Pain Models Workshop

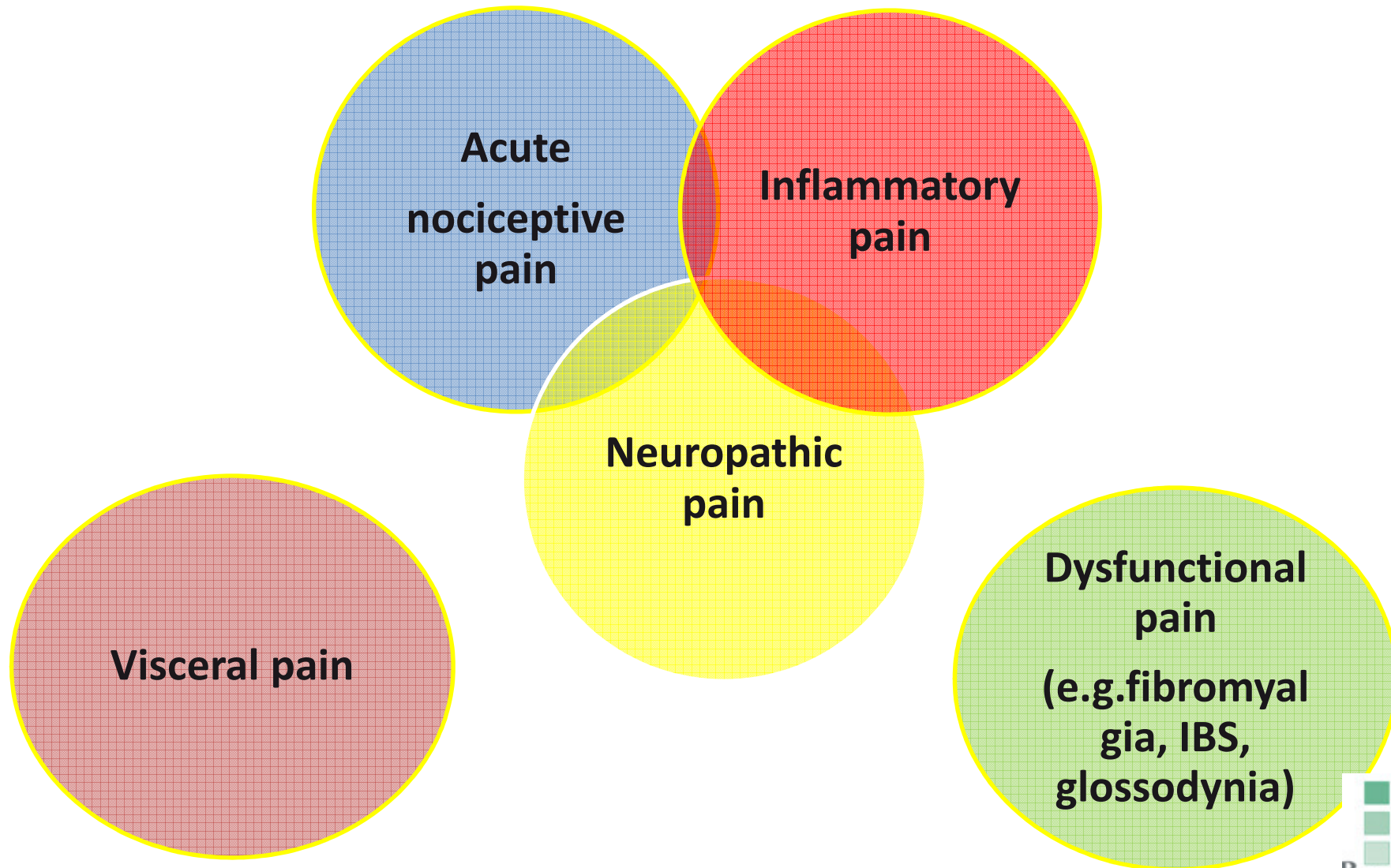**P.Danjou, MD,PhD,MAPS -Paris**

WS 5.b

International Association for the Study of Pain: definition 1994

« An unpleasant **sensory** <u>and</u> **emotional** experience associated with actual or potential tissue damage, or described in terms of such damage »

Different pain syndromes, different pathophysiology

Different time constants and psychological consequences

Type of evolution	Duration	Psychological states associated	Model of therapeutic intervention
Acute Pain	Reasonably related to the affection less than 3 months	Anxiety	Medical, Pasteurian
Chronic Pain	Greater than 3 months	Depression	Bio-Psycho-Social

Development of Pain Medications prior to Phase IIb

- **Relatively easily modelised**
  - Acute pain (both animals and humans)
  - Inflammatory pain (animals > humans)

- **Modelised with more difficulties**
  - Neuropathic pain (animals> humans*)

  -Visceral pain (animals >>humans, in some cases similarities)

- **Impossible to modelise**
  - Dysfunctional pain (e.g. fibromyalgia), Complex Regional Pain Syndromes (algodystrophy,causalgia)
  - Interactions with anxiety and depression

*: intense R&D effort

Types of medical indications in labeling

Pain of mild to moderate intensity

Treatment moderate to severe pain

Neuropathic pain

Postherpetic Neuralgia

Painfull diabetic neuropathy

Trigeminalgia,cluster headache

Treatment of breakthrough pain in non opiate naives

Chronic cancer pain

Acute migraine

Prevention of migraine
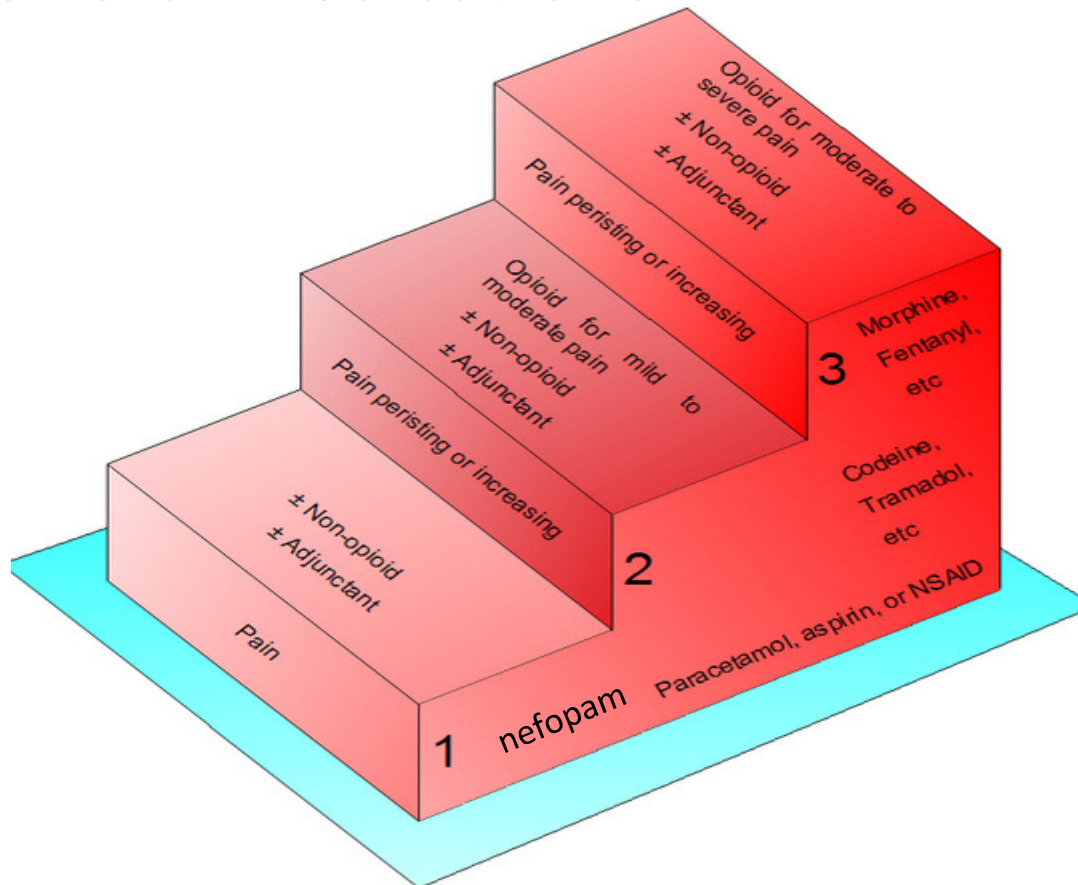
Simple headache

Spasmolytic

Some rhumatological indications for NSAIDs
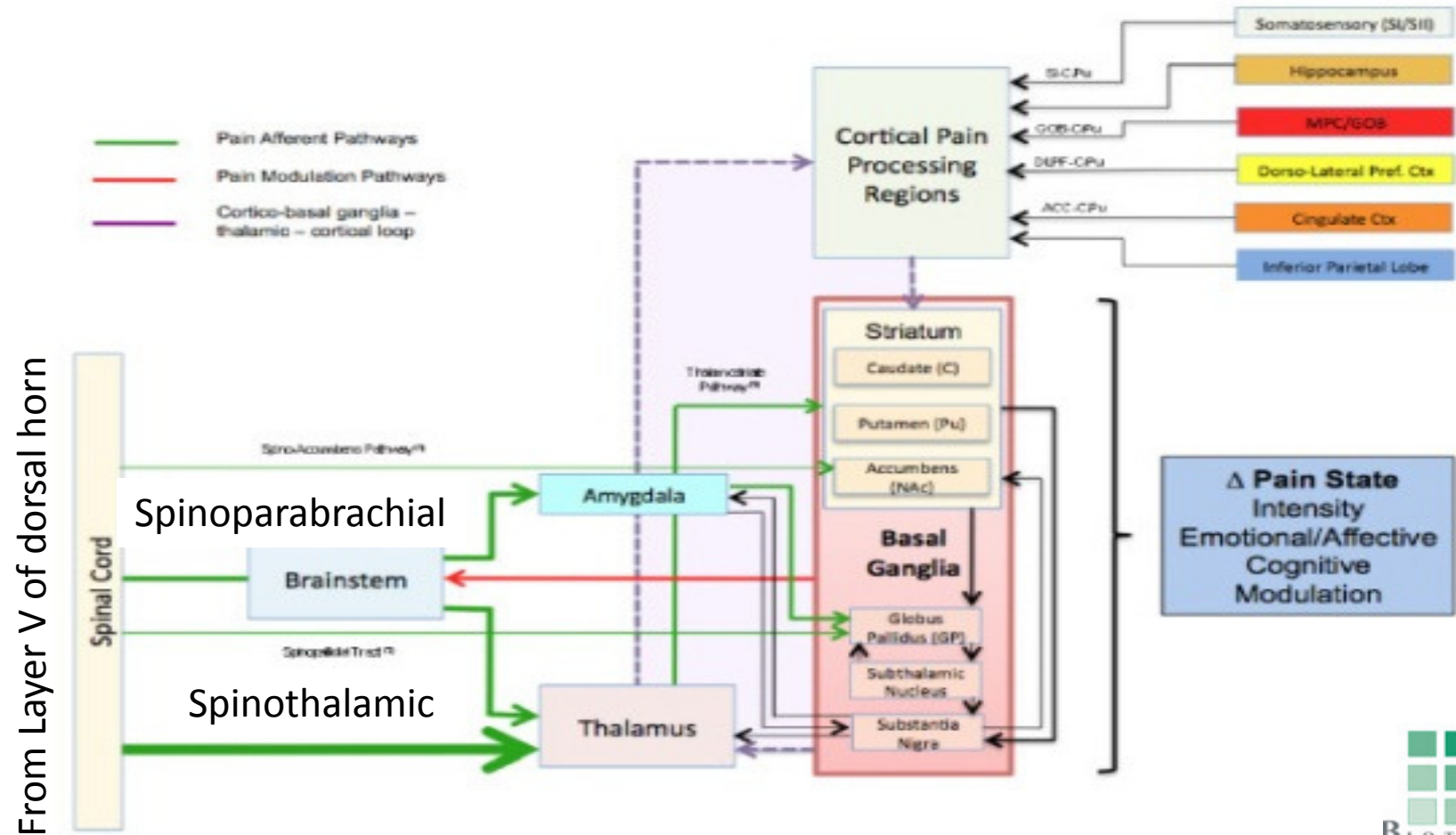
Local anaesthesic

WHO Ladder

- For oral medications

Theoretically progressive but clinical sense needed, not all level 1 equivalent

Anatomy of Pain and Emotions

A few of animal models: read=behaviour

Acute Pain		Chronic	
Paw tests (thresholds) [**phasic pain**]	Tail Flick Randall-Sellito Hot plate	**Inflammatory**	Carraghenan paw oedema Freund's adjuvant paw oedema Air pouch in back UV erythema
Paw (injection) [**tonic pain**]	Formalin Capsaicin Bee venom	**Neuropathic**	Chemical: Capsaicin Streptozotocin Vincristine Nerves ligation : Chung Seltzer Bennet Spare nerve Injury
Visceral	Acetic acid writhing test Barostat		

BIOTRIAL

A few of Human models: read= subject perception n=20 cross-over

Acute Pain		Chronic		
(Thresholds)	-Thermal pain -Mechanical pain (*electronic Von Frey,* *Impactometers,* *Pinch interdigital Web)* -Electrical stimulation cutaneous, RIII reflex -Ischemic tourniquet -hypotonic water injection	**Inflammatory**	UV erythema Skin freezing NGF* injection IM/SC	
		Neuropathic	Capsaicin intradermal Capsaicin topical+heat Repeated electric stimulation by needles/microdialysis probes Transdermal Electric Stimulation (being validated)	
Visceral	Barostat Oesophagal distension or electric stimulation Bladder instillation of KCl and capsaicin		*:no suitable sourcing found with ANSM requirements*	

Alternatives to self- assessment of pain for R&D

- **fMRI pain matrix activation during (any) painful stimuli (Irene Tracey, David Borsook), effect of hypnotic manipulation**

- **Evoked potentials**
  - Requires rapid signal onset/Offset : fast thermodes or lasers (NdYAG or Erbium)
  - Gamma band seems suitable(Hu) 2012

- **EEG changes to painful stimuli by Machine Vector Learning (Gravesen)**

- **RR changes** Metrodoloris^{TM} equipment for surgery (no peer-reviewed papers)

Phase IIa reads: Pain ratings
n=50-150 parallel groups

Single dose	Repeated dose
Postoperative morphine sparing in PCA **Withdom tooth avulsion** Knee arthritis with Moskovitz forced walking test	Oncology morphine sparing Breakthrough pain un patients stabilized with opiates **Knee osteoartritis** (3 months) Lombosciatalgia Rhumatoid arthritis **Post-herpetic neuralgia** **Painful diabetic neuropathy** Chemotherapy induced neuropathy
	« Clever designs » Cross-over in diabetic neuropathy with biopsy, elimination of placebo responders (Merck) Nerve trauma cross-over (Pfizer)