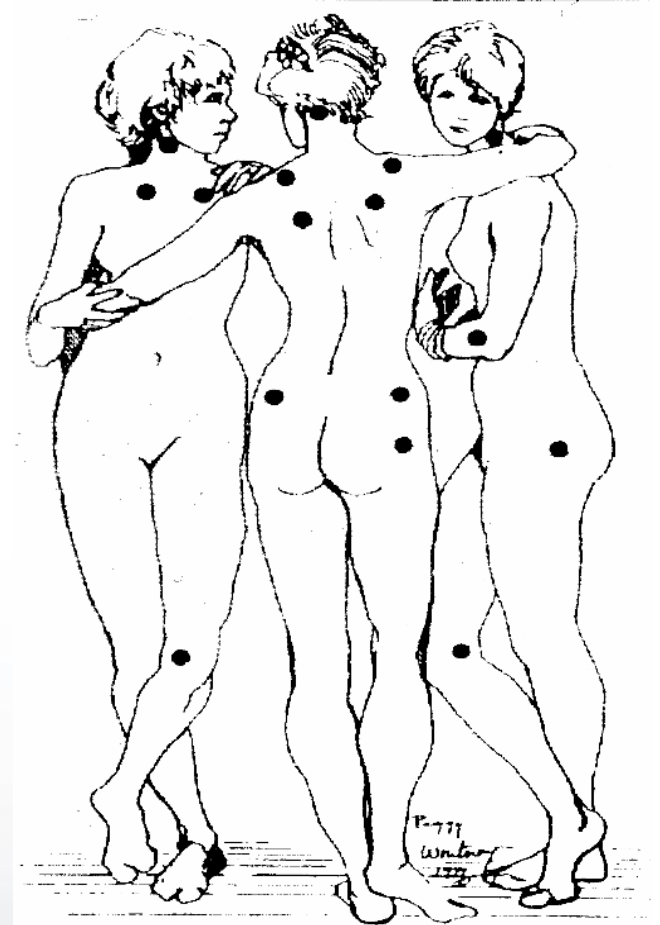
Preliminary results in adolescent (post-puberty: 12-17) are showing the same trends.

Adolescents born at-term, that had a cardiac surgery in the first months after birth also presented a reduced DNIC !



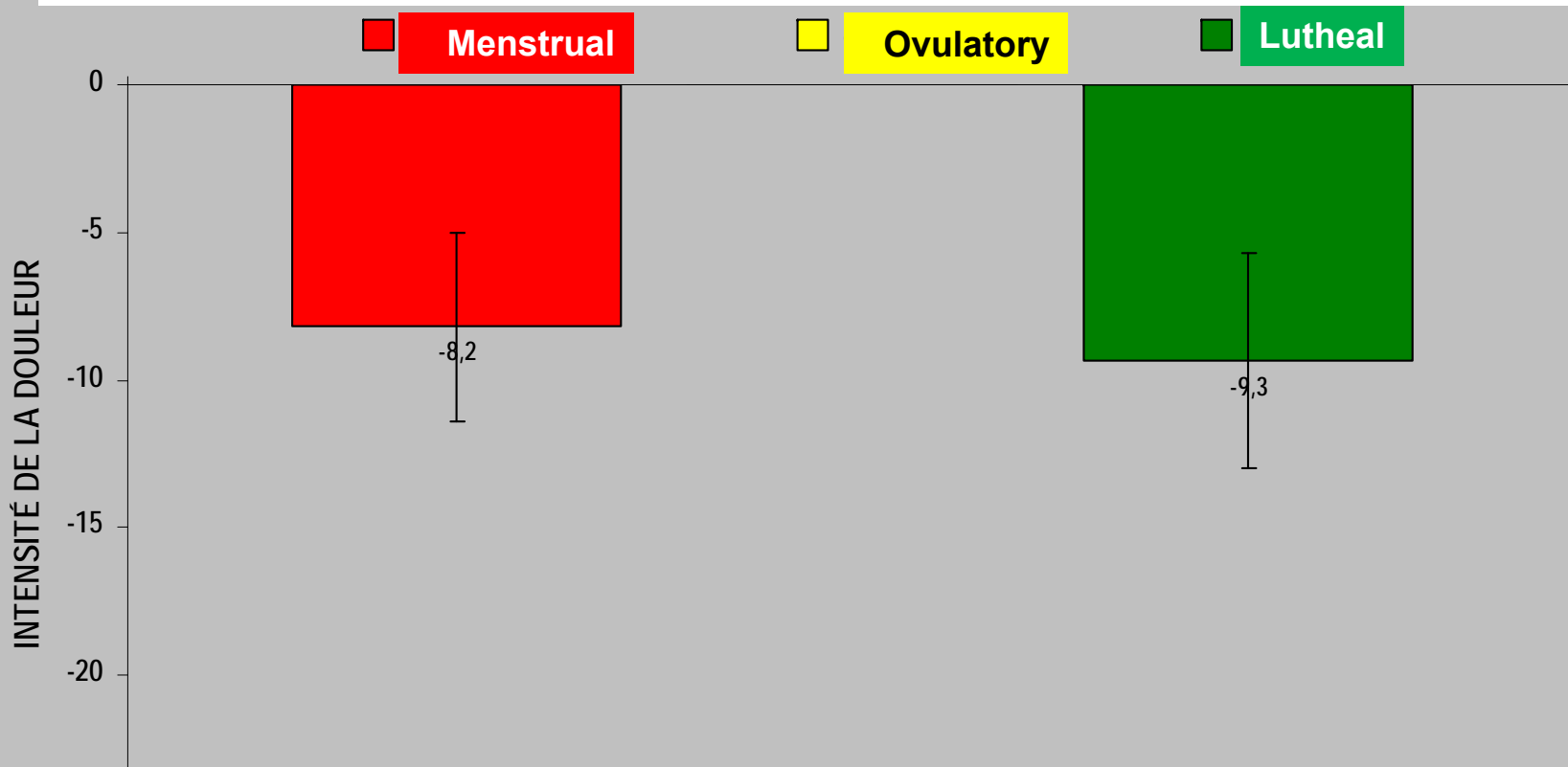
DNIC deficit in Fibromyalgia

Why is it dominant in women ?



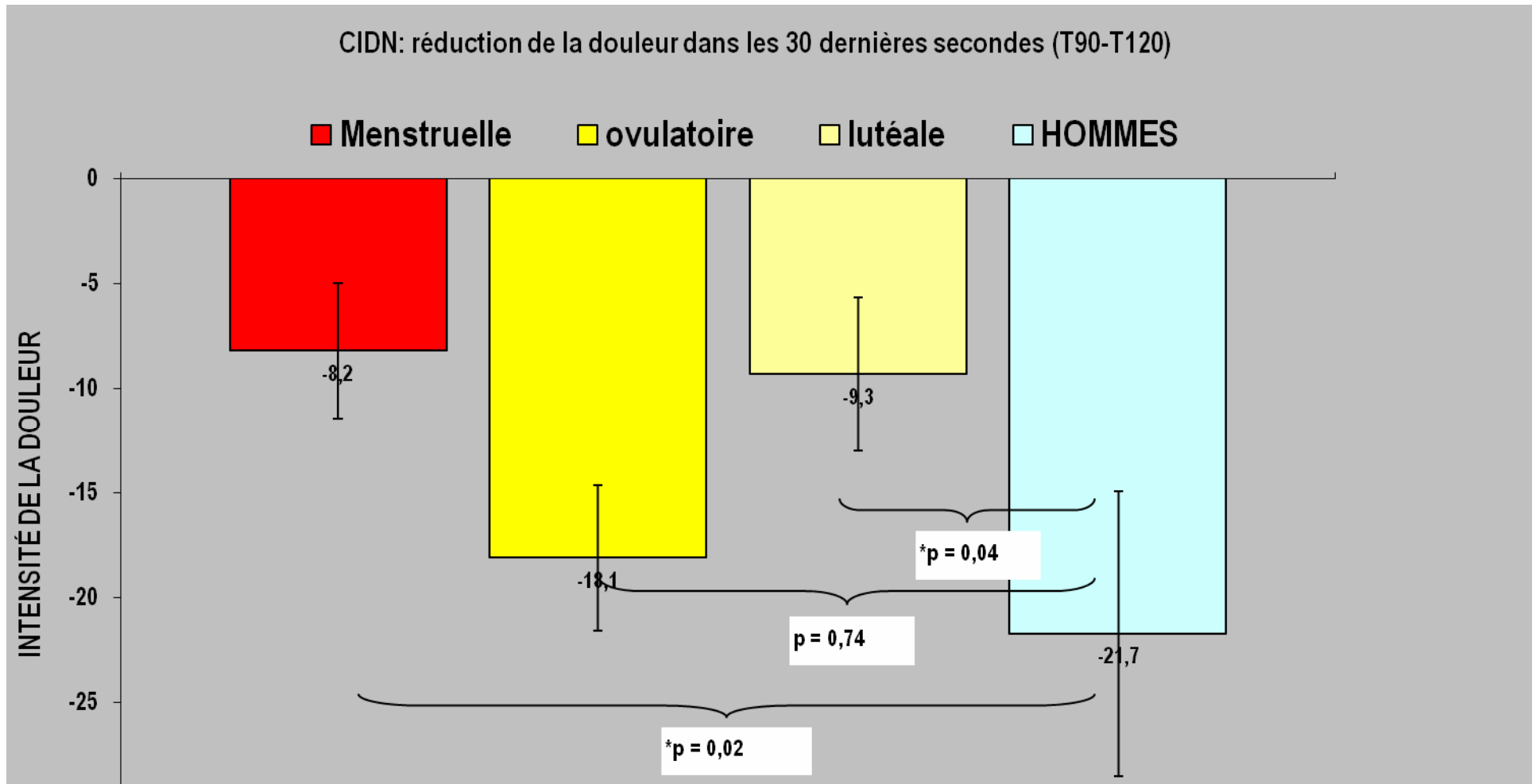
The role of sex hormones !

DNIC % Pain Reduction over the menstrual cycle



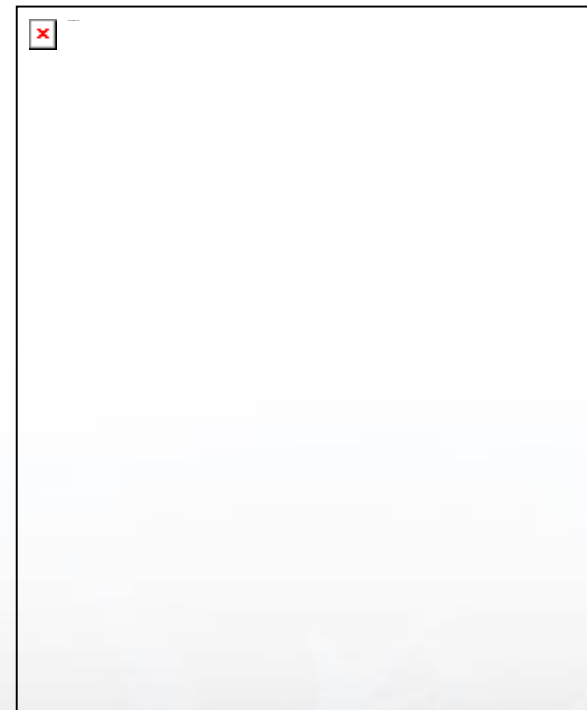
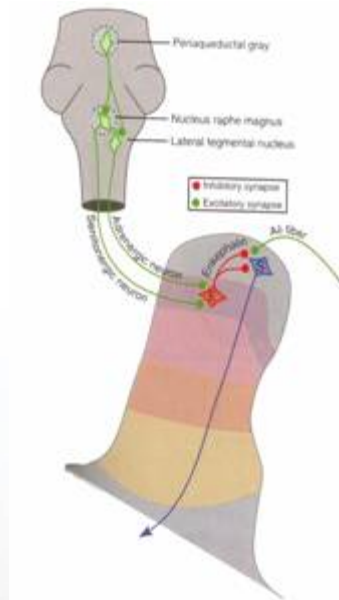
**Significantly more DNIC during the ovulatory period !
Sex hormone have a significant influence on DNIC !**

Women and Men DNIC



during the ovulatory period, women have comparable DNIC with men. The rest of the time it significantly lower !

Early pain affect the development of DNIC, what about aging ?



Changes in Pain Perception and Descending Inhibitory Controls Start at Middle Age in Healthy Adults

Marianne Larivière, MSc, Philippe Goffaux, PhD,† Serge Marchand, PhD,*† and Nancy Julien, MSc**

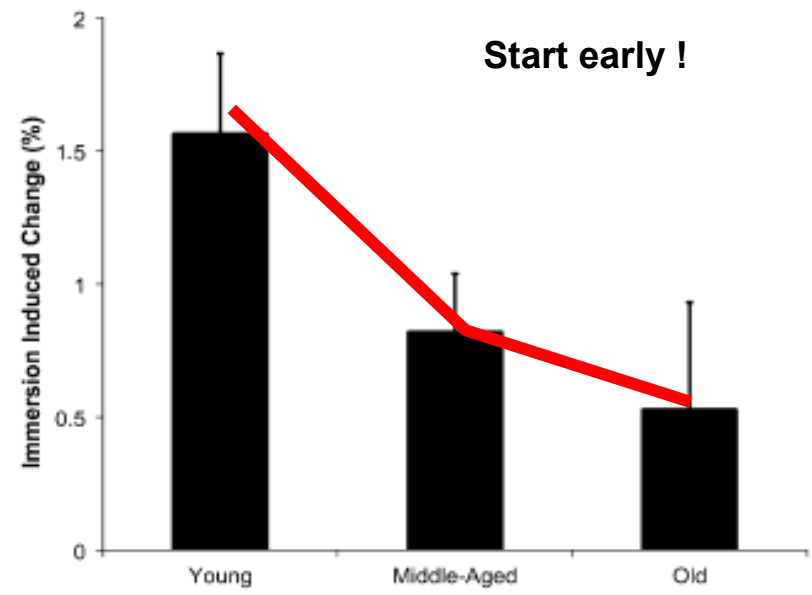
Clin J Pain • Volume 00, Number 00, ■■ 2007 (Sous Presse)

May help understand :

↓ Pain threshold (↓ receptors)

↑ Pain tolerance (↓ DNIC)

Significant reduction of DNIC while aging !



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Genetics of chronic pain states

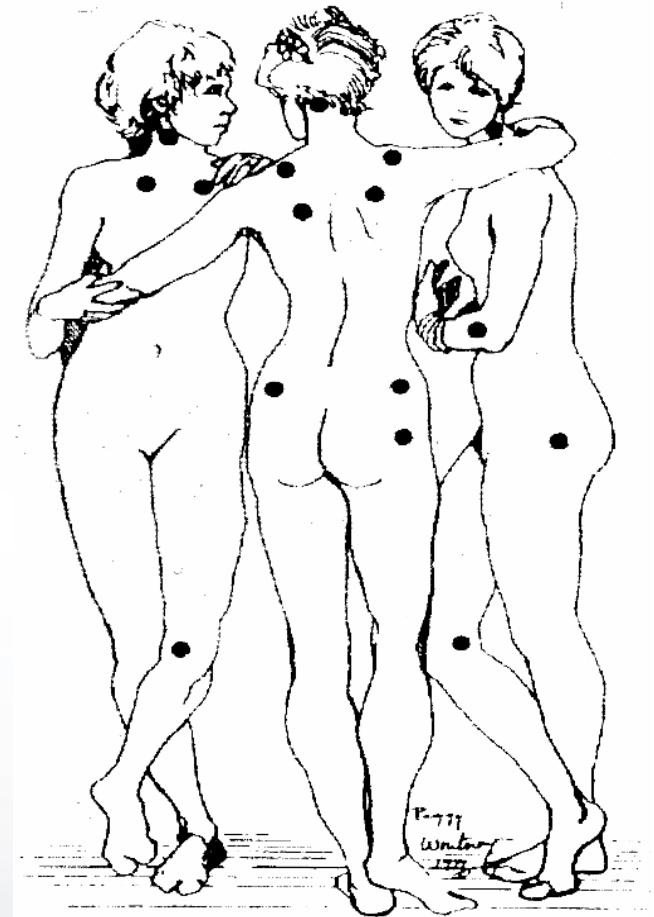
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Ben Gurion University, Beer Sheva, P.O.B 151, Israel 84101*

. . . polymorphisms of genes in the serotonergic, dopaminergic and catecholaminergic systems in the pathogenesis of FMS and related conditions.

Predispositions to Chronic Widespread Pain ?



Fibromyalgia patients show an abnormal dopamine response to pain

Patrick B. Wood,^{1†} Petra Schweinhardt,^{1†} Erik Jaeger,¹ Alain Dagher,² Helene Hakyemez,² Eugenii A. Rabiner,³ M. Catherine Bushnell¹ and Boris A. Chizh³

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³GlaxoSmithKline Addenbrooke's Centre for Clinical Investigation, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2GG, UK

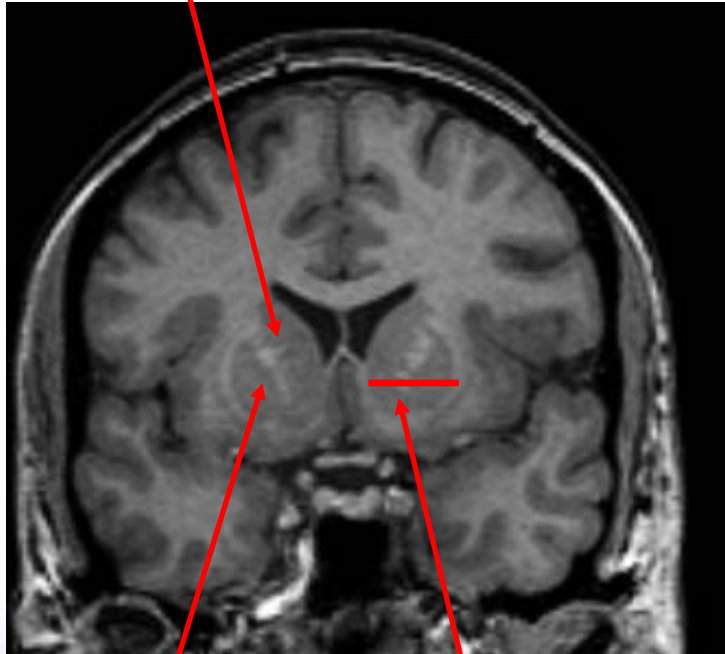
Pain = ↑ DA in basal ganglia in HS not FM

↑ DA in basal ganglia = relation to pain perception in HS, not FM



Dopaminergic Phenotype

Caudate Nuclei



Putamen

Ventral Striatum

- **Prefrontal Cortex**
 - $D_1 > D_2$
 - Catéchol-O-méthyltransférase (**COMT**)
- **Ventral Striatum**
 - D_1, D_2 & **D₃**
 - MAO-A/B
- **Dorsolateral Striatum**
 - D_1 & D_2
 - MAO-A/B

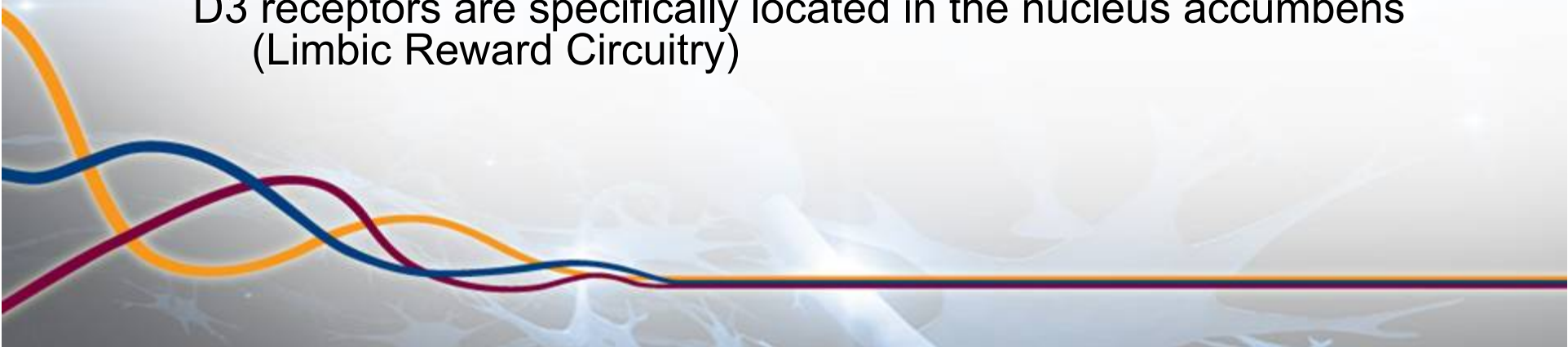
Genotyping DRD3 Polymorphisms

Participants: 23 HS & 23 FM

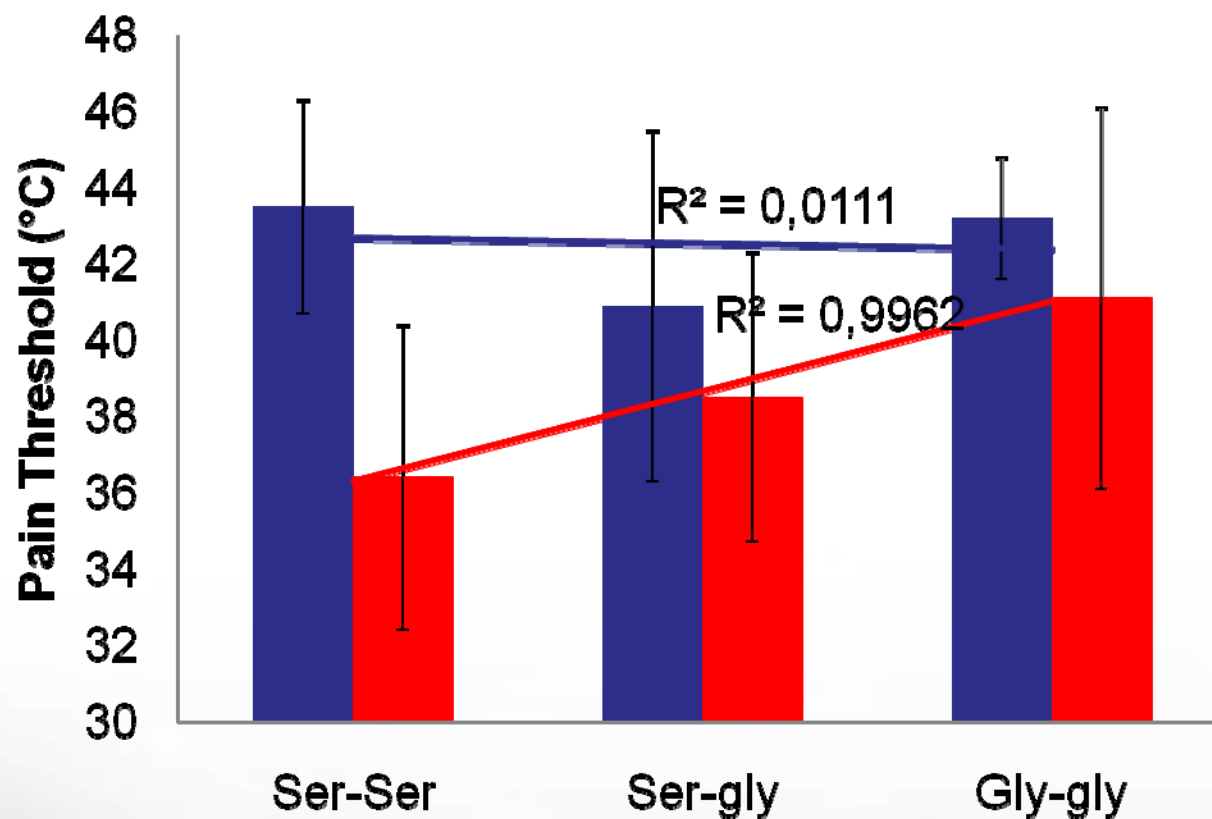
- Preliminary results
 - DRD3 \leftrightarrow Pain Threshold
 - Group ($p=0.0001$)
 - DRD3 ($p=0.050$)
 - Interaction ($p=0.013$)

		T° threshold
FM	Ser/ser	34.4 (2.2)
	Ser/gly	38.2 (3.3)
	Gly/gly	41.4 (5.0)
HS	Ser/ser	43.1 (1.8)
	Ser/Gly	41.8 (3.9)
	Gly/gly	43.0 (1.8)

D3 receptors are specifically located in the nucleus accumbens
(Limbic Reward Circuitry)



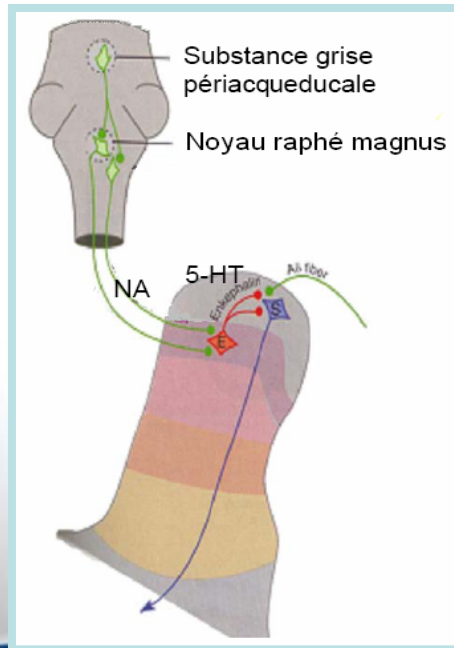
DRD3 phenotype is positively correlated to Pain threshold in FM but not controls



Potvin, Larouche, Normand, de Souza, Grignon, Marchand, 2008

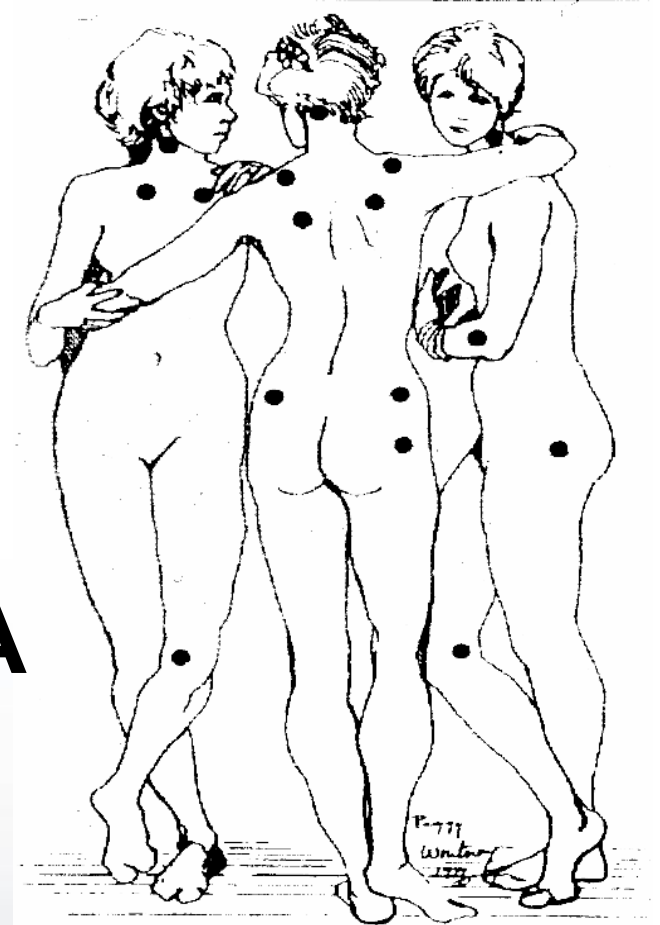
DNIC deficit in Fibromyalgia

Depression and Chronic Widespread Pain?

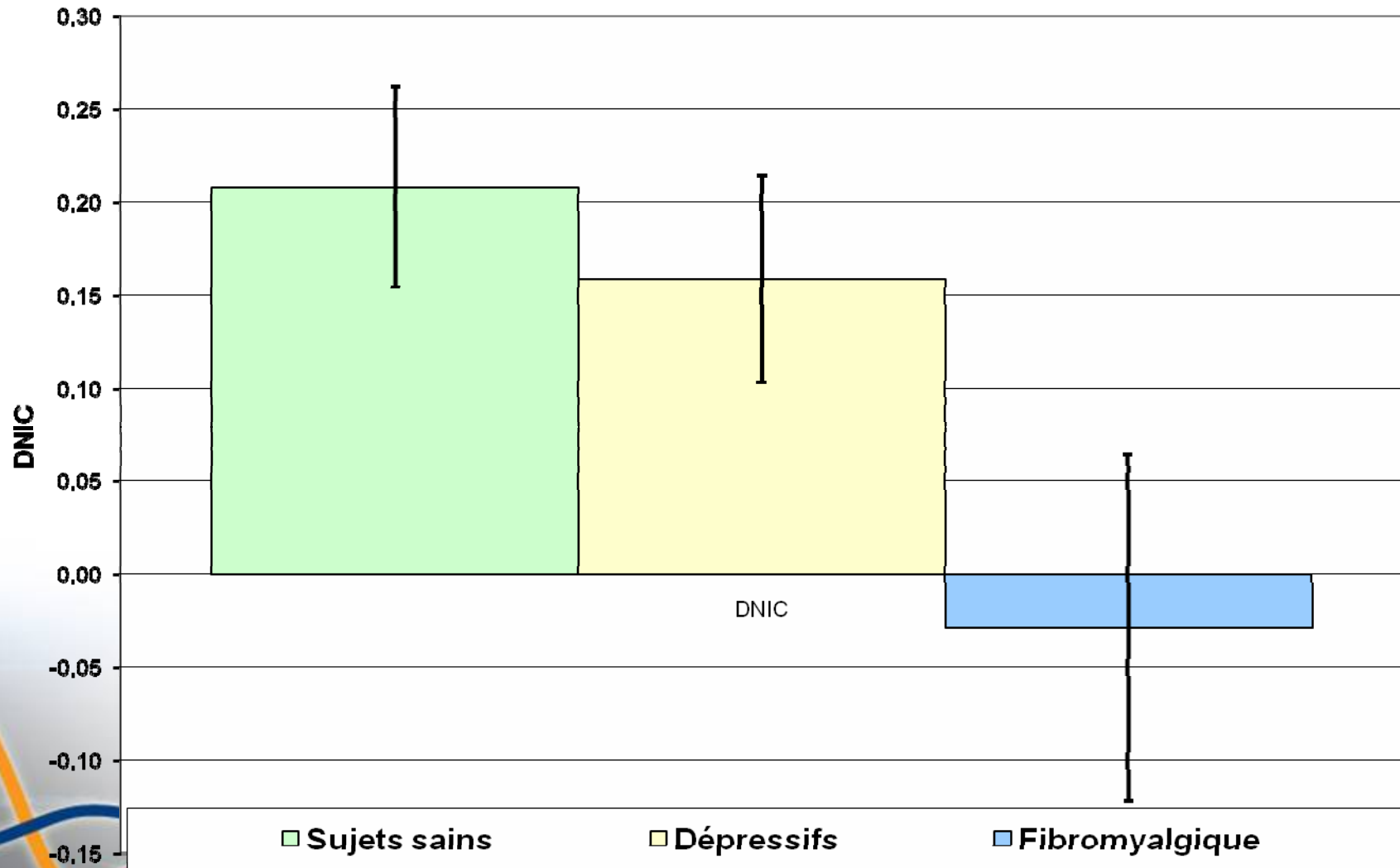


↓ **5-HT and NA**

DNIC deficits?



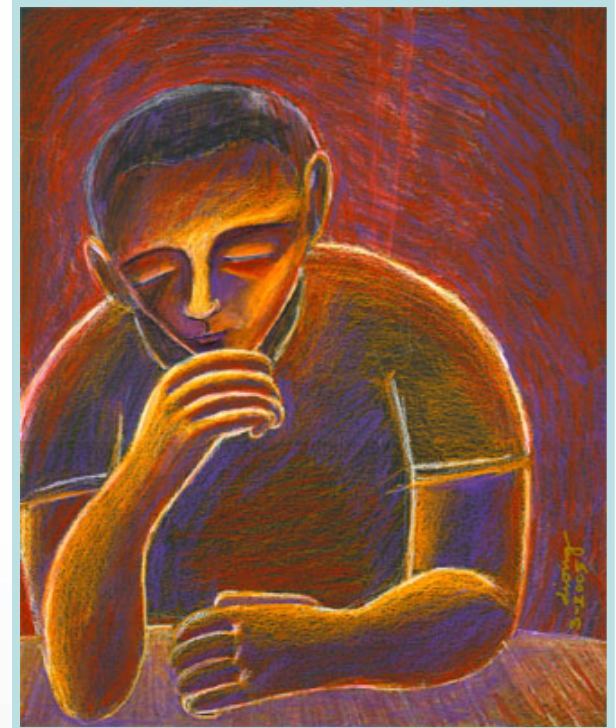
No Significant Deficit of DNIC in Major Depression !



Major depression vs fibromyalgia !

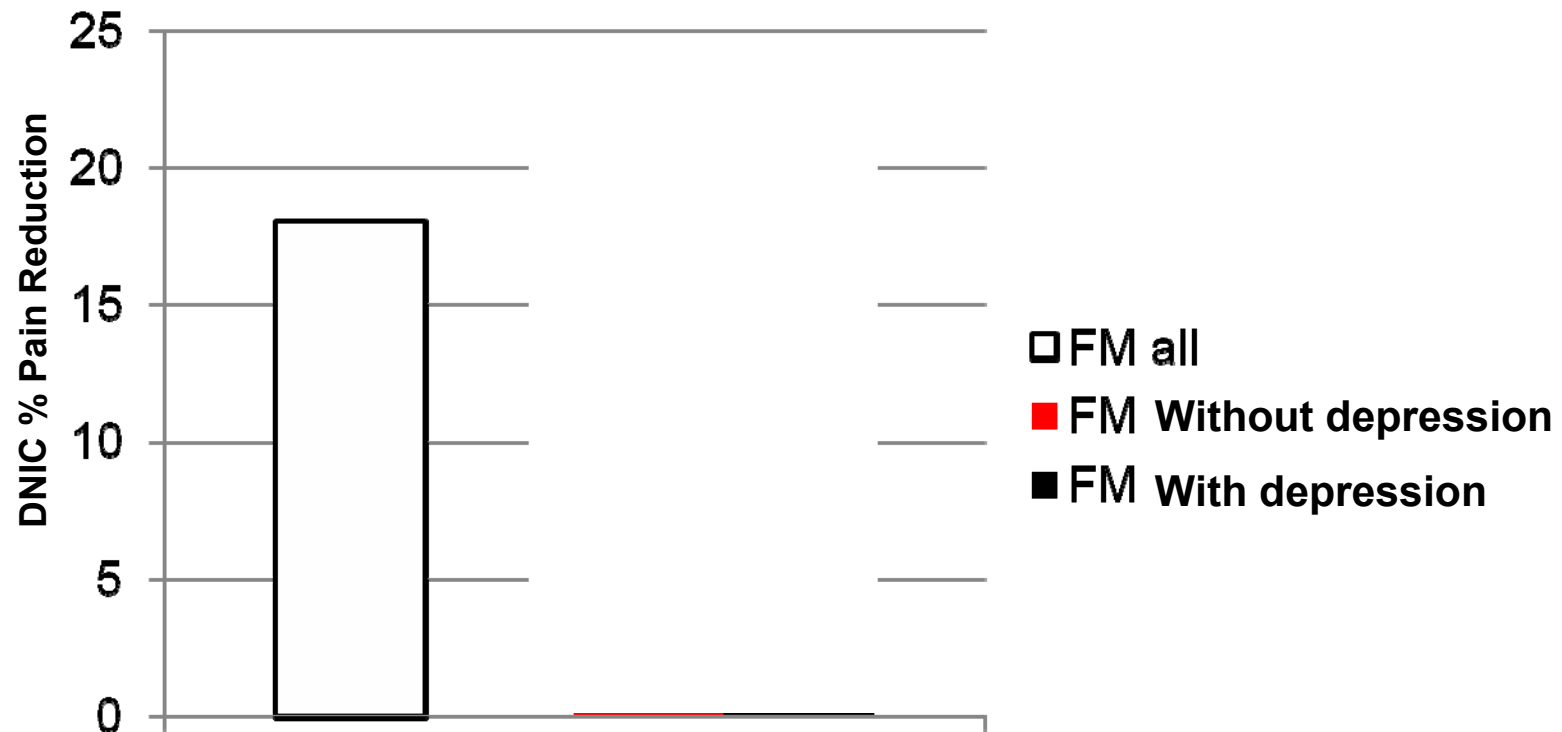
- A reduction, but no clear deficit of DNIC in MD

**Fibromyalgia is not a
masked depression!**



What about DNIC in FM with and without depression?

De Souza, J.B., Potvin, S., Marchand, S.



FM + depression have a significantly larger deficit of DNIC compared to FM - depression !
– Effect of 5HT, NA ?

Individual differences

Environmental
and
Genetic factors



Factors implicated in the development and persistency of Chronic Pain

- Predisposition (Phenotypes)
- Early Stress (psychological or physical)
- Sex hormones
- Cognitive factors (expectations)
- Depression
- Aging
- DNIC affected by: all of the above !





Étudiants

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Réseau de recherche en douleur (FRSQ)
Réseau de recherche sur le placebo (IRSC)
American Fibromyalgia Syndrome Association (AFSA)
Investigator Initiated Projects:
Pfizer, Astra-Zeneca, Valeant**