Clinical Development of MP intended for treatment of pain

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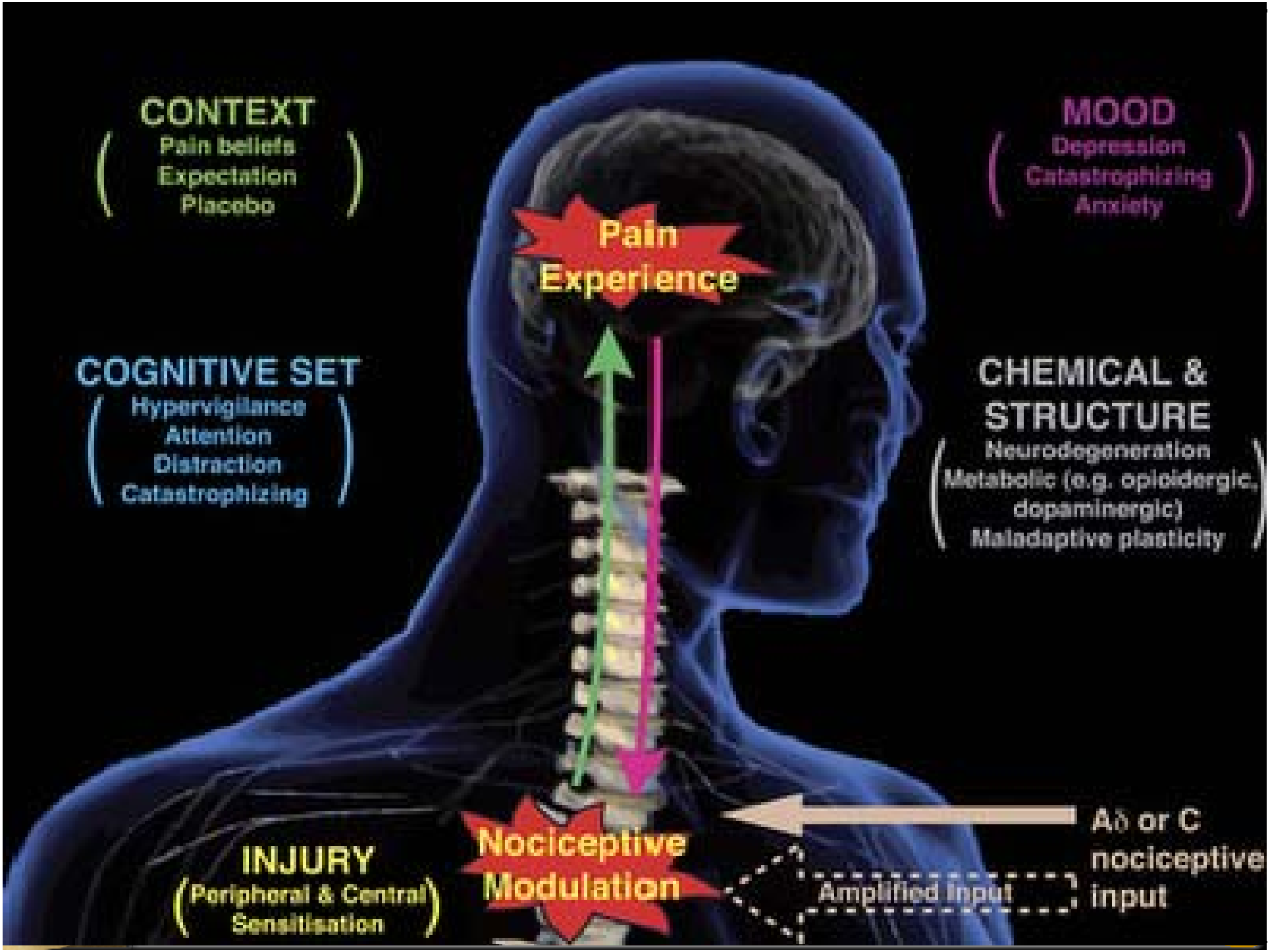
Summary

- The concept of clinical models to drive indications.
- The problem of exceptions:
  - Absence of adequate model.
  - Syndromes that are not represented by the accepted model.
  - Cancer pain.
  - Chronic lumbar pain.
- The need for active comparators.
- Outcomes


CONTEXT
Pain beliefs
Expectation
Placebo
MOOD
Depression
Catastrophizing
Anxiety
Pain Experience
COGNITIVE SET
Hypervigilance
Attention
Distraction
Catastrophizing
CHEMICAL & STRUCTURE
Neurodegeneration
Metabolic (e.g. opioidergic, dopaminergic)
Maladaptive plasticity
Aδ or C nociceptive input
Amplified input
Nociceptive Modulation
INJURY
Peripheral & Central Sensitisation

"Pain caused by the nervous system itself!"

PAIN

Nociceptive Pain	Neuropathic Pain	Specific diseases / syndromes
Acute	Peripheral	Migraine
Chronic	Central	Dysmenorrhae
Somatic		Fibromialgia
Visceral		Burning Mouth Syndrome (BMS)

Cancer pain

CPMP guidance: purpose

- Establish the consensual grounds in a certain medical field.
- Harmonize assessors approach to dossier data.
- Help industry establish development plans.

CPMP guidance

- Usually not useful for highly innovative medicinal products.
  - *There are not many of these!!!*
- Extremely conservative.
  - Consensus among several European experts is difficult.
  - Avoid controversial topics where advice is most need (-> Scientific Advice)
- Generic
  - Do not deal with details.
- Risk to become easily out-of-date

Nociceptive pain

Type of pain	Intensity	Duration of studies	Model studies examples
Acute	Mild – moderate	Days, < 1 week	Tooth extraction, sprain, minor surgery (e.g. cutaneous surgery, hernia), headache (other than migraine), sore throat, low back pain, primary dysmenorrhoea
Acute	Moderate-severe	<48 h – 1 week	-Surgical removal of impacted teeth -Renal and biliary colic -Well-defined major orthopaedic surgery -Well-defined major abdominal/thoracic surgery -Episiotomy -Major skeletal trauma
Chronic	Mild – moderate	≥ 3 months (specific guidance to be followed)	Osteoarthritis, reumathoid arthritis, low back pain
Chronic	Moderate-severe	≥ 1 month	Cancer, skeletal metastasis with movement related pain


Europe
CPMP
MRP/DECentralised
0 500 Miles
0 500 Kilometers
NORTH AMERICA
Greenland (Denmark)
40° W
20° W
0°
20° E
40° E
60° E
Arctic Circle
60° N
ASIA
Barents Sea
Ural Mountains
Lapland
Scandinavia
European Plain
Norwegian Sea
Finland
Norway
Russia
Estonia
Sweden
Latvia
Lith.
Russ.
Belarus
Denmark
North Sea
Ireland
ATLANTIC OCEAN
Neth.
Northern
Germany
Poland
Ukraine
Czech Rep.
Slovakia
Lux.
Belgium
France
Liech.
Austria
Switz.
Alps
Hungary
Moldova
Caucasus Mts.
Caspian Sea
40° N
Bay of Biscay
Slovenia
Croatia
Romania
Black Sea
San Marino
Yug.
Bulgaria
Italy
Turkey
Andorra
Monaco
Bosn. & Herzg.
Macedonia
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Quadramet, 2003

- Quadramet is samarium [153Sm] lexidronam pentasodium INN, i.e. 153Sm complexed with EDTMP(ethylenediaminetetramethylenephosphonic acid), also referred to as 153Sm- EDTMP.
- The clinical indication for Quadramet relates to the relief of bone pain in patients with multiple painful osteoblastic skeletal metastases.
- In the three pivotal studies, 288 patients received the active drug and 85 received the placebo. Patients included had confirmed histological diagnosis of malignancy and of metastatic lesions in bone (as evidenced by pain overlying at least one site of enhanced uptake on 99m Tc bone scan).
  - BA 108: Single-blind, comparative between doses, multicentre, parallel group, randomised study.
  - BA 106/110: Double-blind, 3-arm comparative (vs placebo & 2 doses),multicentre, parallel groups, randomised study
  - 424Sm10/11: Double-blind, placebo-controlled, multicentre, parallel group, randomised study
    - 16 week follow-up

IONSYS, fentanly, 2005

- The IONSYS (fentanyl HCl) system is designed to provide 24-hour preprogrammed, disposable, noninvasive, delivery of fentanyl with a sufficient number of on-demand doses to allow the majority of patients to achieve safe and effective analgesia without the need for i.v. PCA.
- The indication is for "the management of acute moderate to severe post-operative pain in a medically supervised setting."

IONSYS, fentanyl, 2005

Table: Overview of main Phase III efficacy and safety studies (Study C-2001-011, C-2000-008, C-95-016, C-2000-007)

Type of Study	Study No Location	Objectives	No. of Subjects, Population	Study Design/ Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Duration of Dosing
Placebo-controlled Clinical Trials						
Safety and efficacy	C-2001-011[26] USA	Compare E-TRANS (fentanyl HCl) and E-TRANS (placebo)	484 treated post-operative patients (n=244 in Treatment A, n=240 in Treatment B)	Multicentre, randomized, double-blind, parallel-group Placebo-controlled	A. E-TRANS (fentanyl HCl) 40 µg up to 6 doses/h B. E-TRANS (placebo) Each dose from each treatment administered over 10 min	Up to 24 h
Safety and efficacy	C-2000-008[28] USA	Compare E-TRANS (fentanyl HCl) and E-TRANS (placebo)	305 treated post-operative patients (n=154 in Treatment A, n=51 in Treatment B)	Multicentre, randomized, double blind, parallel-group Placebo-controlled	A. E-TRANS (fentanyl HCl) 40 µg up to 6 doses/h B. E-TRANS (placebo) Each dose from each treatment administered over 10 min	Up to 24 h
Safety and efficacy	C-95-016 New Zealand	Compare E-TRANS (fentanyl HCl) and E-TRANS (placebo)	102 treated post-operative patients (n=77 in Treatment A, 25 in Treatment B)	Single-centre, parallel-group, double-blind Placebo-controlled	A. E-TRANS (fentanyl HCl) 40 µg up to 6 doses/h B. E-TRANS (placebo) Each dose from each treatment administered over 10 min, up to 80 doses available over 24 h	Up to 24 h
Active-controlled Clinical Trial						
Safety and efficacy	C-2000-007[27] USA and Canada	Compare E-TRANS (fentanyl HCl) and IV PCA morphine	636 treated post-operative patients (n=316 in Treatment A, n=320 in Treatment B)	Multicentre, randomized, stratified, open-label, parallel-group Active-controlled	A. E-TRANS (fentanyl HCl) 40 µg up to 6 doses/h, each dose administered over 10 min B. IV PCA morphine (1 mg/dose) up to 10 doses/h), each dose administered as a bolus, followed by a 5-min lockout period	Up to 72 h

PRIALT, Ziconotide

- Prialt is indicated for the treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia.
- Ziconotide selectively blocks the neuronal N-type voltage sensitive calcium channels (N-VSCC), which are responsible for the spinal processing of pain.
- **Main studies** ***Three pivotal placebo-controlled clinical trials were performed: ▪ Study 95-001: patients with chronic malignant pain (associated with cancer or AIDS) – 112 patients (72 ziconotide and 40 placebo). ▪ Study 96-002: patients with chronic non-malignant pain, especially neuropathic pain – 257 patients (170 ziconotide and 87 placebo). ▪ Another randomised, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain was submitted during the evaluation process (study 301). The first two studies were prolonged into a long-term open-label study (95-002).***

Effentora, fentanyl citrate, buccal tablet, CHMP Jan 2008

- Effentora is indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain. It is proposed that Effentora is prescribed by physicians experienced in the management of opioid therapy in cancer patients.

COX-2

- Lumiracoxib
- Parecoxib

Nociceptive pain: crossroads

- **Chronic pain**
  - Chronic lumbar pain as an indication
  - Validity of chronic visceral pain models
    - Interstitial cystitis.
    - Pelvic pain

CHRONIC LOW BACK PAIN

- Acceptable as an indication.
- All types of patients that correspond to te category must be included.
- Active control not needed if the test drug is used on top of a liberal protocol that allows analgesics, which should be detailed on CRFs
- Follow-up, longer than 3 months.
- Chronic specific syndromes like fibromialgia or dysmenorrhae cannot be used as models to compose a boarder chronic pain indication.

Neuropathic pain

Extrapolation from clinical trials

- Mixed pain types should be excluded from pivotal trials (ex: Chronic low back pain)
- **Peripheral CM-> peripheral neuropathic indication.**
- **Central CM -> central neuropathic pain indication.**
- **Peripheral + Central CM -> neuropathic pain indication.**
  - Syringomielia

Neuropathic pain licenses.

- Pregabaline
- Duloxetine

Painful HIV-associated neuropathy.

Tramadol, Capsiciain, COMP decision 2006

- The negative opinion is based on the following elements: for the purpose of designation as orphan medicinal product, justification has not been provided for limiting the condition to "painful HIV-associated neuropathy". **Thus the proposed condition was not considered as a valid subset of the broader condition "peripheral neuropathy";**
- the sponsor has not provided data to establish that peripheral neuropathy (hereinafter referred to as 'the condition') affects not more than 5 in 10,000 persons in the Community at the time the application was made*;
- although satisfactory methods of treatment of "peripheral neuropathic pain" have been authorised in the Community, no sufficient justification has been provided that tramadol hydrochloride may be of significant benefit over current satisfactory treatments.

Neuropathic pain crossroads

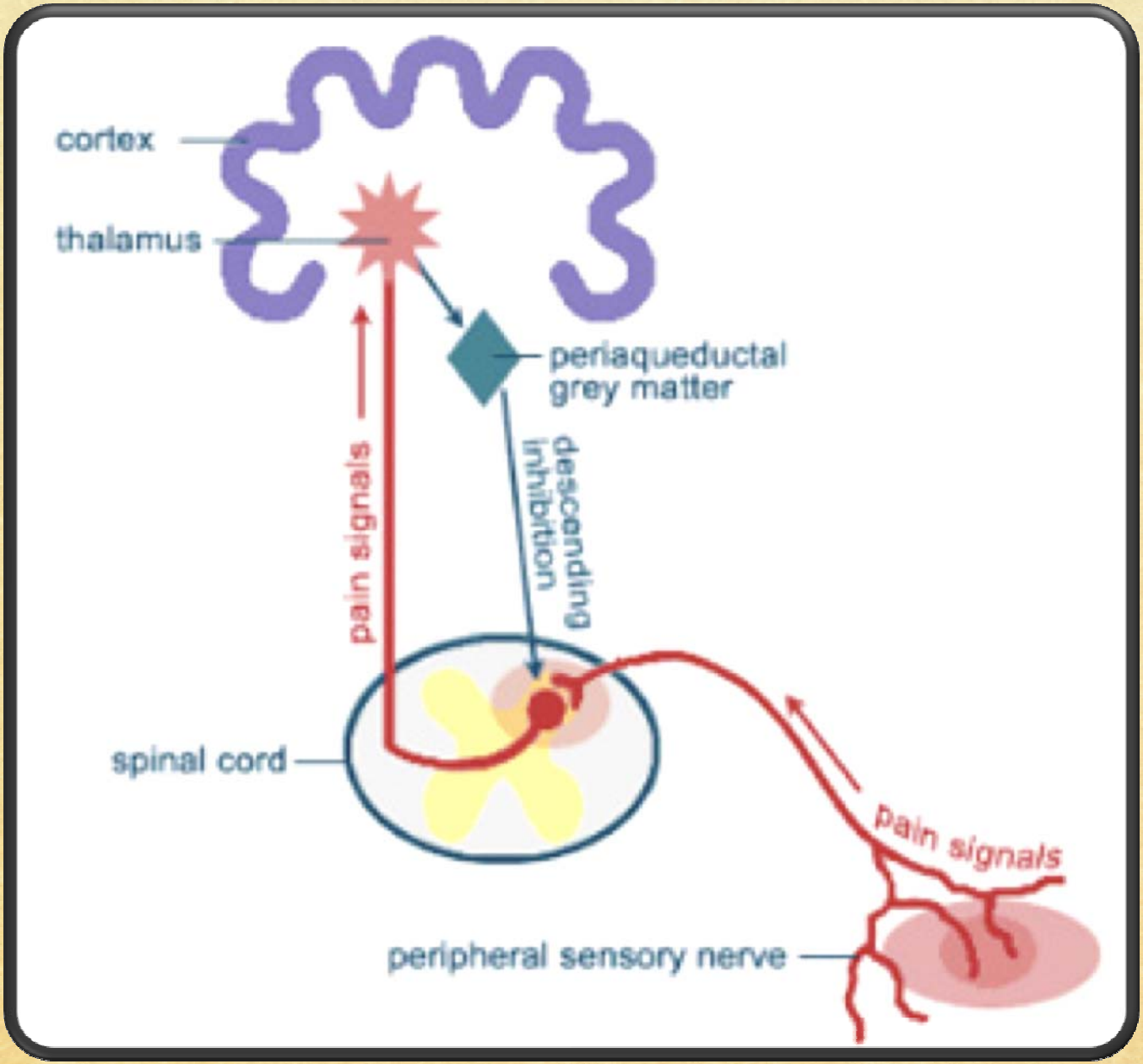
- Which syndromes will be considered stand alone indications worth pursuing?
  - CRPS I and II
- 3 arm trials with an active comparator.

Pain Outcomes

- Currently,
  - The primary outcome is based on pain intensity and it is likely that it will remain so.
    - Mean differences and
    - Responders rates
  - Other outcomes might be quoted in SPC, 5.1 if they are considered to be relevant for the prescriber decision but...
    - The new SPC guideline strong recommends that only primary endpoints are mentioned in 5.1

Conclusions

- The CHMP for pain has been helful in standardizing CDP without stalling that development.
- It might have conduct to an exaustion of the resources to conduct trials in PHN and PDN. The populations being studies might be evolving: bigger placebo effects, lower severities.
- There are new challanges posed by potential independent indications.


cortex
thalamus
periaqueductal grey matter
descending inhibition
pain signals
spinal cord
pain signals
peripheral sensory nerve