Traitements pour l'Addiction

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L'addiction

- **Le Comportement de**
  - **recherche de la drogue**
  - **une pulsion**
  - **presque irrésistible**
- **La Tolérance +/-**
- **La Dépendance +/-**
  - **sevrage, pharmacologique**

Risque de l'addiction

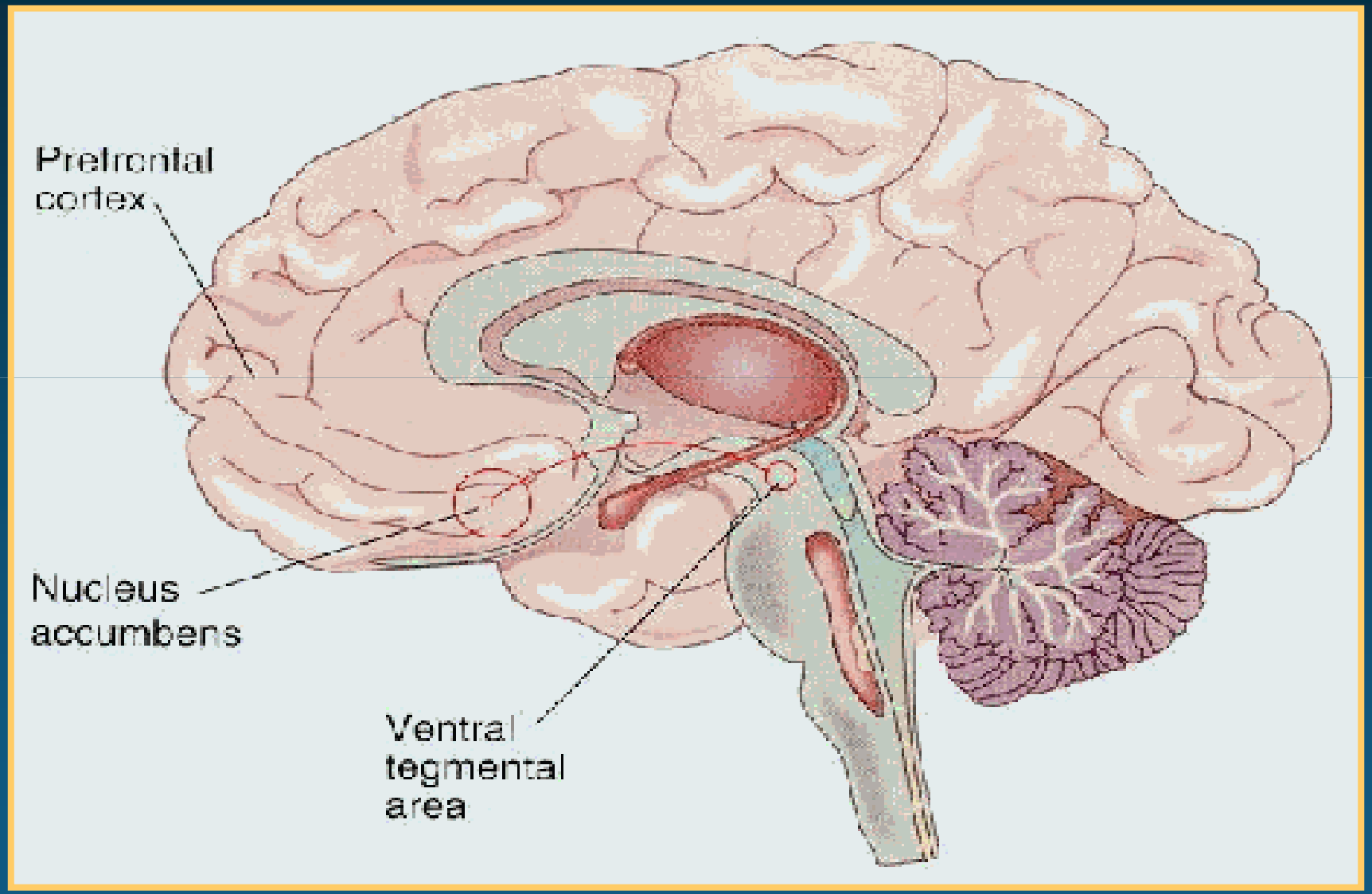
	Utilisé	Dépendance	Risque
Tabac	75.6%	24.1%	31.9%
Cocaïne	16.2	2.7	16.7
Héroïne	1.5	0.4	23.1
Alcool	91.5	14.1	15.4
Cannabis	46.3	4.2	9.1

Anthony et al, 1994

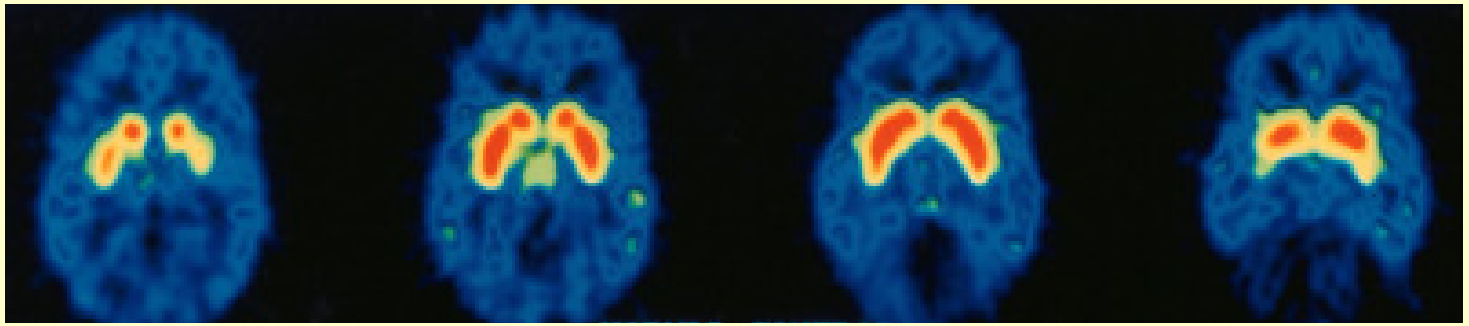
Hypothèse

- **Les stimuli environnementaux provoquent : une libération de la dopamine, une activation du système limbique**

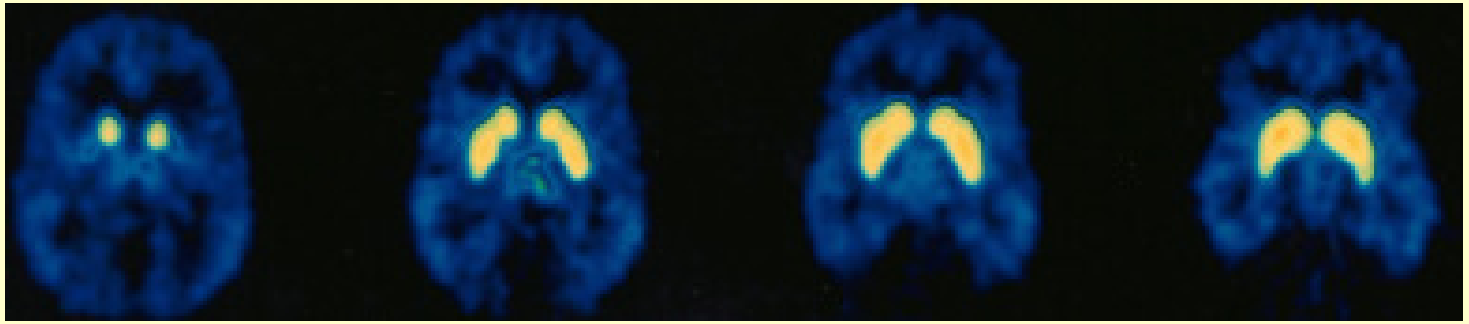
Système de récompense



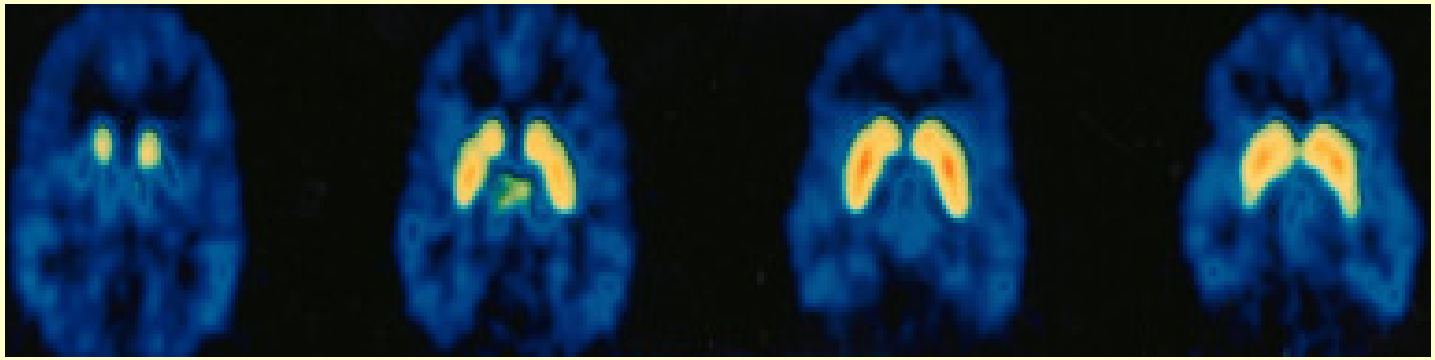
Les effets de la Cocaïne sur les récepteurs Dopamine D2



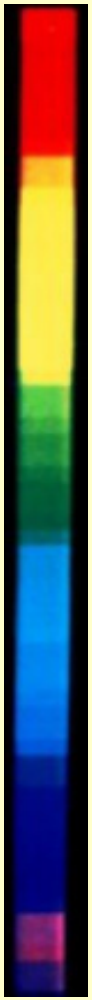
Normal (C11 raclopride- PET)



cocaïnomane (1 moi post dernière dose)

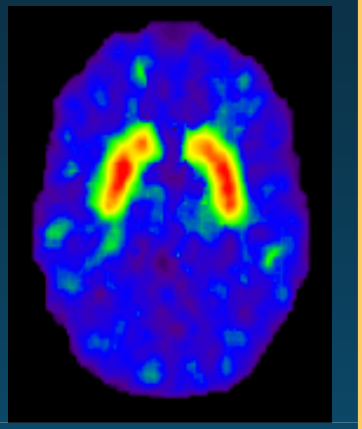


Cocaïnomane (4 mois post dernière dose)

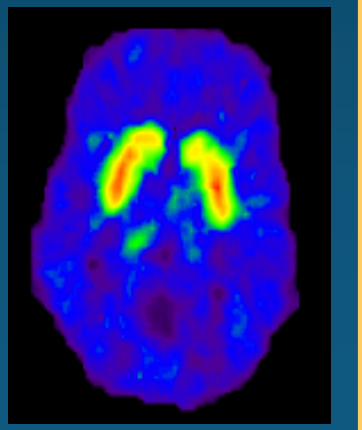


Normal volontaires
IV Methylphenidate

DA D2 récepteur disponibilité



déplaisante



euphorie

Haut niveau D2 récepteurs = déplaisante réponse à MP

Bas niveau D2 = Euphorie

Dopamine D2 Receptors in Addiction

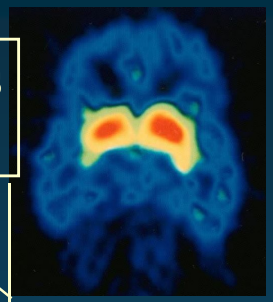
Cocaïne

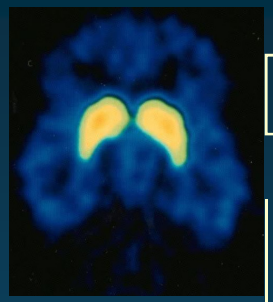
Methamphetamine

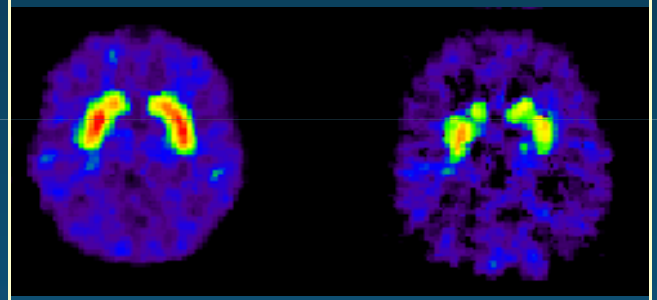
Alcool

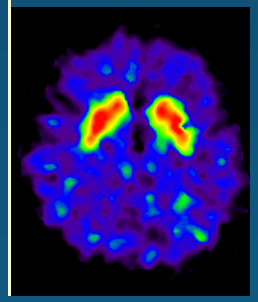
Témoins

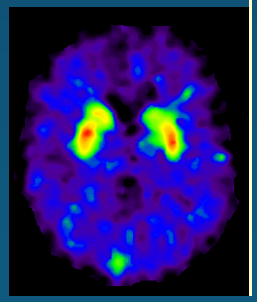
Patients



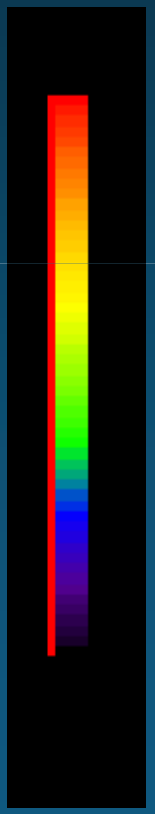






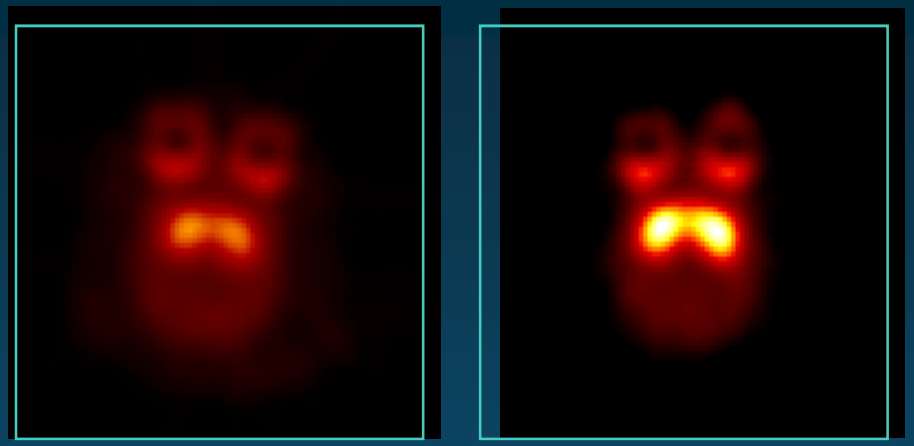


DA D2 Receptor Availability

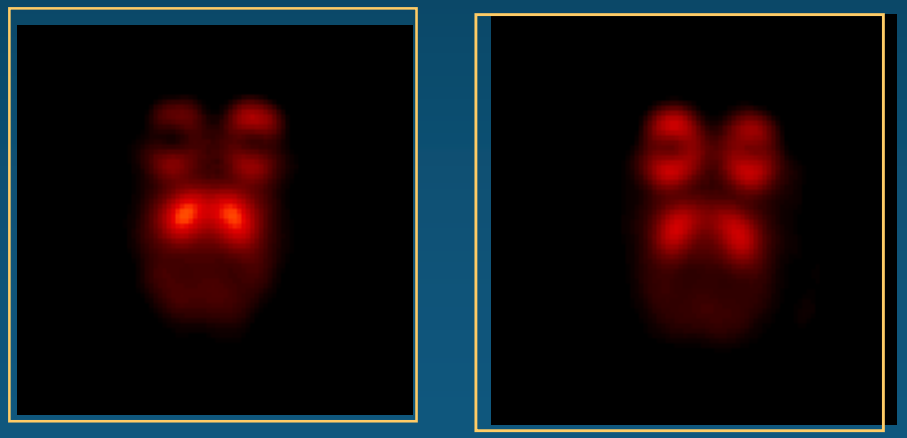


Logé seule

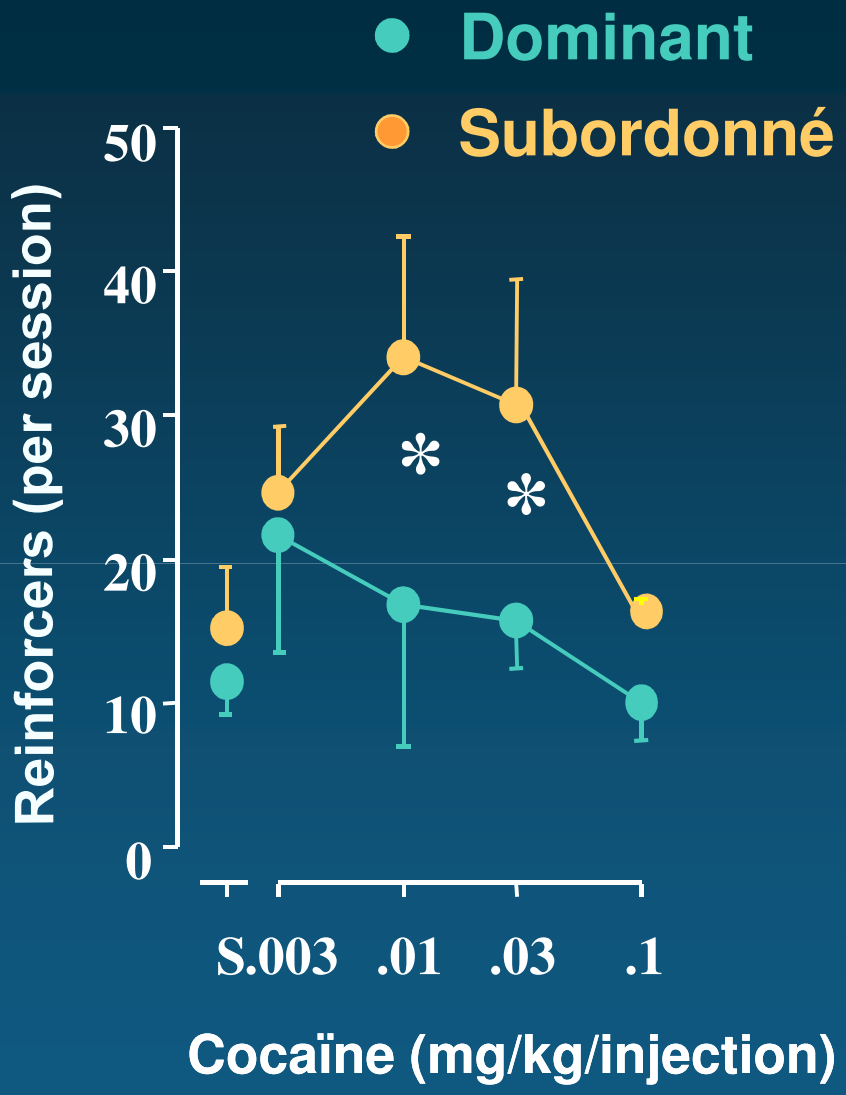
Logé en groupe



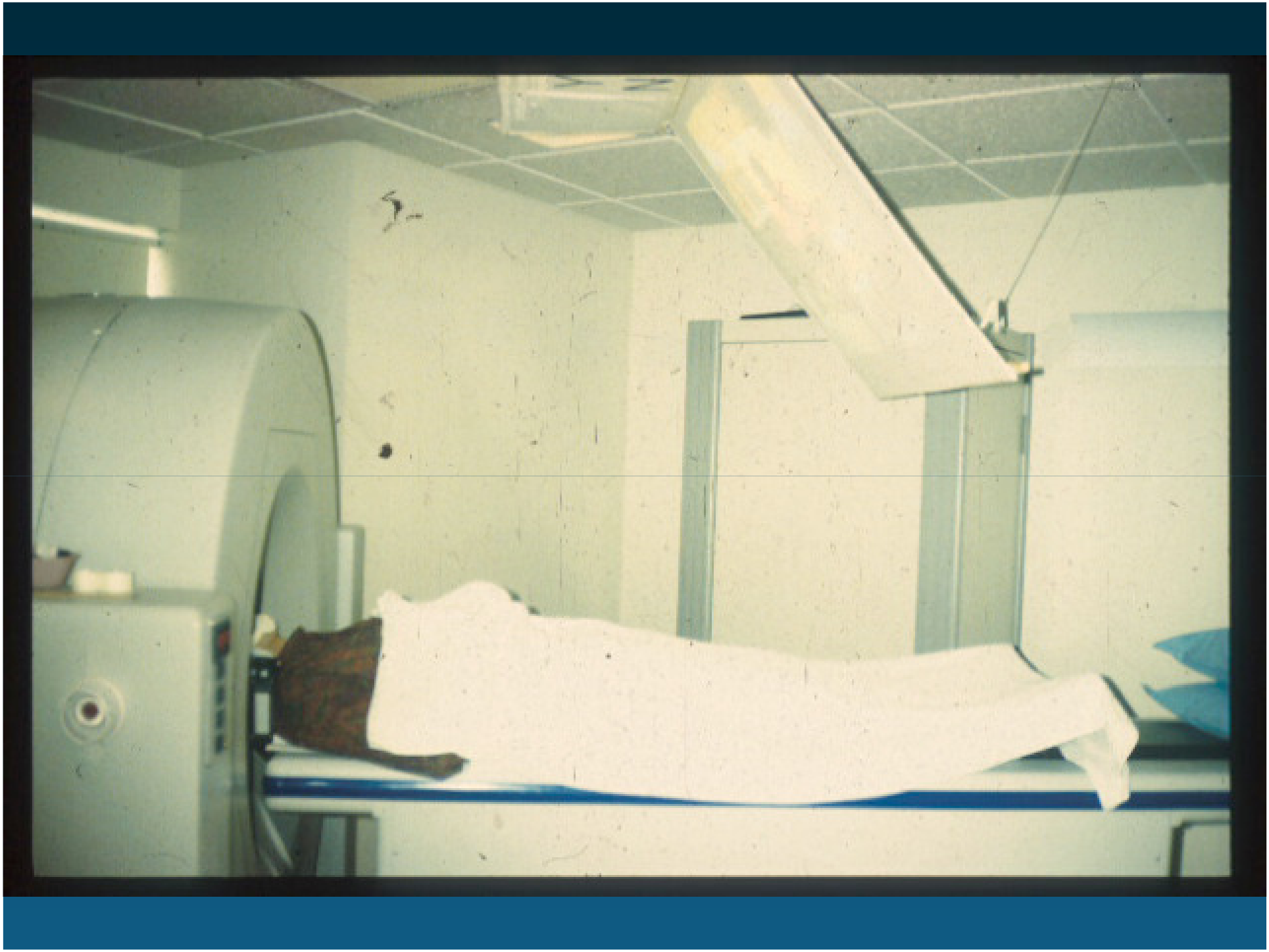
Dominant



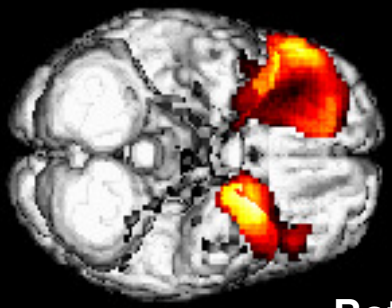
Subordonné



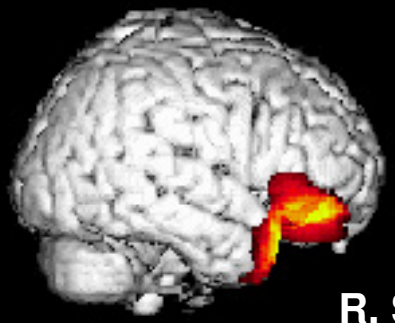
Morgan, D. et al. Nature Neuroscience, 5: 169-174, 2002.



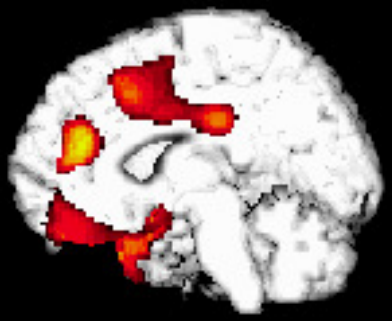
Brain Activation During Craving Triggered By Cocaine Cues



Bottom



R. Side



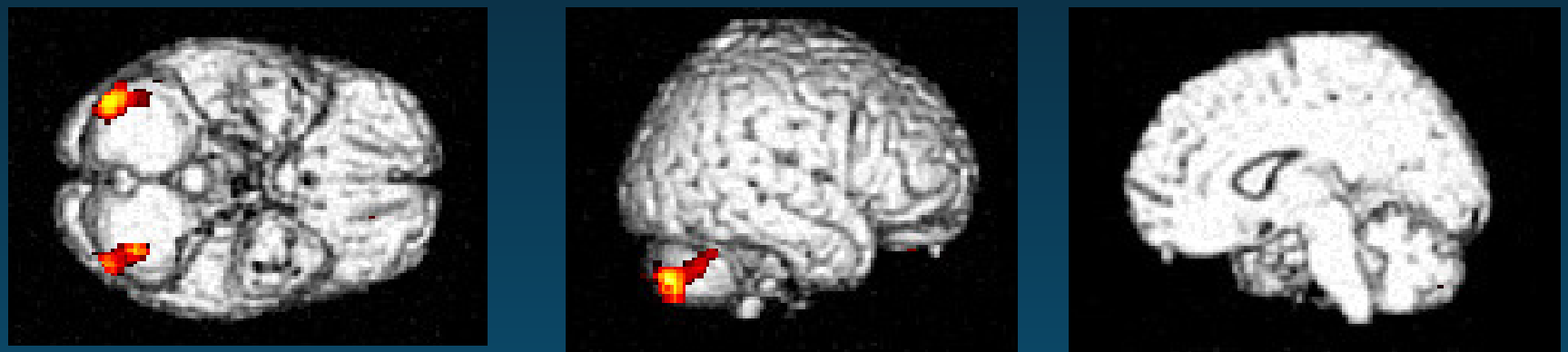
Middle

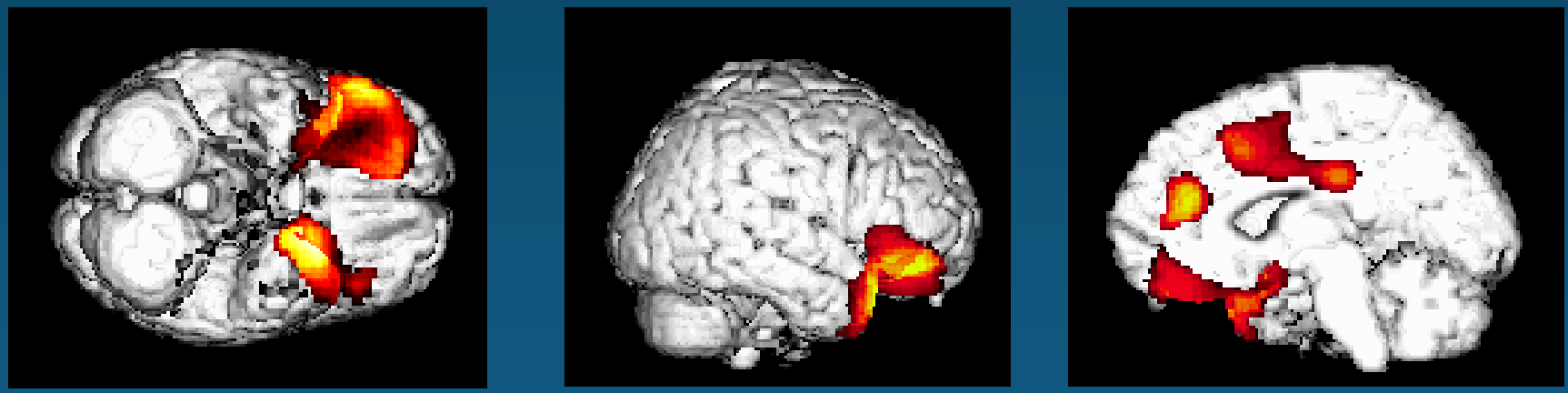
Three views of the brain's activity* in cocaine patients viewing a cocaine video which triggered desire for cocaine.

**Statistical parametric map showing brain regions differentially activated by a cocaine video as compared to a non-drug (nature) video.*

Childress, et al. 1999

Absence of Limbic Activation During Cocaine Cue Exposure in a Cocaine Patient (BAC_07) Taking the GABA B Agonist Baclofen Chronically





Limbic Activation During Cue-Induced Cocaine Craving in Unmedicated Cocaine Patients (n=14)

Le Traitement pour les addictions

1. **Psychothérapie**
   de tout genre: familial, groupe, comportamentale, etc
2. **Médicaments**

Médicaments pour dépendance à la Cocaïne

Augmente le système GABA

Baclofen, Topiramate, Vigabatrine

Disulfiram: Bloquer alcool, produire effets négatives avec la cocaïne

Modafinil: augmenter la glutamate prévenir sevrage, réduire euphorie

Propranolol: réduire cue réactivité et rechute

Actuellemnt en Amérique

Il n'y a pas de médicament registré par le FDA pour traitement de la dépendance sur la cocaïne.

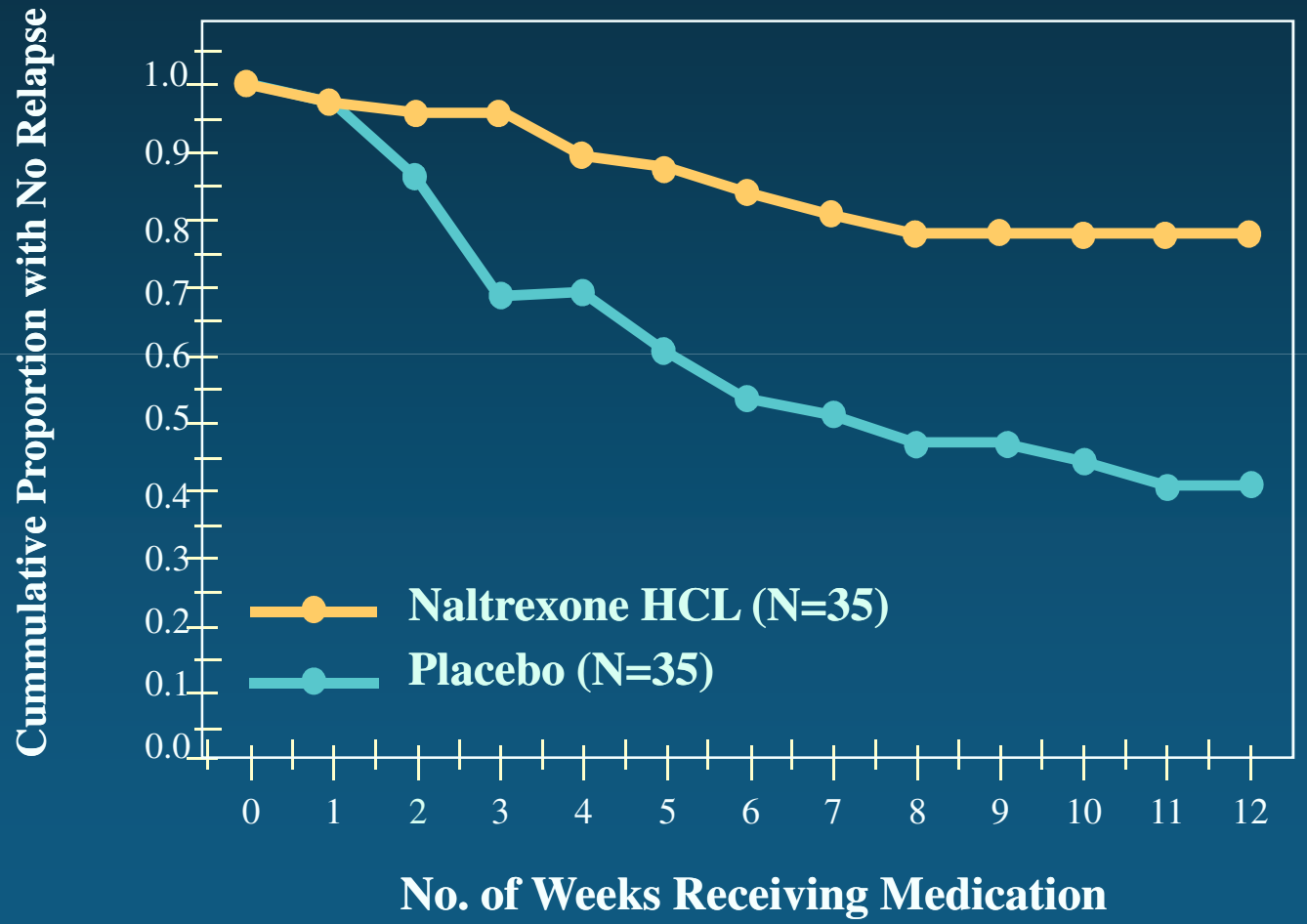
Médicaments registrés pour l'alcoolisme

- **La disulfiram**
- **La naltrexone (orale et dépôt)**
- **L'acamprosate**
- **La topiramate (pas encore)**

Hypothèse : l'alcool active le système opioïde endogène

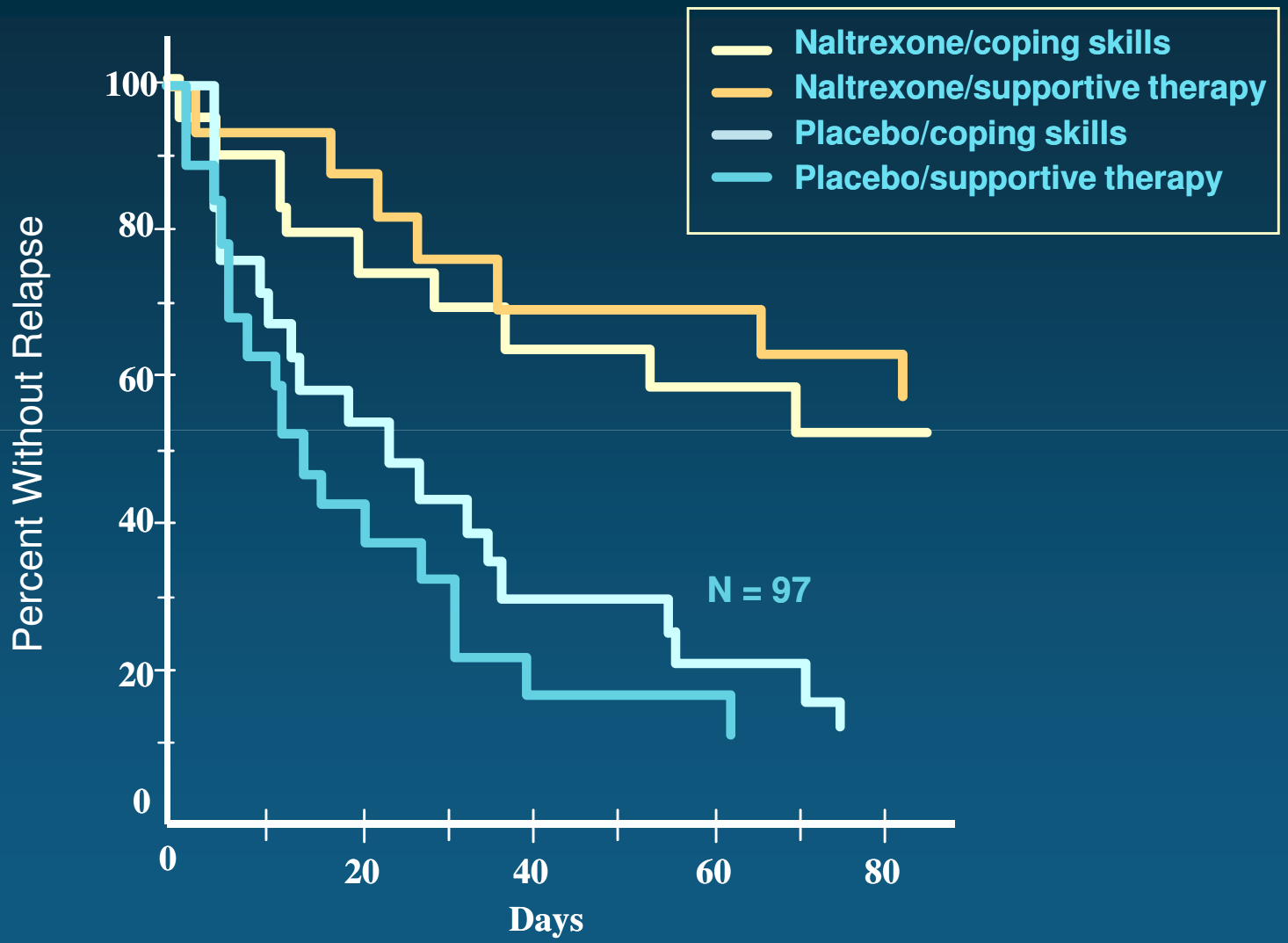
- **Bloquer récepteurs opiacés chez les alcooliques -IND (permit FDA, 1983)**
- **Les essais cliniques, (double insu) 1983 à la présente :**
  - **diminution de récompense alcoolique**
  - **réduction de "craving" pour l'alcool**
  - **meilleur effet parmi des alcooliques avec histoire familiale d'alcoolisme**

Non-rechute "Survival"



Volpicelli et al, Arch Gen Psychiatry, 1992; 49: 876-880

Non rechute selon group de traitement (n=97)



O'Malley et al, *Arch of Gen Psychiatry*, Vol 49, Nov 1992

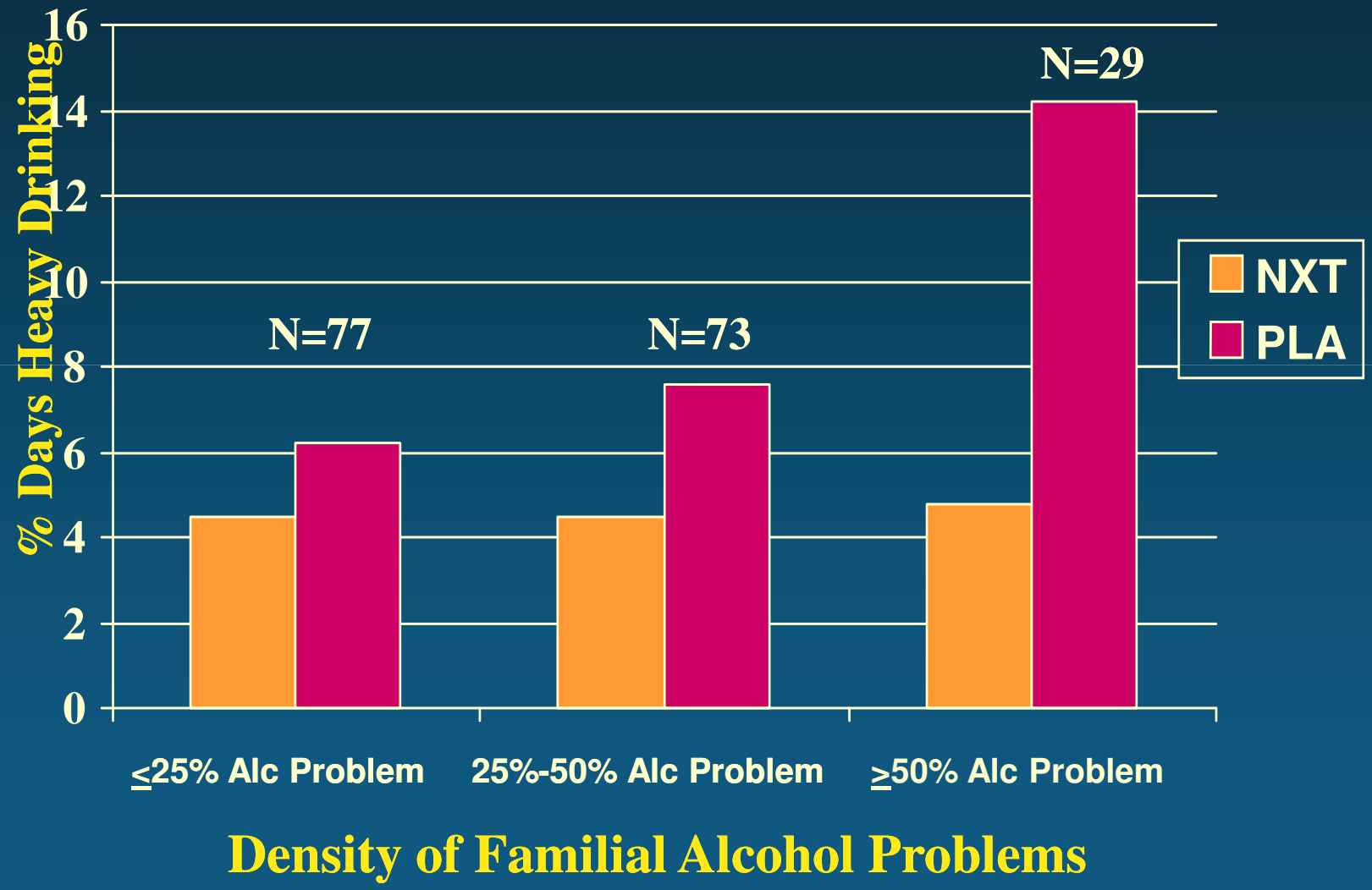
29 Essais cliniques contre placebo

Une grande majorité montre l'efficacité de la naltrexone (score meilleur que celui des antidepresseurs, SSRI)

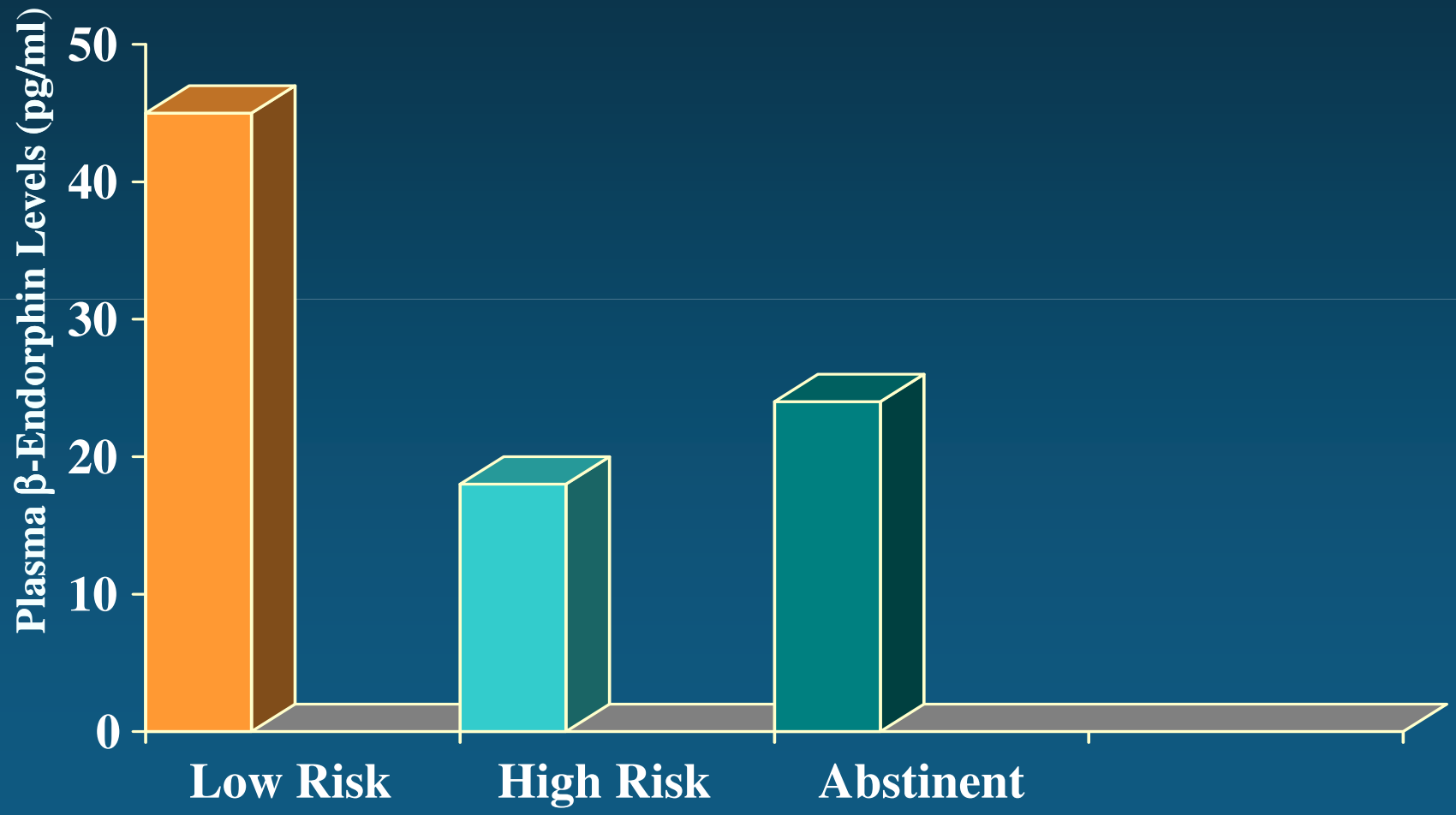
MAIS, quelques alcooliques ne répondent pas à la naltrexone.

Une question génétique ??

Efficacité Naltrexone selon Hérédité

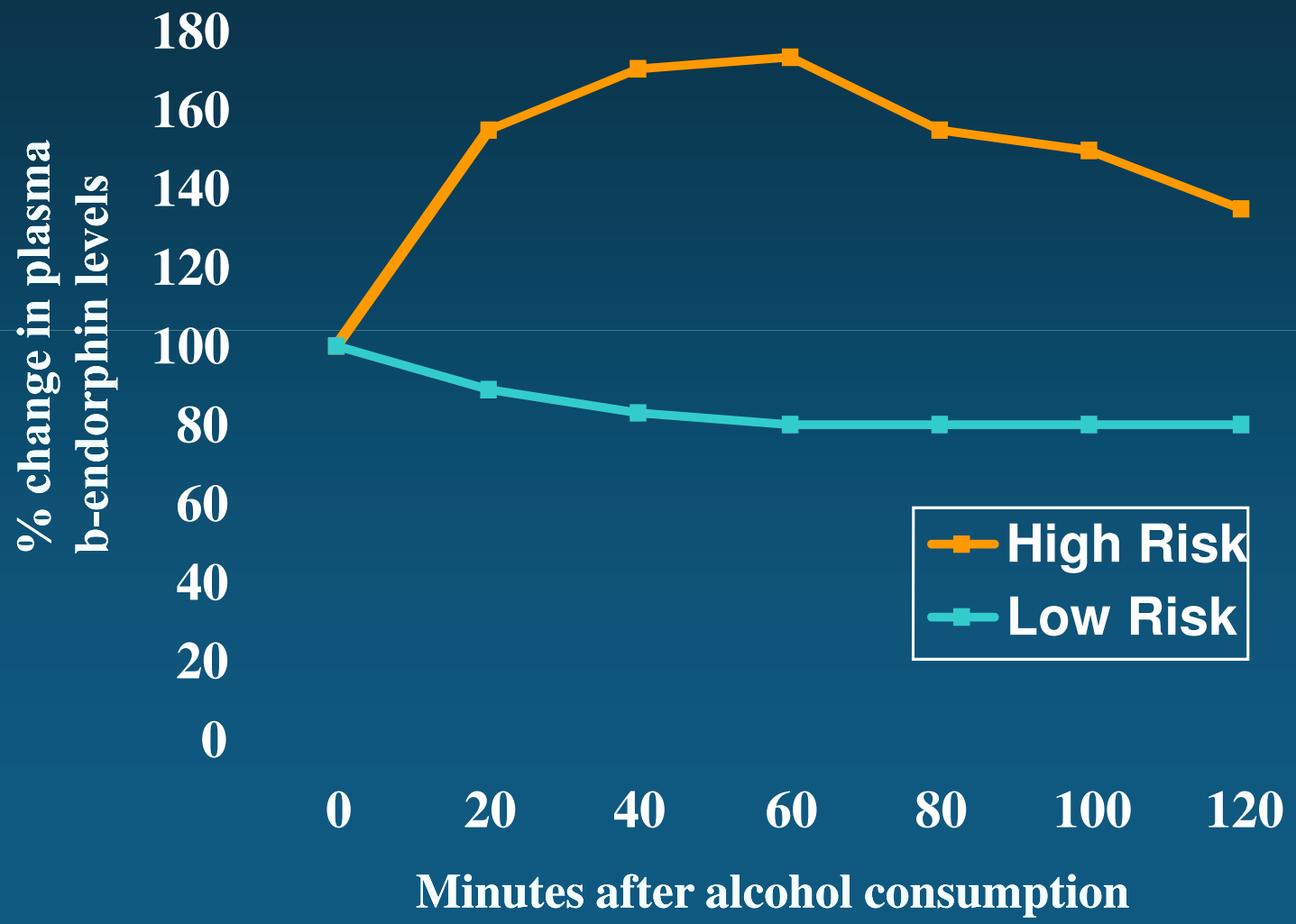


Nivueau sanguin B -Endorphine Selon histoire familiale d'aloolisme

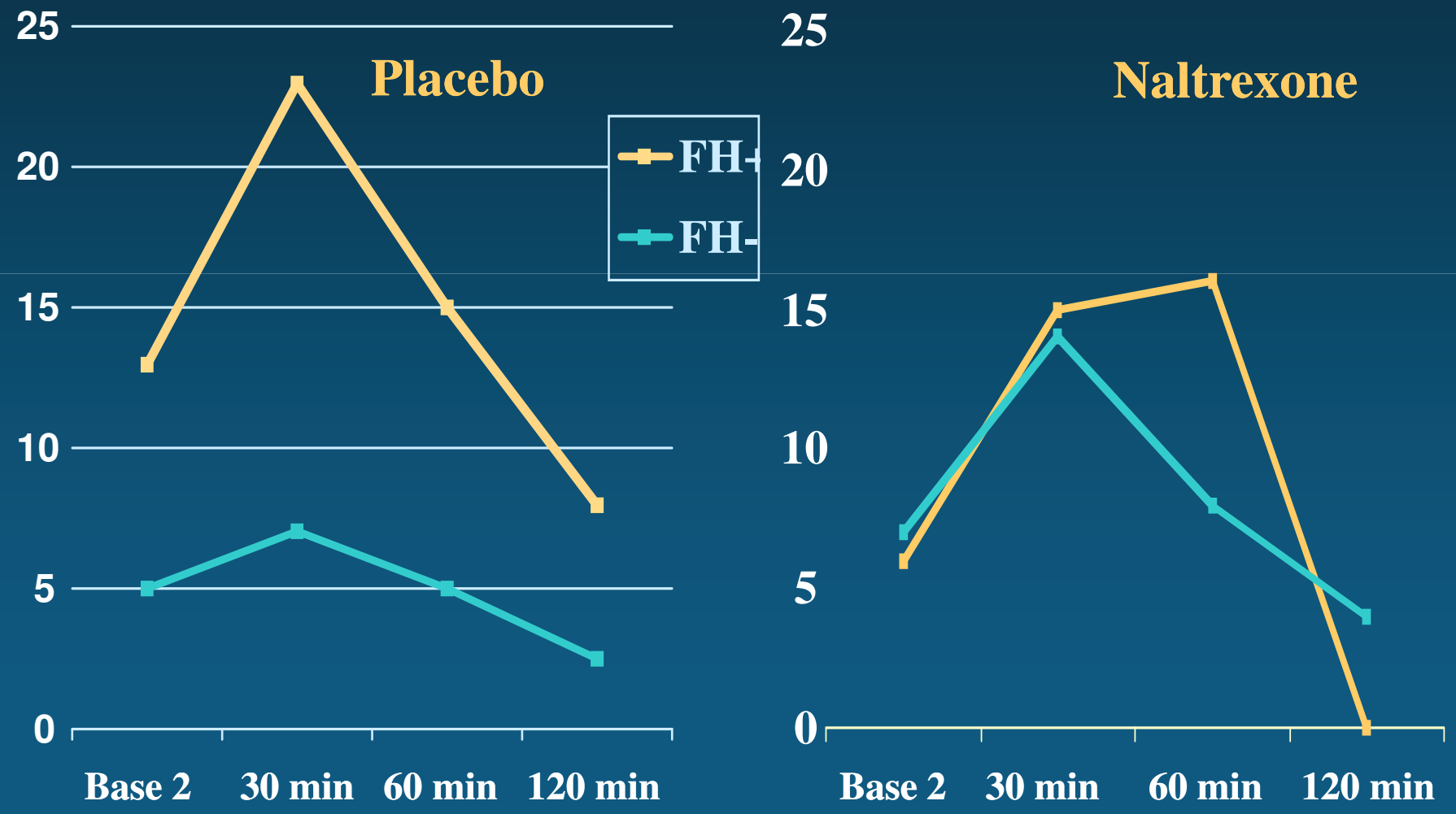


Gianoulakis C. Eur J Pharmacol. 1990; 180-21-29.

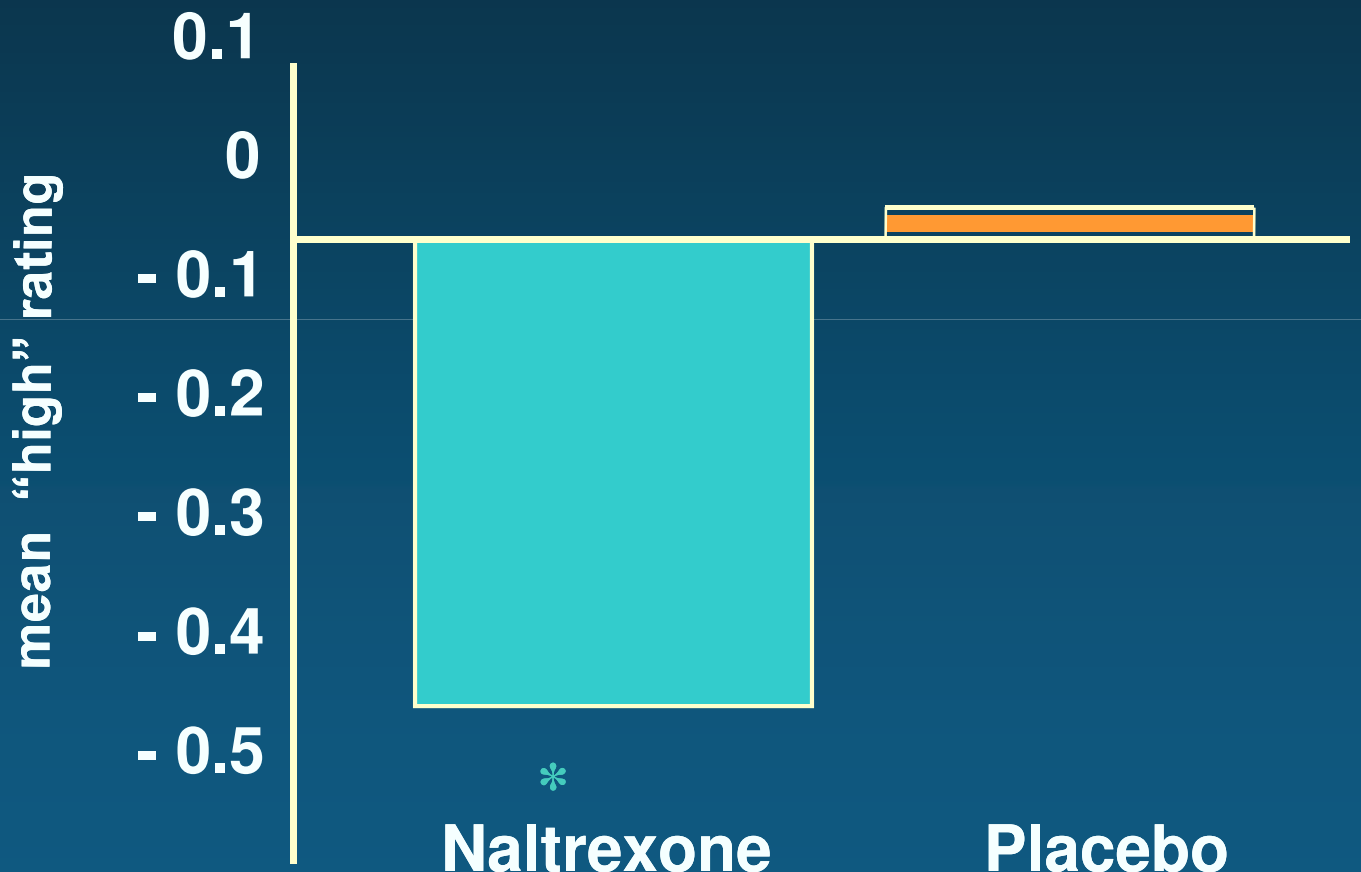
B-Endorphine après consommation d'alcool



BAES Stimulation Scores Parmi FH+ et FH- Volontaires

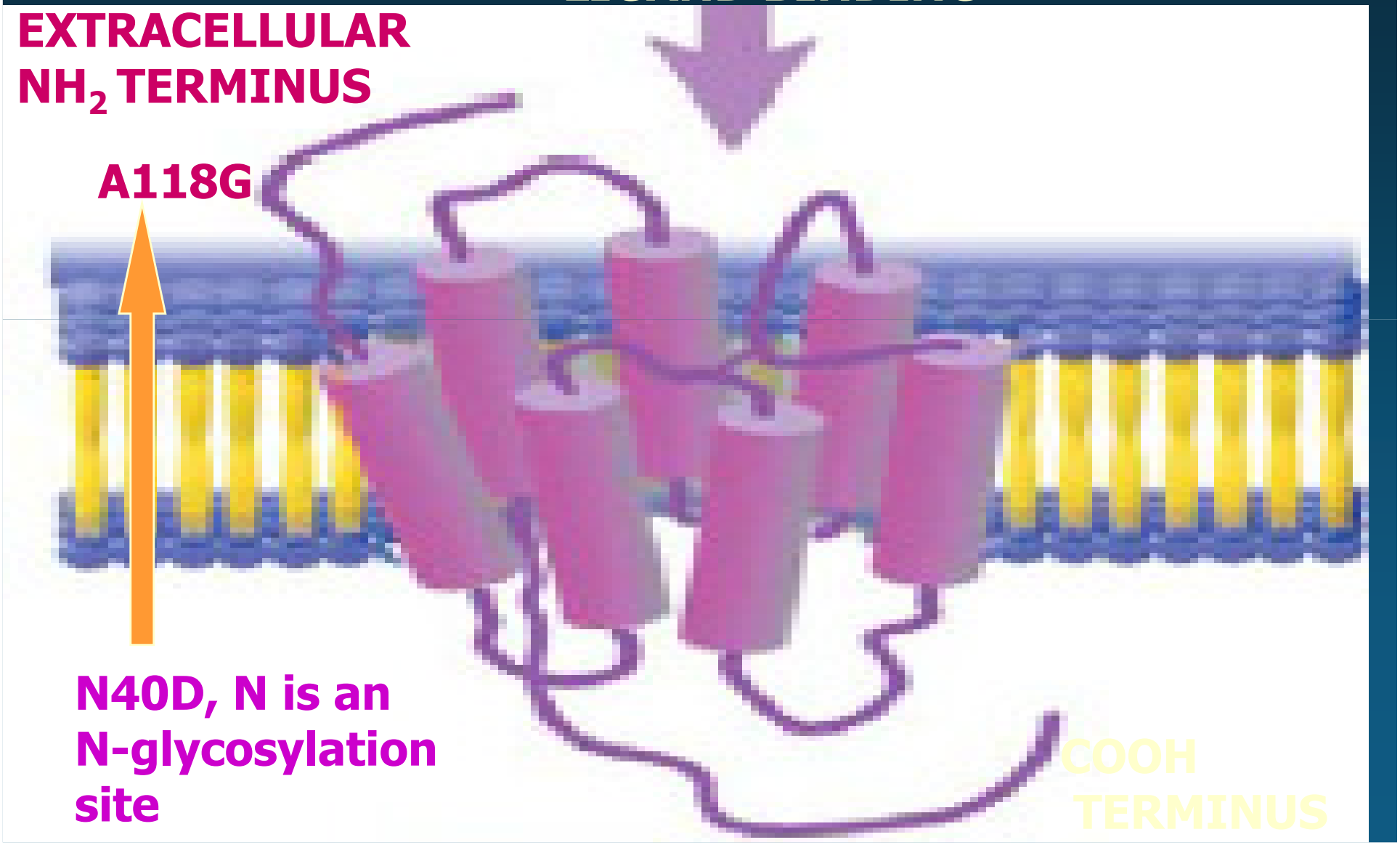


Subjective “high” (euphorie)

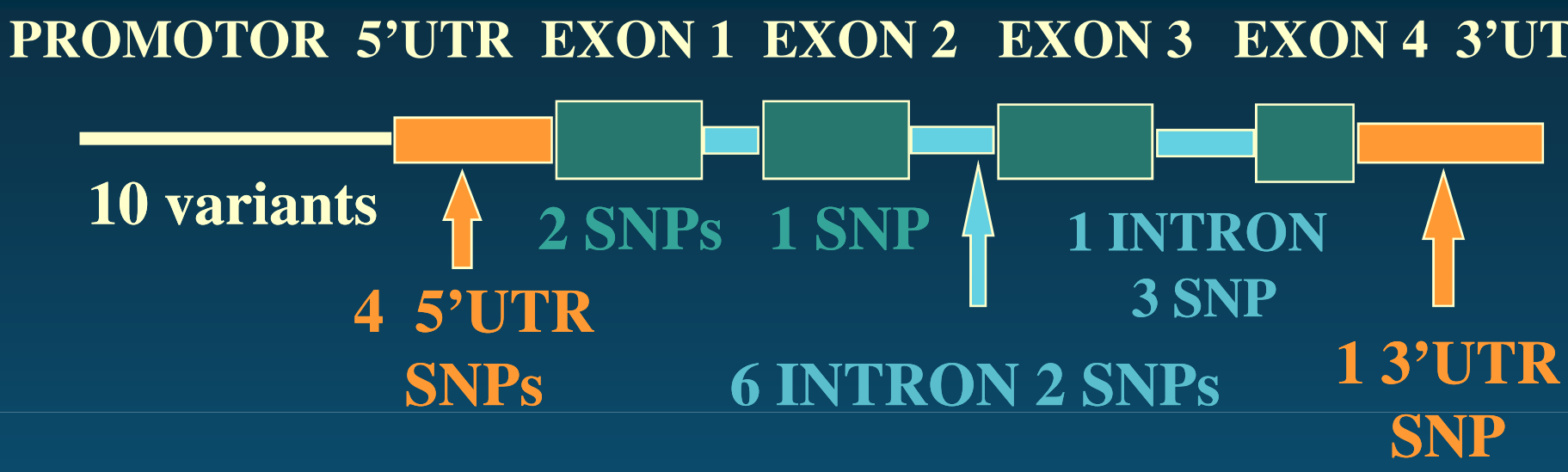


* p<.05

OPRM1 PROTEIN STRUCTURE



Human Mu Opioid Receptor Gene

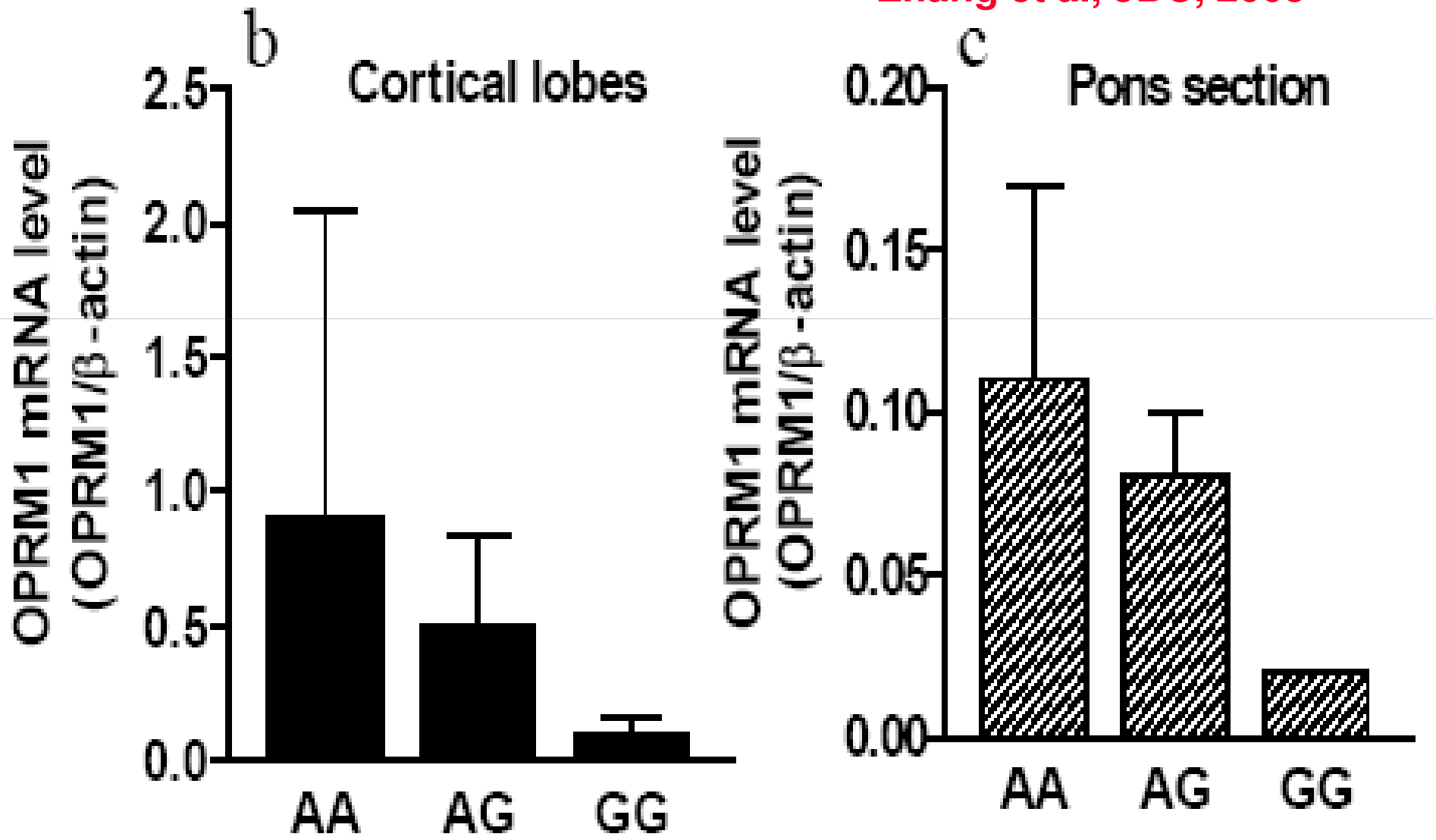


6.6 kb of OPRM1 gene sequence was determined in ~200 persons; 25 variants occurred at a frequency >1%.

The 118 A>G exon 1 SNP increases OPRM1 affinity for beta-endorphin. The functional significance of other variants remains unknown.

OPRM1 A118G EFFECT ON TRANSCRIPTION

Zhang et al, JBC, 2005



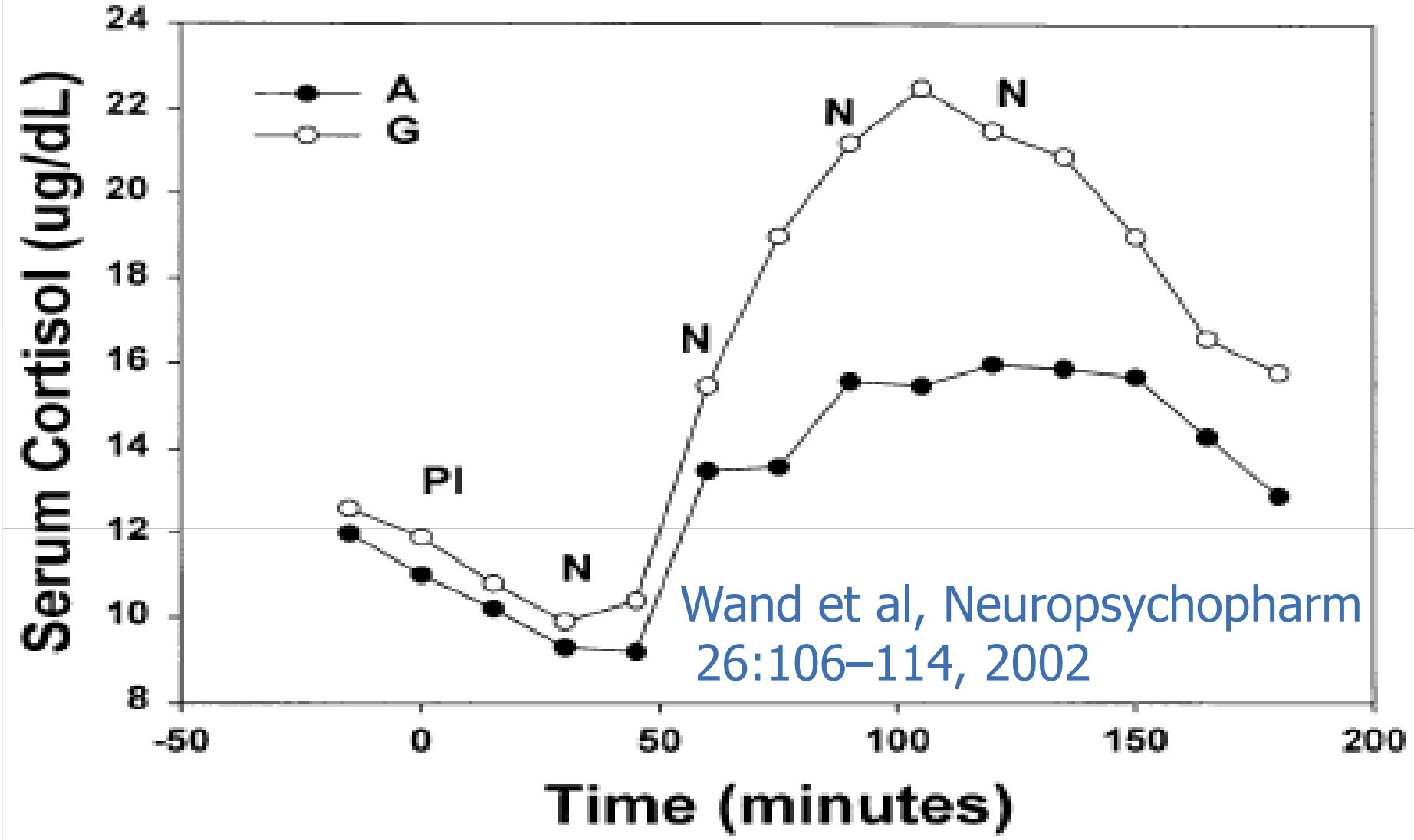


Figure 3. Cortisol responses to Naloxone by mu-opioid receptor genotype. PI denotes time of placebo (saline) administration. N denotes times of incremental Naloxone administration.

Ethnicity & A118G Allele Frequency

Based on multiple studies, allele frequencies differ markedly across ethnicities for the A118G SNP in the mu opioid receptor gene. It arose after the out-of-Africa migration.

Crowley et al, 2003

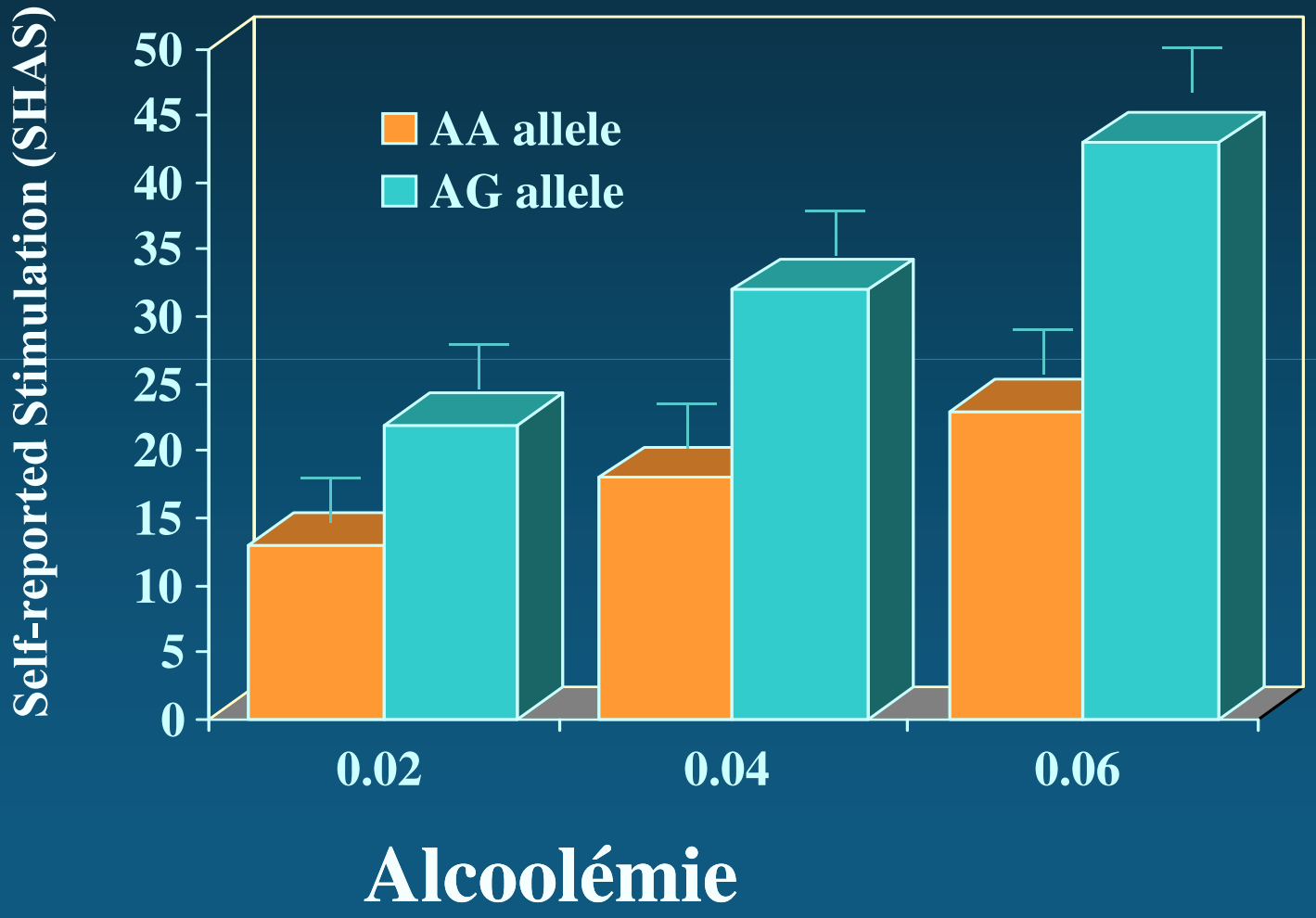
Gelernter et al, 1999

Tan et al, 2003

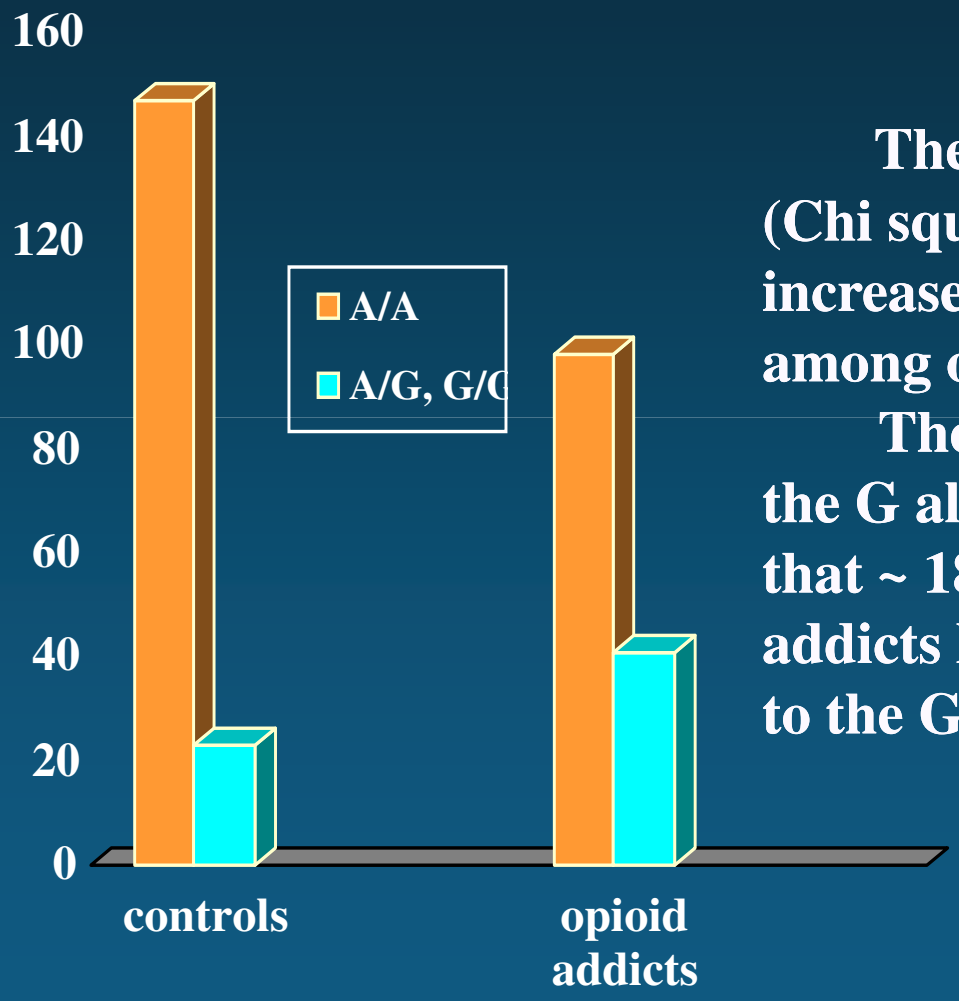
Bart et al, 2004

ETHNICITY	f(G)	ETHNICITY	f(G)
African	1%	Koreans	31%
African-American	3%	Chinese	35%
Swedish	17%	Malaysian	45%
European-origin US	15%	Indian	47%

Les effets d'alcool IV selon le génotype



OPRM1 A118G et l'addiction opioïde

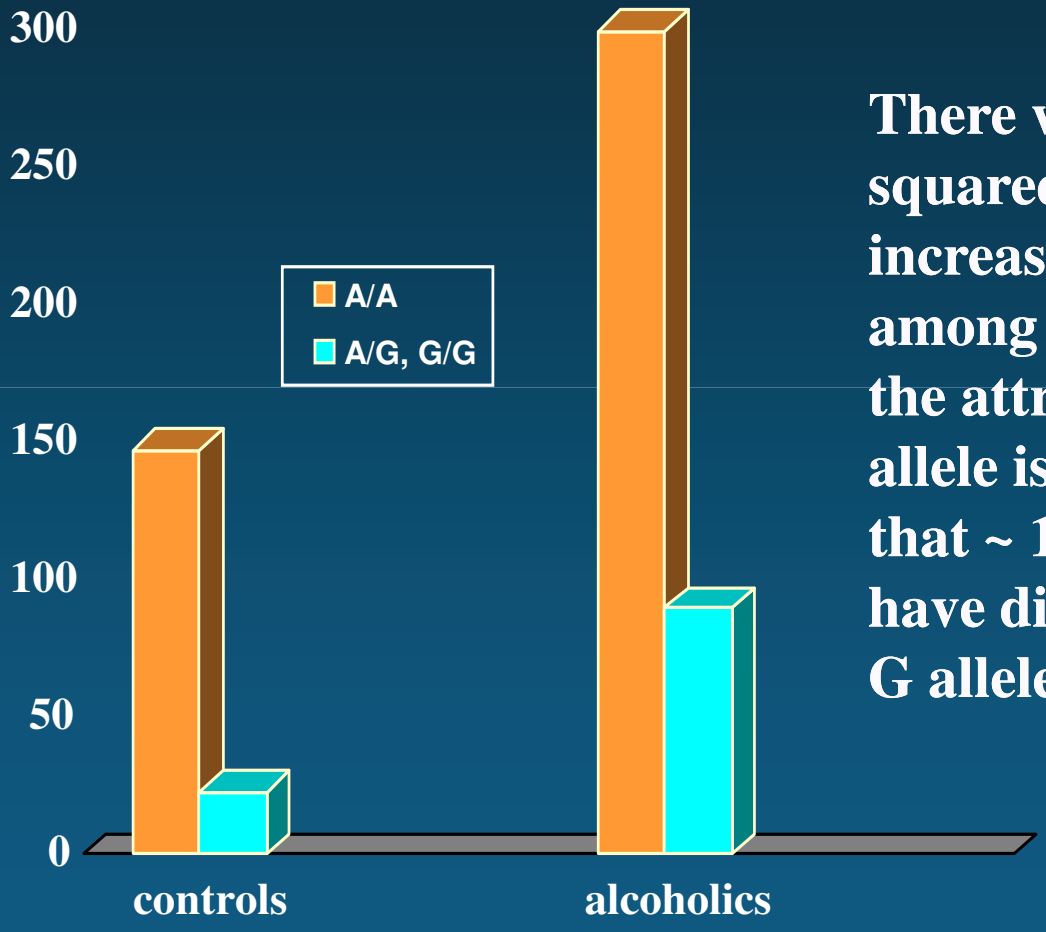


There was a significant (Chi squared = 13, p = 0.00025) increase in A/G, G/G genotype among opioid addicts.

The attributable risk for the G allele is ~ 18%, suggesting that ~ 18% of Swedish opioid addicts have disease in part due to the G allele.

Bart et al (Mol Psychiatry 9:547, 2004) studied opioid addicts in Sweden for A118G.

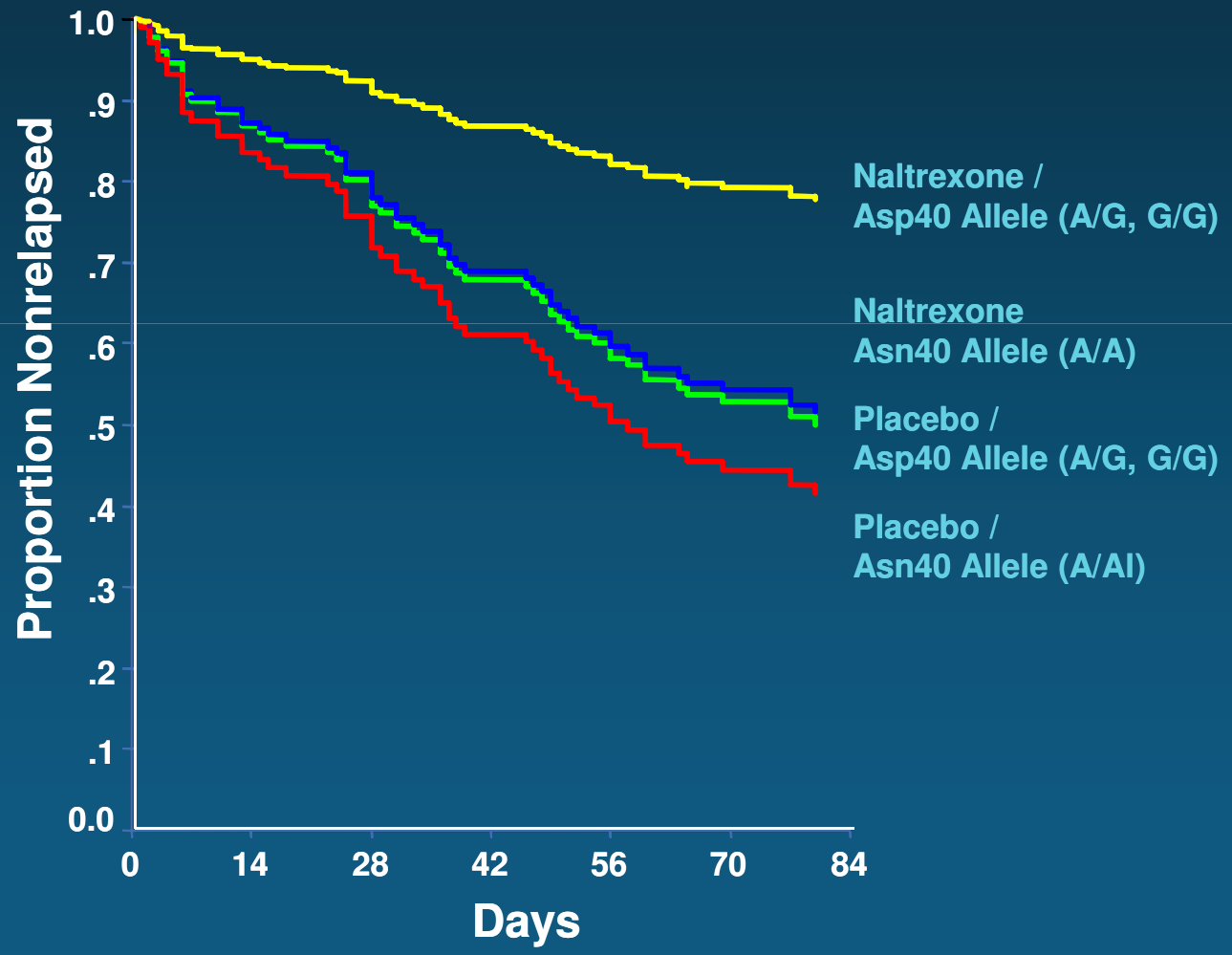
OPRM1 A118G et Alcoolisme



There was a significant (Chi squared = 7.2, p = 0.007) increase in A/G, G/G genotype among alcoholics. In this study the attributable risk for the G allele is ~ 11%, suggesting that ~ 11% of Swedish alcoholics have disease in part due to the G allele.

Bart et al (Neuropsychopharmacol, 2005) studied alcoholics in Sweden for the A118G.

Relapse Rate by Genotype



Alcooliques: bons resultats

Nalt	A/G, GG	95%	N = 28
Nalt	A/A	73%	N = 86
Plac.	A/G, GG	63%	N = 60
Plac.	A/A	65%	N = 205

Odds ratio, nalt good regs, GVA = 10.25 (95% CI 1.31 - 80.0 P= .03)

Sous-categorie
Endorphine Dépendant Alcoolisme

- Alcool → Opioïdes endogène
- Euphorie/Stimulation
- Sensible μ Recepteurs
- Histoire familiale d'alcoolisme
- Craving pour l'alcool

Traitement d'avenir

Vraiment individuel

Une prise par égratigner la peau dans la bouche

Faire le génotype

Choisir un médicament logiquement au lieu de "deviner"

Penn/VA Center Team

Arthur Alterman
Wade Berrettini
John Cacciola
Anna Rose Childress
James Cornish
Charles Dackis
Ronald Ehrman
Teresa Franklin
Kyle Kampman
Joe Volpicelli
A. Thomas McLellan
David Metzger
David Oslin
Helen Pettinati
Michael Stromberg
Elmer Yu
George Woody
James McKay

Pour davantage de renseignement

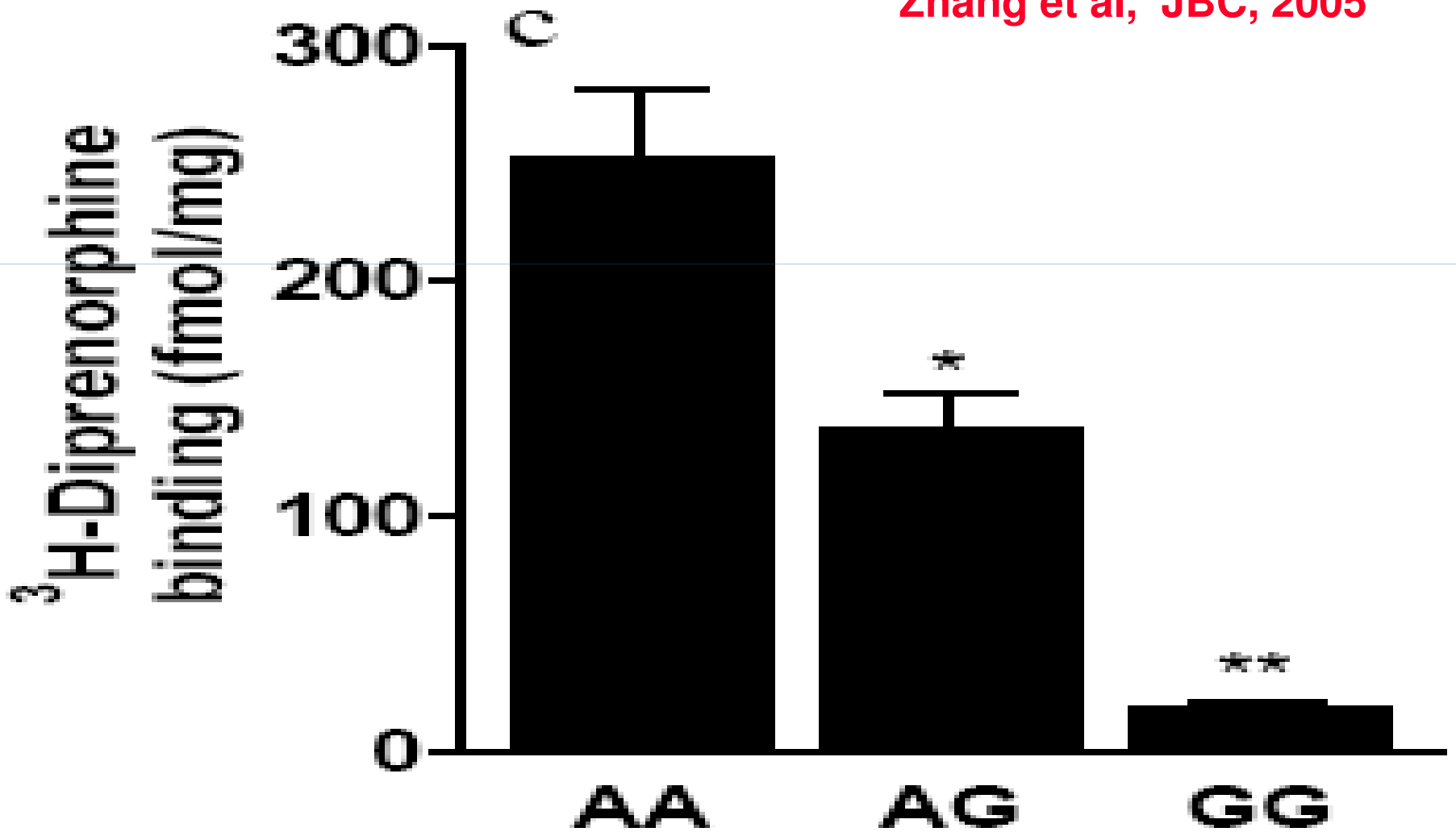
www.uphs.upenn.edu/trc

ou

obrien@mail.trc.upenn.edu

OPRM1 A118G EFFECT ON TRANSLATION

Zhang et al, JBC, 2005



Un haplotype

L'allèle "G" prédit une plus grande réponse aux antagonistes opiacés et une réduction de la réponse aux agonistes.

En somme, cela signifie une personne plus sensible à l'alcool. Mécanisme ??

G Allele Carriers Hyporesponsive aux mu Opioïde Recepteurs Agonists

- Romberg et al. Polymorphism of mu-opioid receptor gene (OPRM1:c.118AG) does not protect against opioid-induced respiratory depression despite reduced analgesic response. Anesthesiology 2005;102:522-30.
- Klepstad et al. The 118 A G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 2004;48:1232-9