

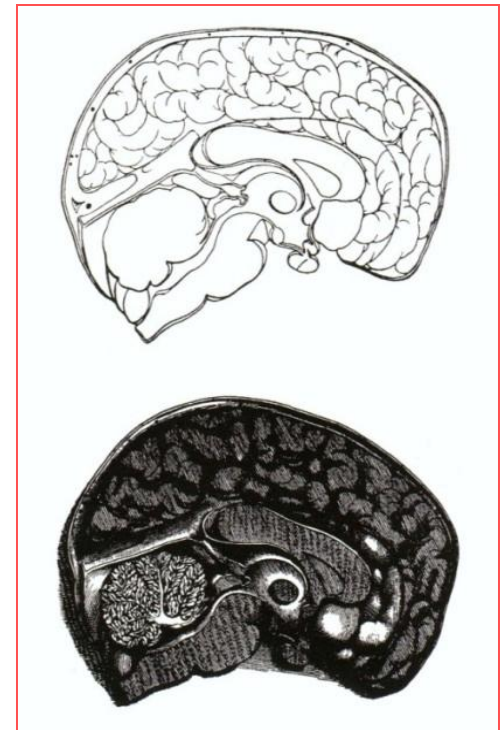


Mystery of Central Post stroke Pain

Hong Kong Pain Society April 24-25, 2010

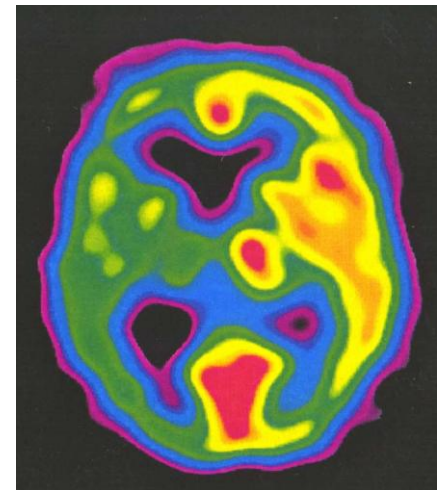
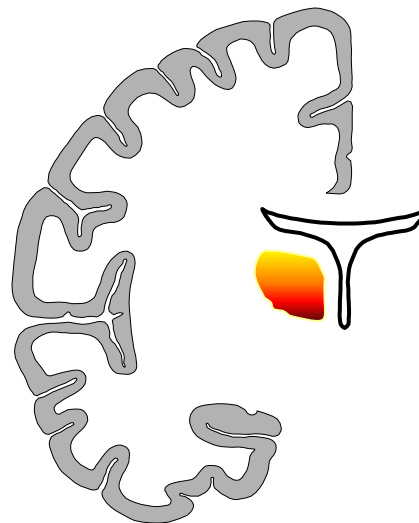


Troels Staehelin Jensen, MD, DMSc
Dept. of Neurology &
Danish Pain Research Center
Aarhus University Hospital, Denmark



Central pain:

- Definition and causes
- CPSP and other types of post stroke pain
- Mechanisms
- Management of central pain

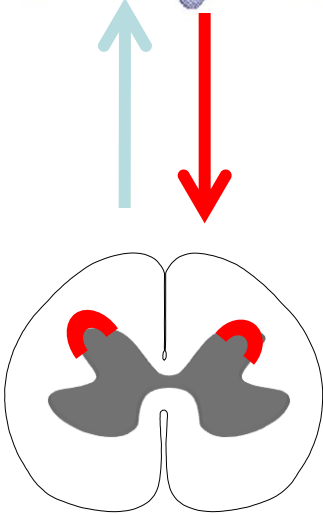
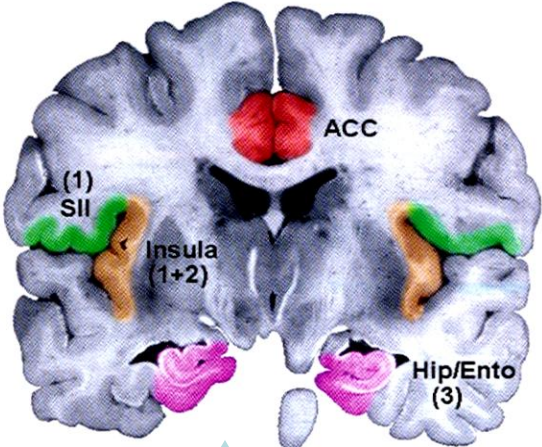


Pain: From static to dynamic

Sensory
Affective
Cognitive

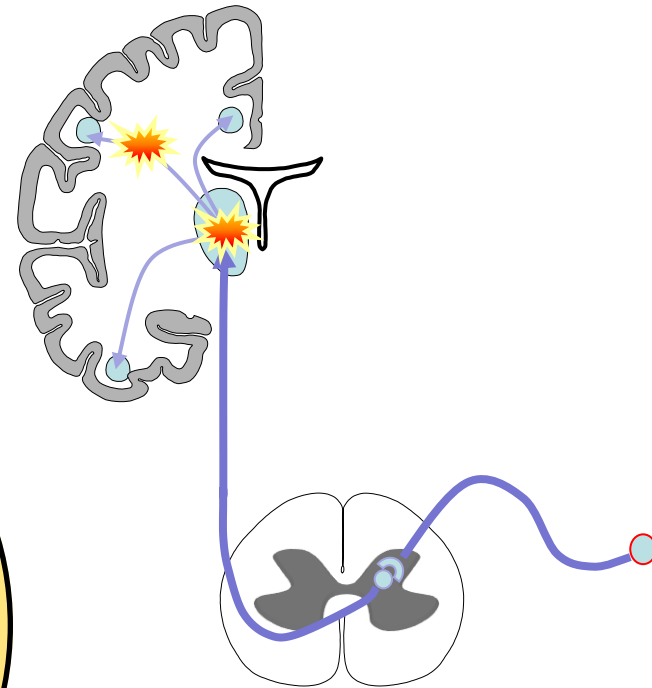
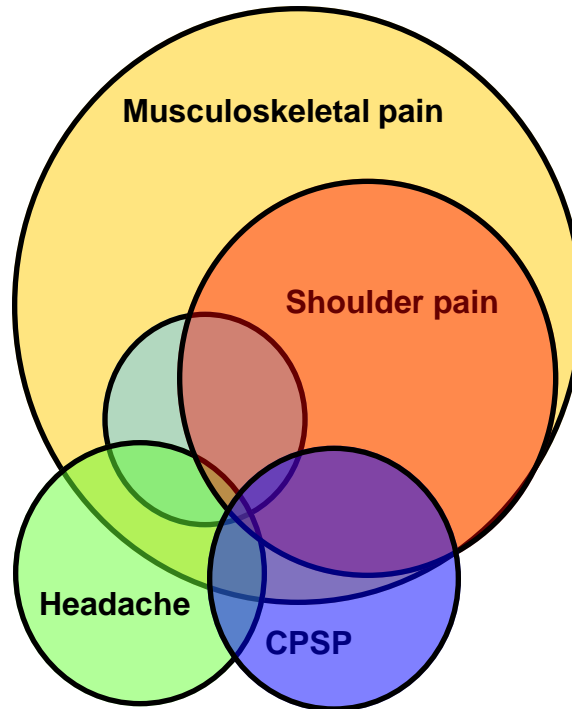


Noxious input →



Modified from
Casey 2006
Tracey & Mantyh ,2007

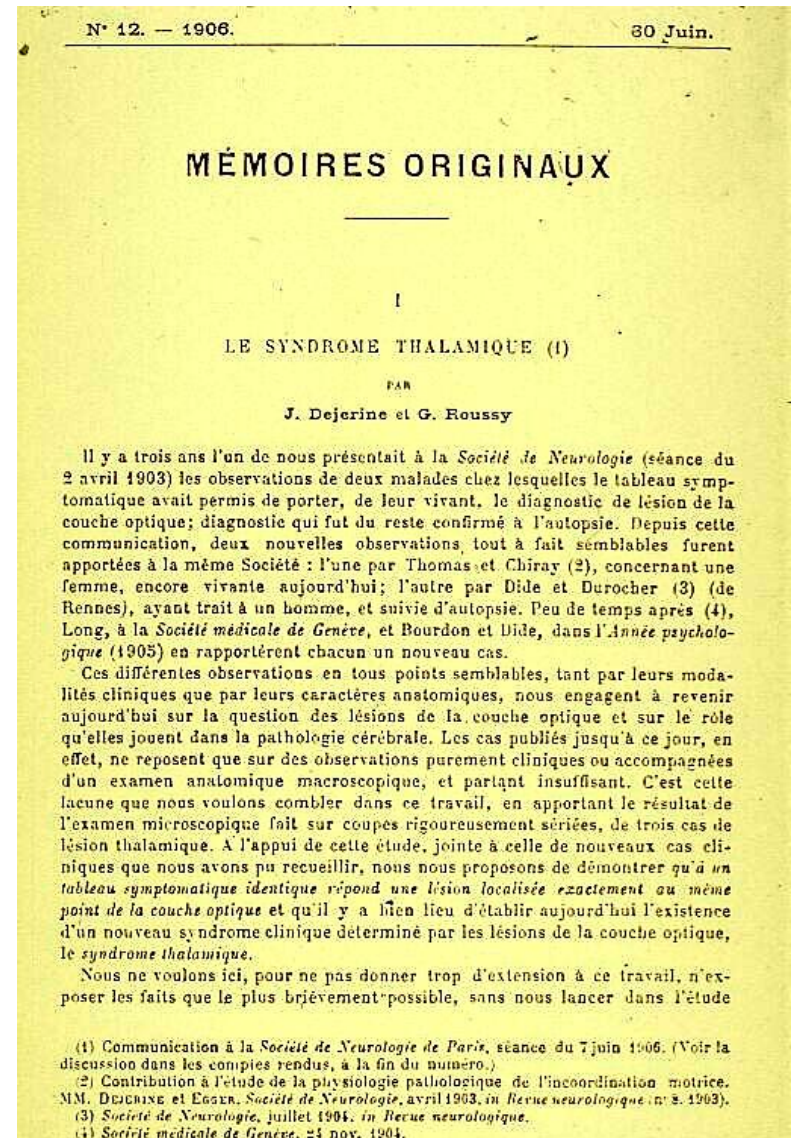
Central Pain: Pain arising as direct consequence of a lesion or disease affecting the somato-sensory system (Neurology 2008).



Central Post Stroke Pain: Thalamic syndrome

- Slight hemiplegia
- Sensory disturbance
- Hemiatxia, hemiastereognosis
- Intolerable pain
- Choreo-athetoid movements

Dejerine and Roussy 1906



Central pain: Characteristics and causes

Characteristics

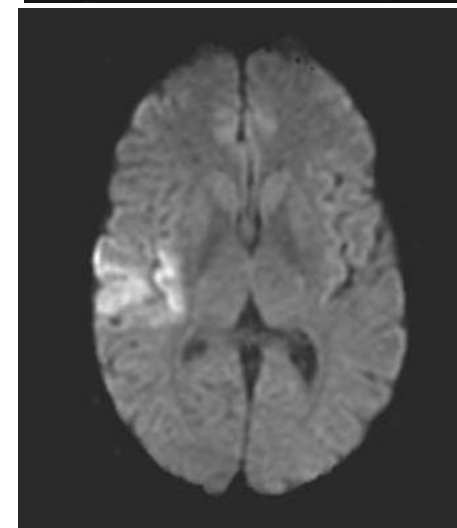
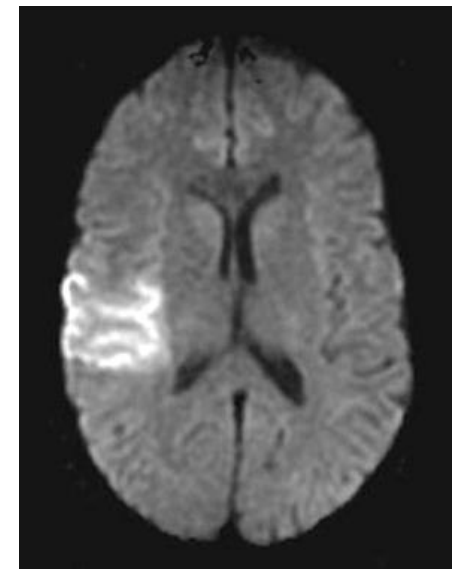
Central nervous system lesion
Spontaneous and evoked pains
Deep and superficial pain
Paradox sensation: loss and hyperalgesia
Thermal loss obligatory
Thermal hyperalgesia

Causes

- **Spinal**
- **Stroke**
- Spinal cord injury
- myelitis
- syringomyelia
- MS
- cordotomy
- DREZ
- **Brain**
- **Stroke**
- brain injury
- MS
- epilepsy
- syringobulbia
- Parkinson disease ?

Post stroke pain: case

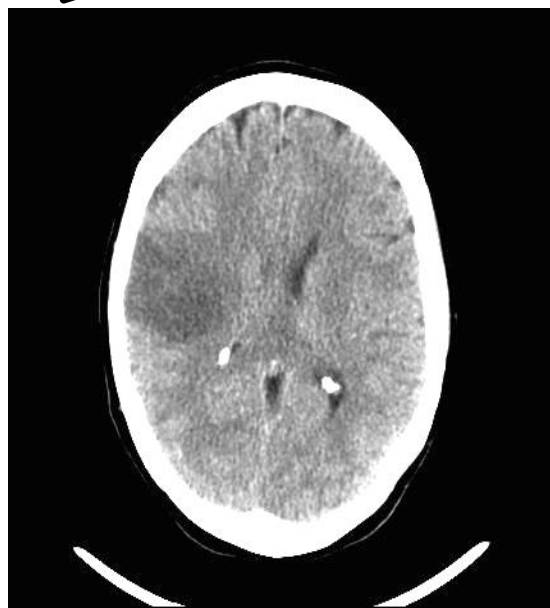
48 yr, F. Sudden left hemiparesis
Gaze palsy, L hemiparalysis
L. sensory loss
DWI lesion in the R. hemisphere
Thrombolysis
Day 2 large MCI infarction



Acute MR – DWI



CTC Day 1



CTC Day 2

Post Stroke Pain: Case

2007: Day 3 after stroke pricking
sticking sensation L side

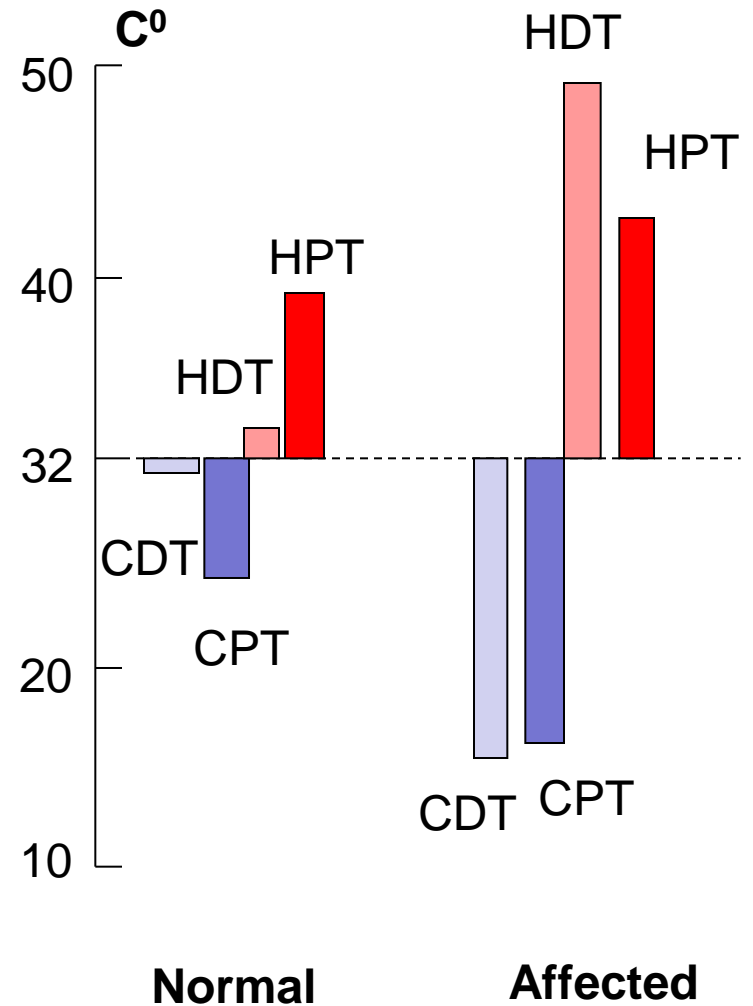
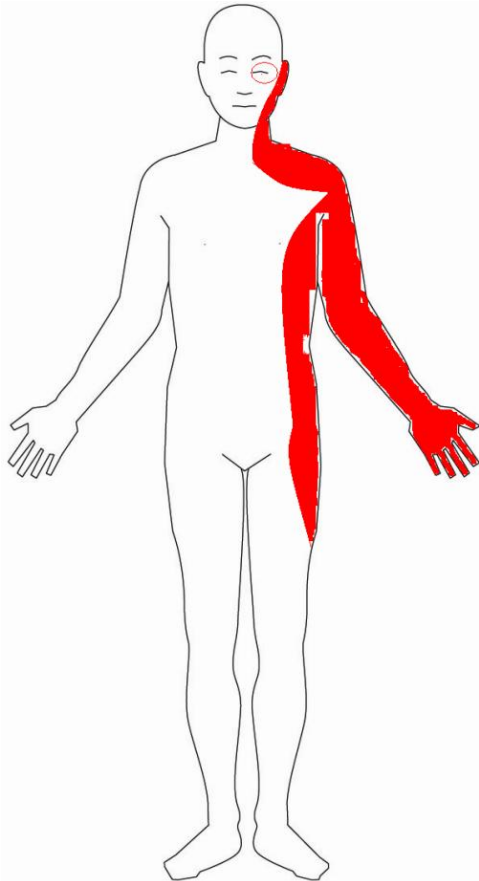
Cold allodynia L side

2010 : 3 yrs after stroke

Constant pain L. face, arm, trunc

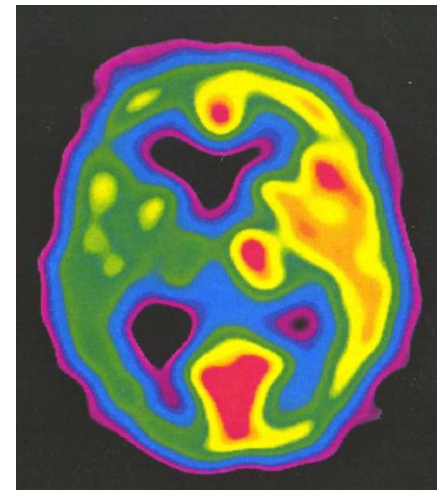
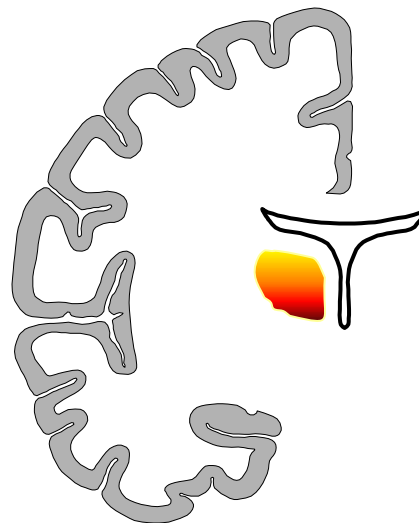
Deep burning, pricking pain

VAS pain intensity 8



Central pain:

- Definition and causes
- CPSP and other types of post stroke pain
- Mechanisms
- Management of central pain



CPSP

Study	N with stroke	Total with Pain	Follow- up (Months)	N with CPSP (%)
Andersen et al. 1995	207	-	12	16 (8%)
MacGowan et al. 1997	63 with LMI	-	60	16 (25%)
Bowsher et al. 2001	72 (Q to 1071 pts)	-		8(11%)
Weimar et al. 2002	119	-	12	11 (9.2%)
Widar et al. 2002	616 (356 included)	43	24	15 (4%)
Glader et al. 2001	3203	20%	24	Not specified
Kong et al. 2004	107	45	19.8	13 (12%)
Jönsson et al. 2006*	297	62	16	4 (1%)*

* If the investigator suspected CPSP the patient was referred to a neurologist who diagnosed CPSP according to established criteria

Post stroke Pain Case

2004

- 65 yr F Acute L hemiparalysis
- CT: Haemorrhage R thalamus
- Within months severe pain L. side

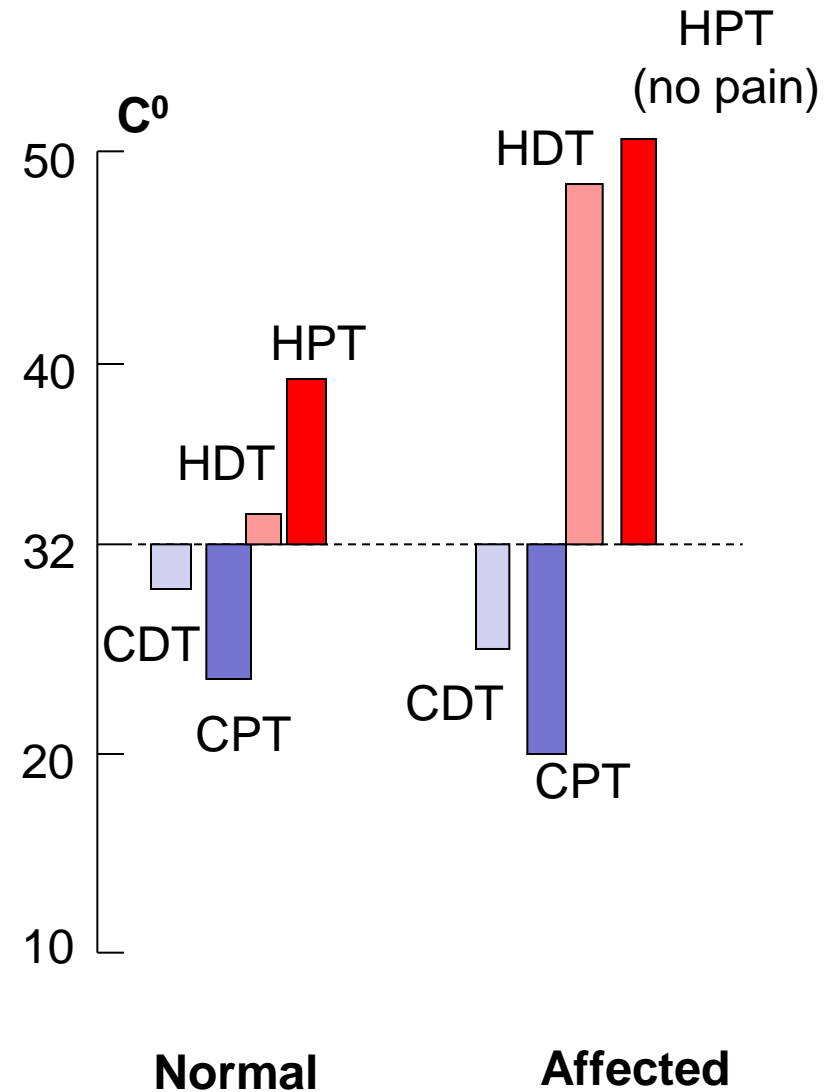
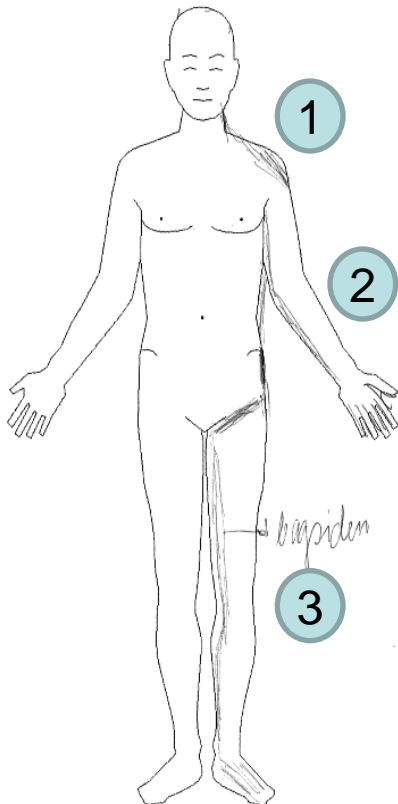
2008

- Spastic L. hemiparesis.
- Sensory disturbance L. side



Post Stroke Pain case

1. Shoulder pain
2. Sharp cutting pain L arm and hand (NRS:6) and leg (NRS:9).
Cold allodynia
3. Painful spasms and spasticity L. leg

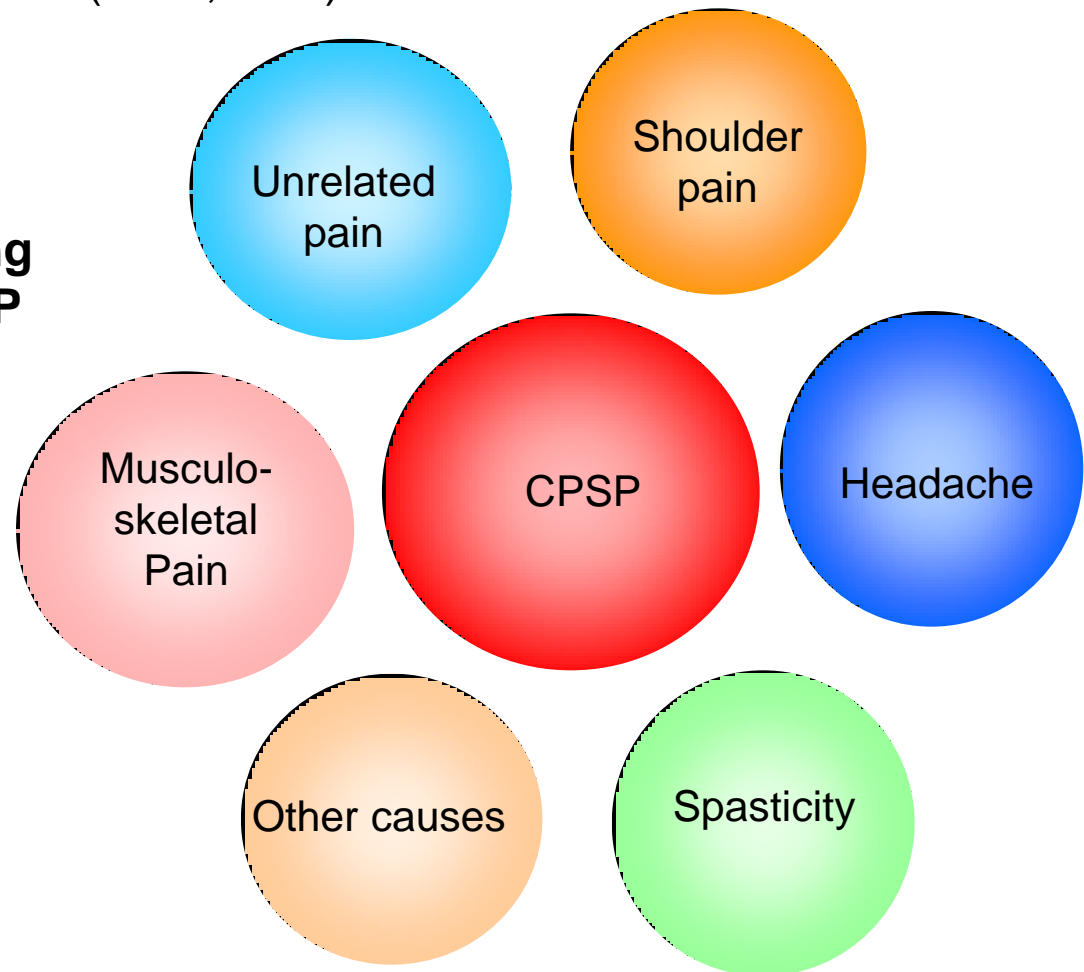


Post stroke pain

Central Pain = Pain caused by lesion or disease in the central nervous system (IASP,1994)

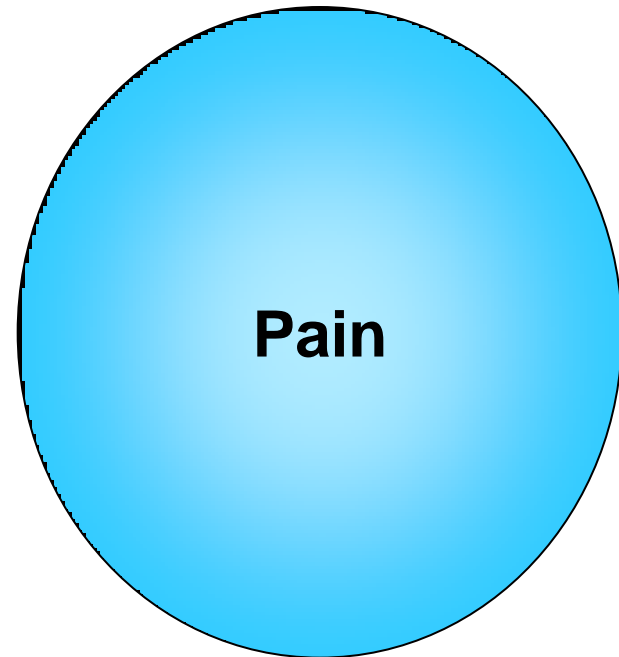
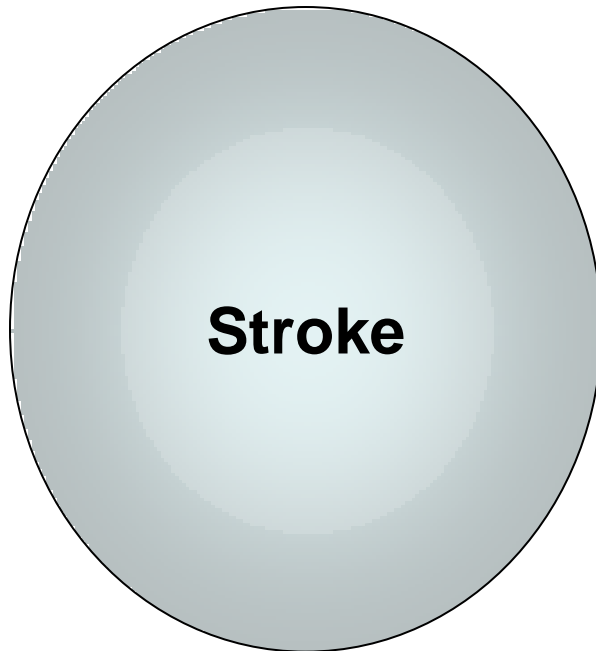
Problems:

No precise criteria for delineating other pain conditions from CPSP



CPSP: Delineation

Stroke unrelated pain



CPSP: Delineation

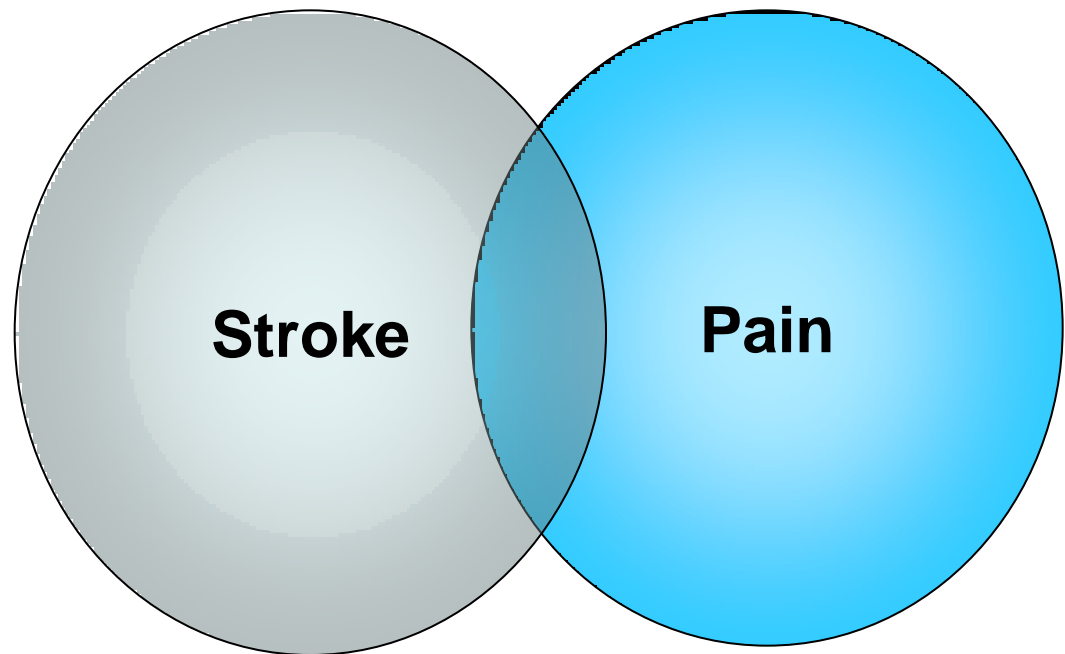
Stroke related pain:

Musculoskeletal pain

Spasticity

Headache

Central Pain

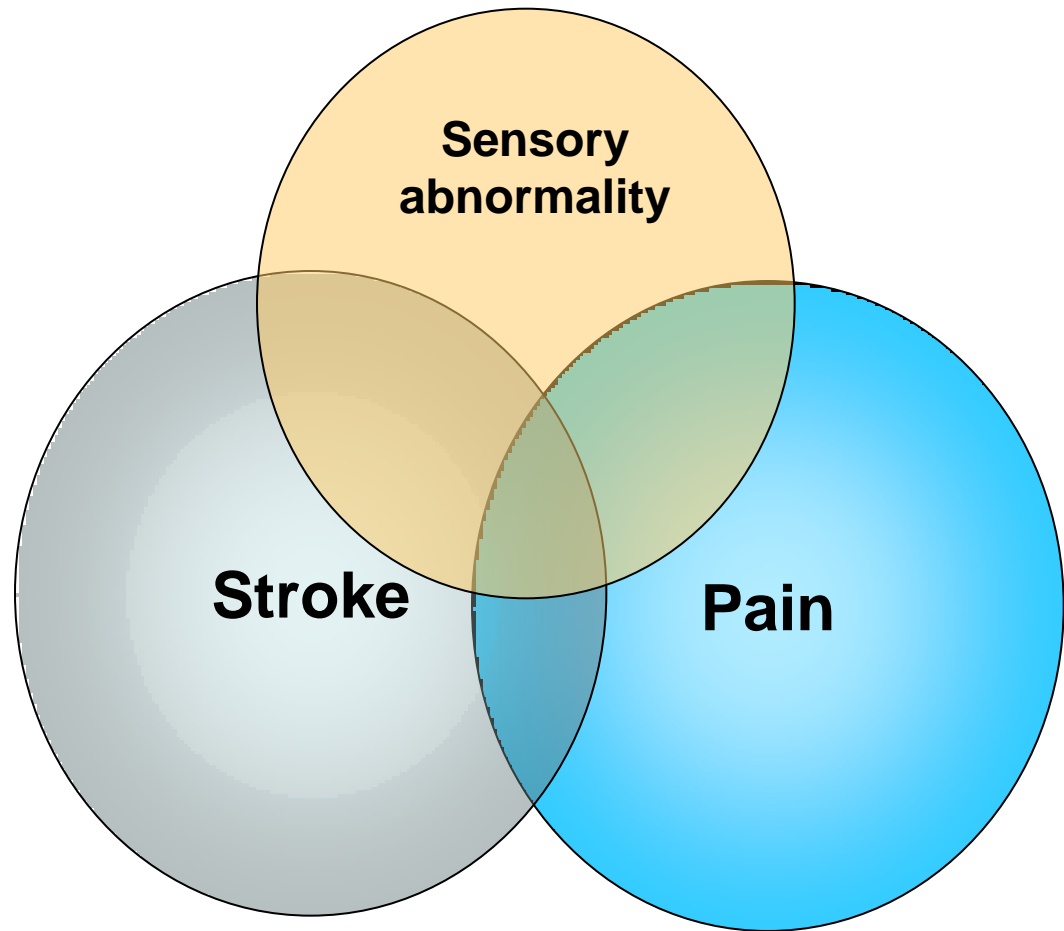


CPSP: Delineation

Stroke related pain:

Musculoskeletal pain

Central Pain



CPSP: Delineation

Stroke related Pain

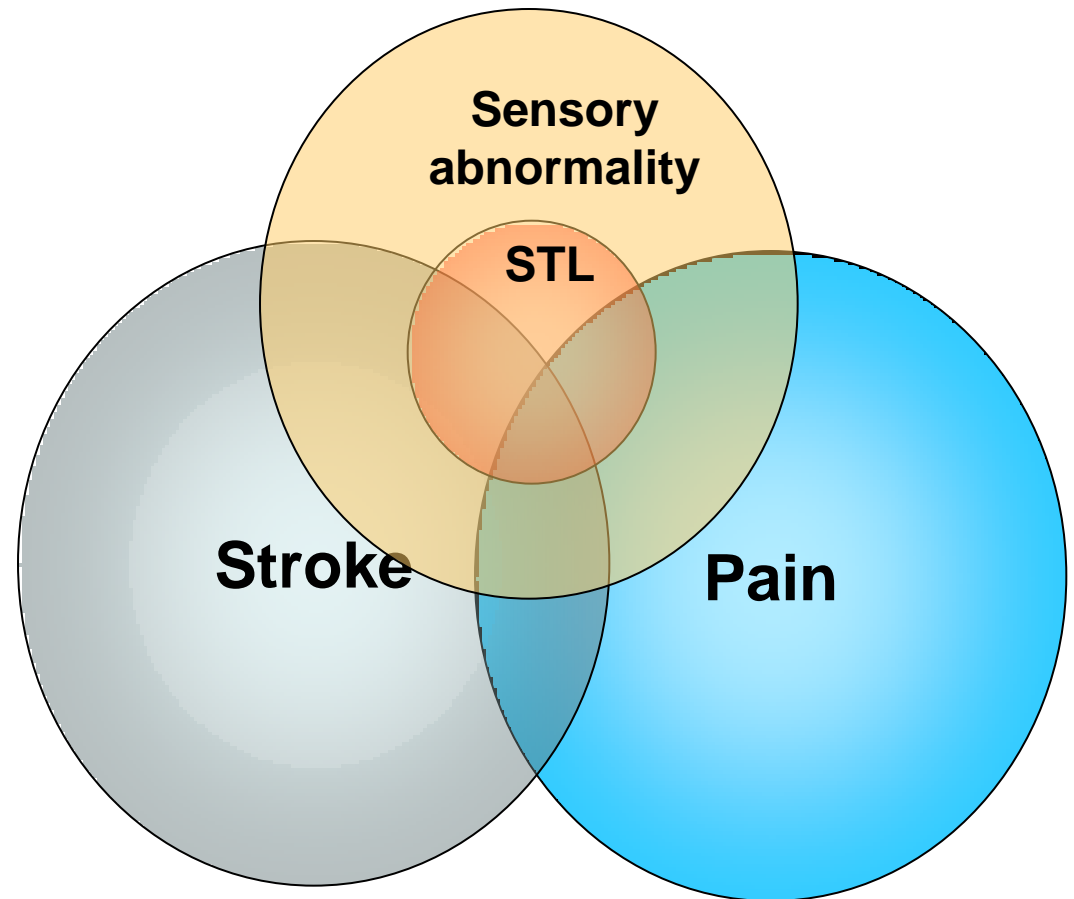
Central pain

The epidemiology and characteristics of post stroke pain incl. CPSP is addressed in two ongoing studies:

Retrospective

Prospective

Criteria for CPSP will affect the incidence of CPSP



Criteria for CPSP

1. Development of pain after stroke onset

1A Development of pain after onset of stroke, not attributed to headache, shoulder pain or joint pain

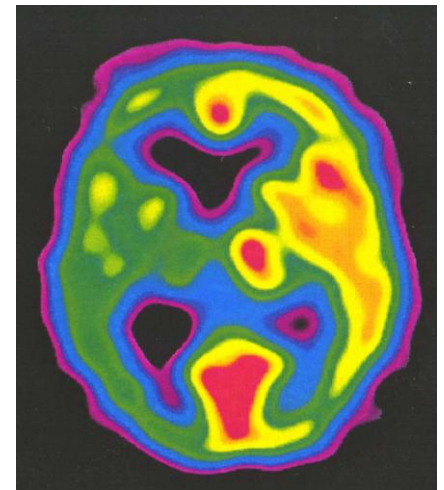
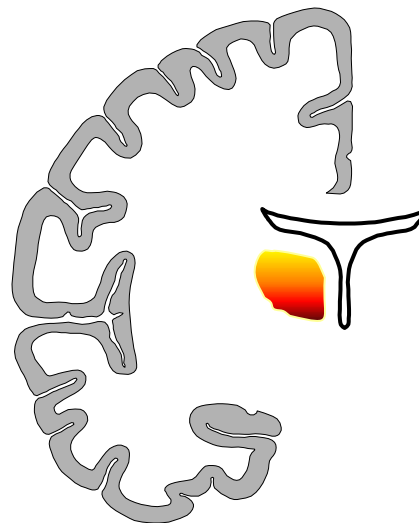
2. Overlap between areas of altered sensation and pain

3. Plausible distribution of area of pain or altered sensation (unilateral or crossed)

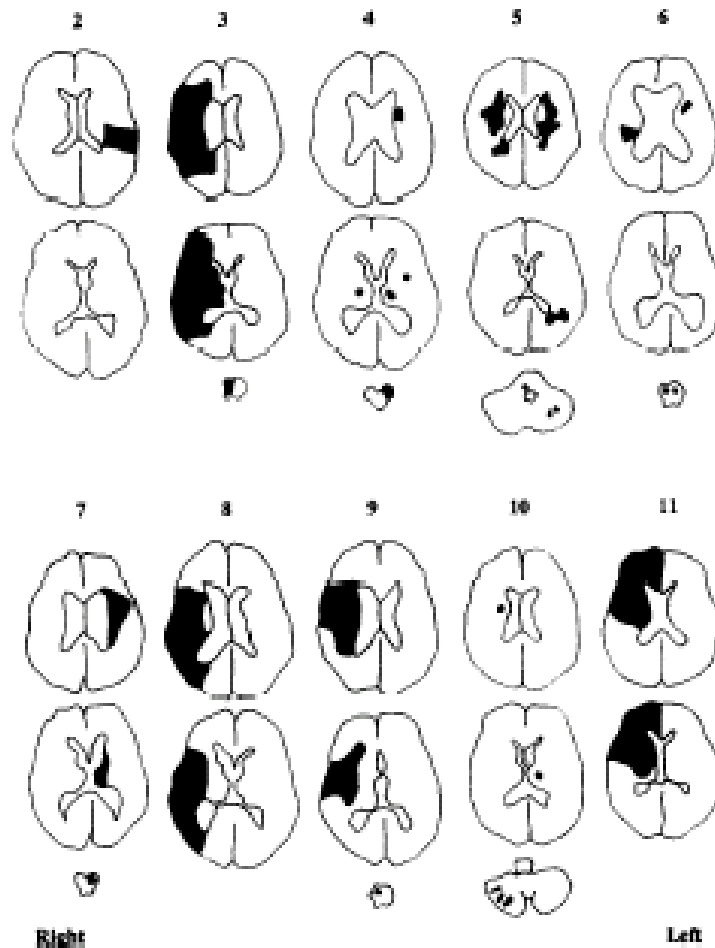
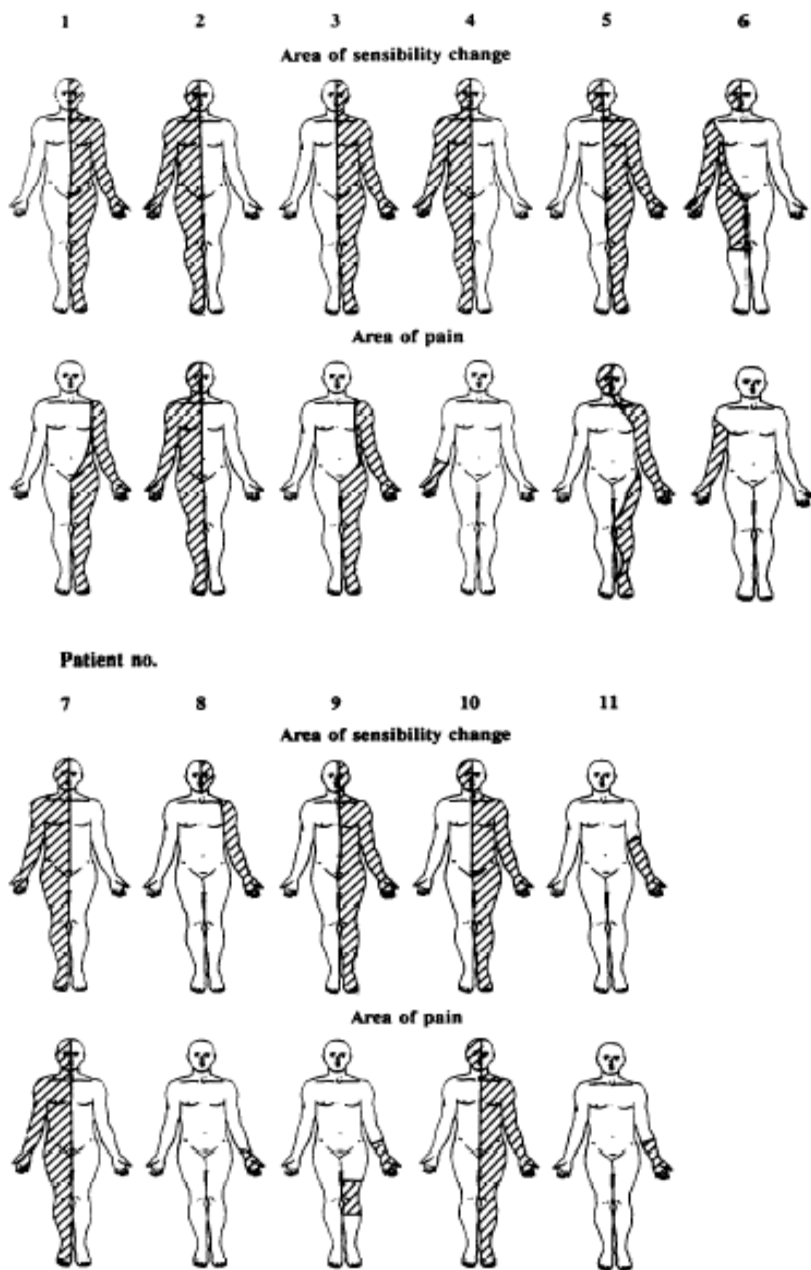
4. No other obvious source of pain

Central pain:

- Definition and causes
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- Mechanisms
- Management of central pain

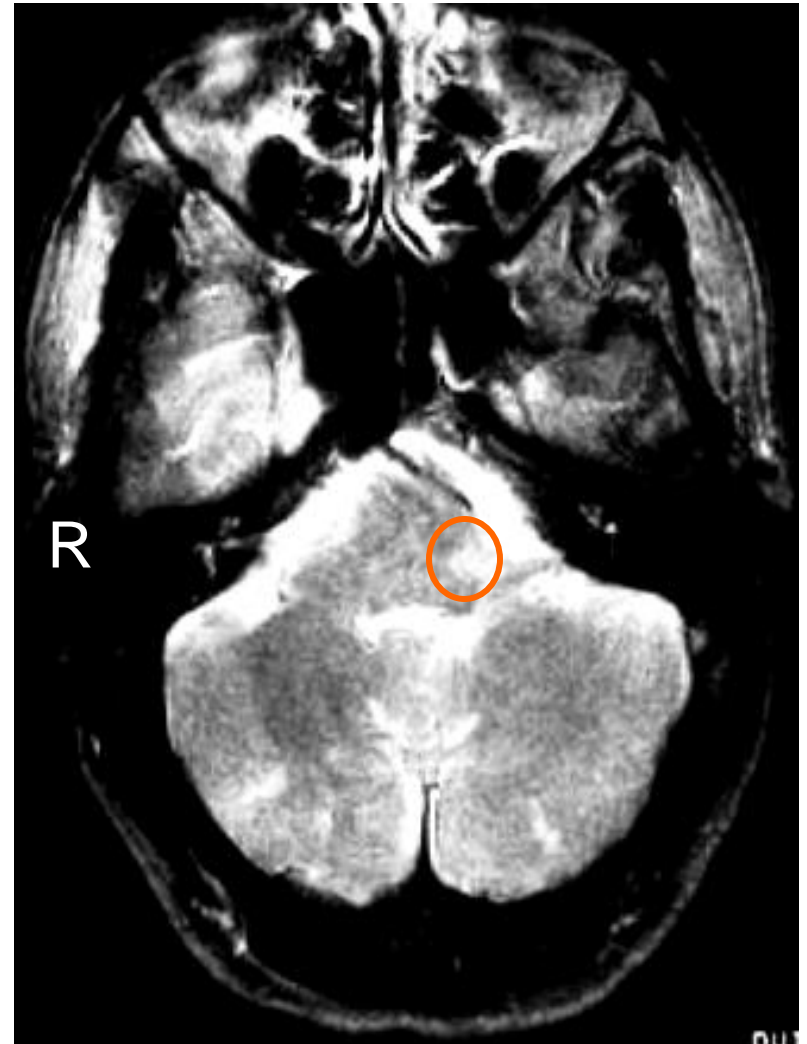
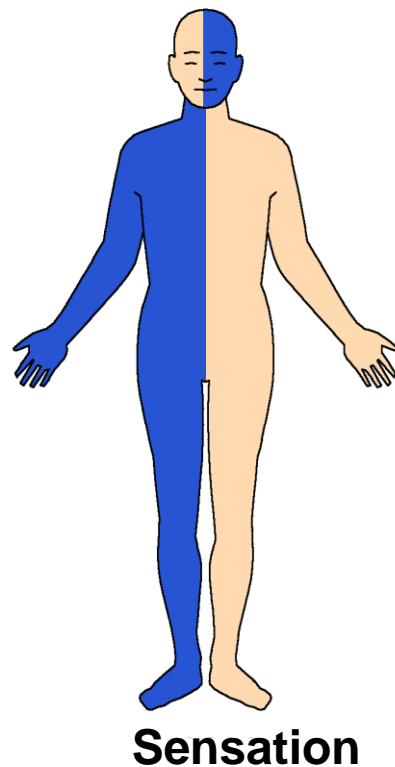
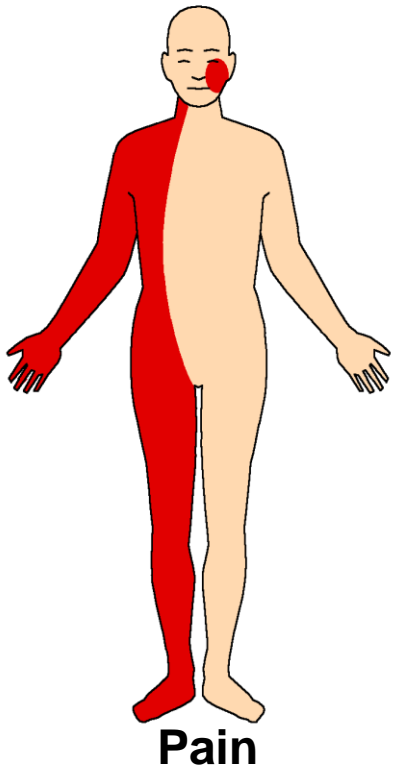


Stroke Pain: Distribution of Pain and sensory abnormality corresponds to brain territory destroyed by lesion



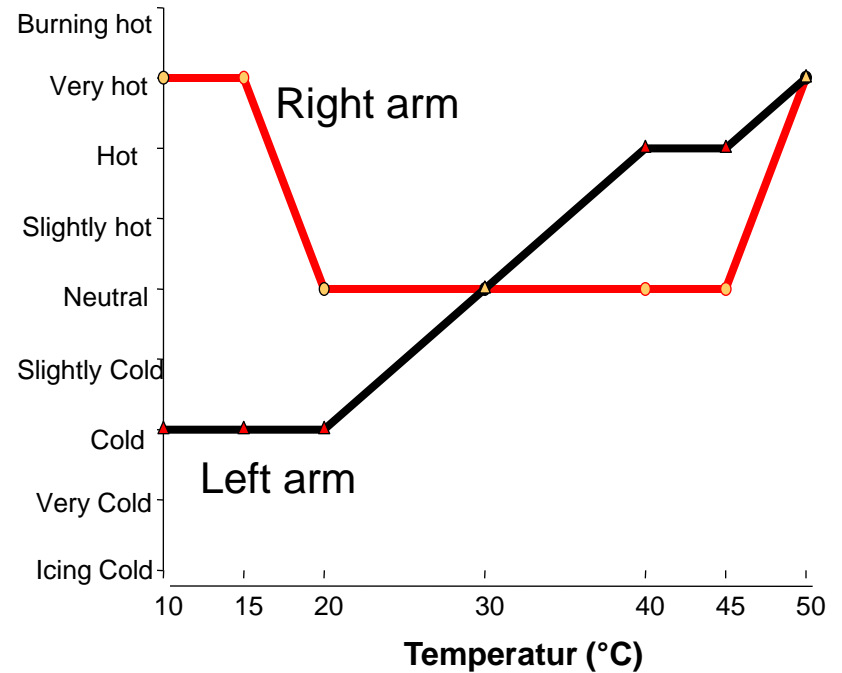
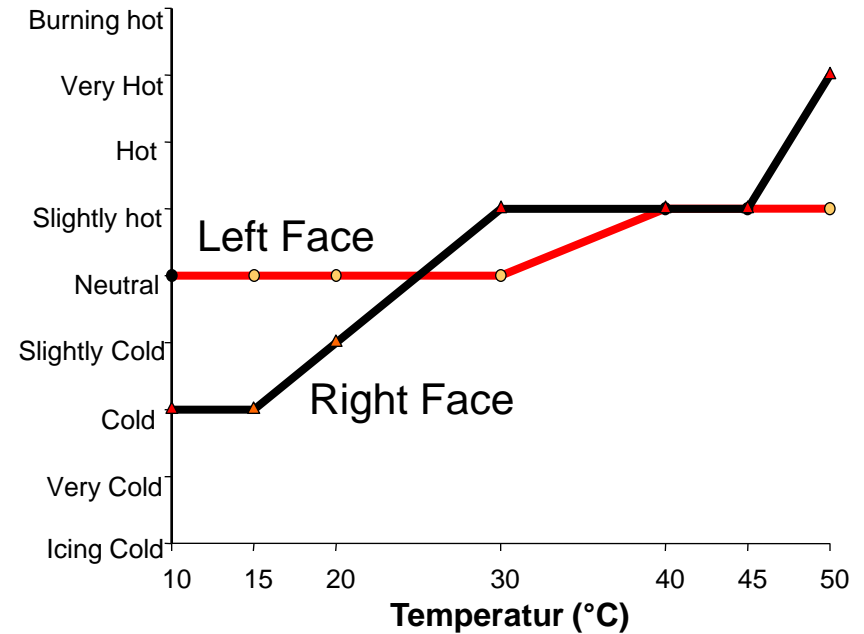
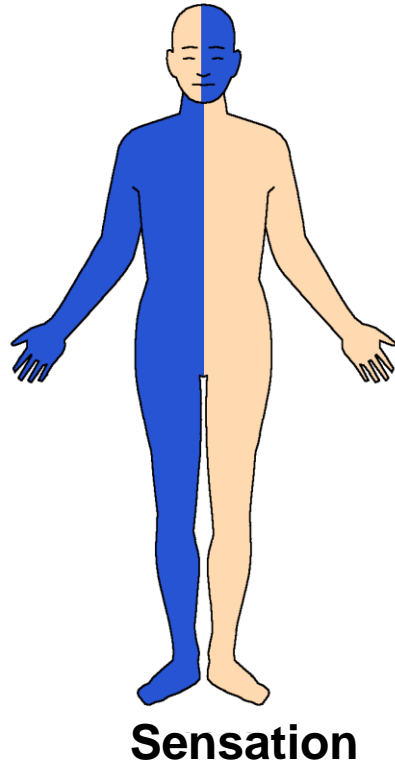
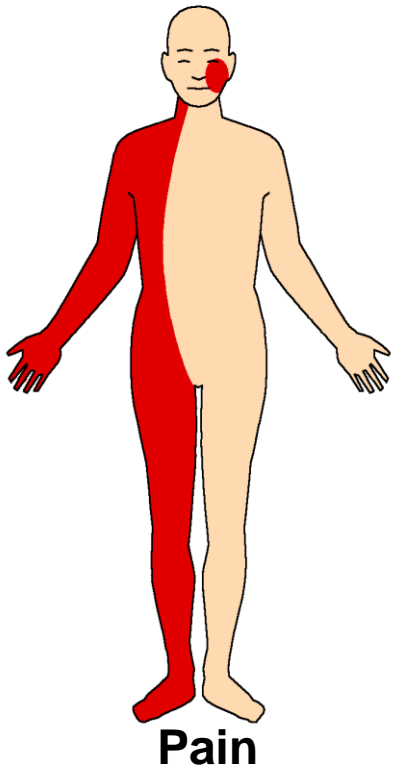
75 yr old M: Crossed central pain syndrome

- Age 68: shortlasting vertigo
- Age 72: L. brainstem infarction
- L. facial and R. hemibody pain
- Burning Pain evoked by touch

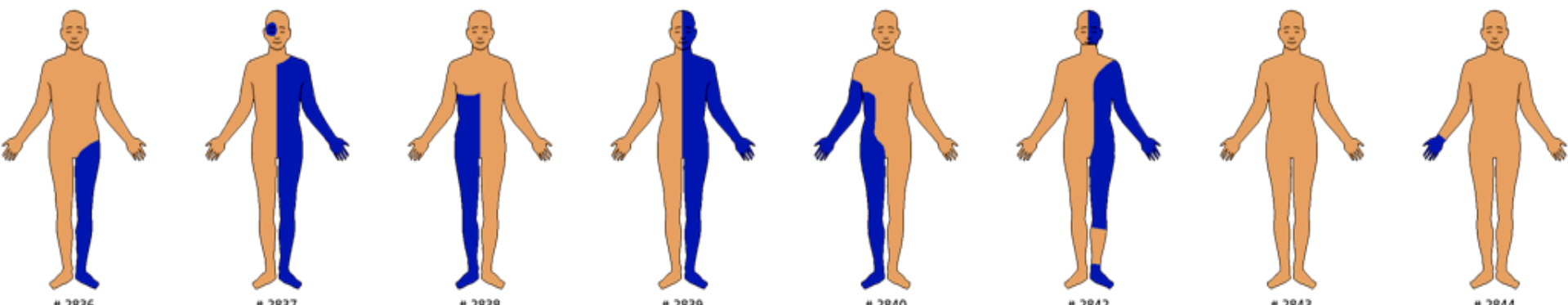
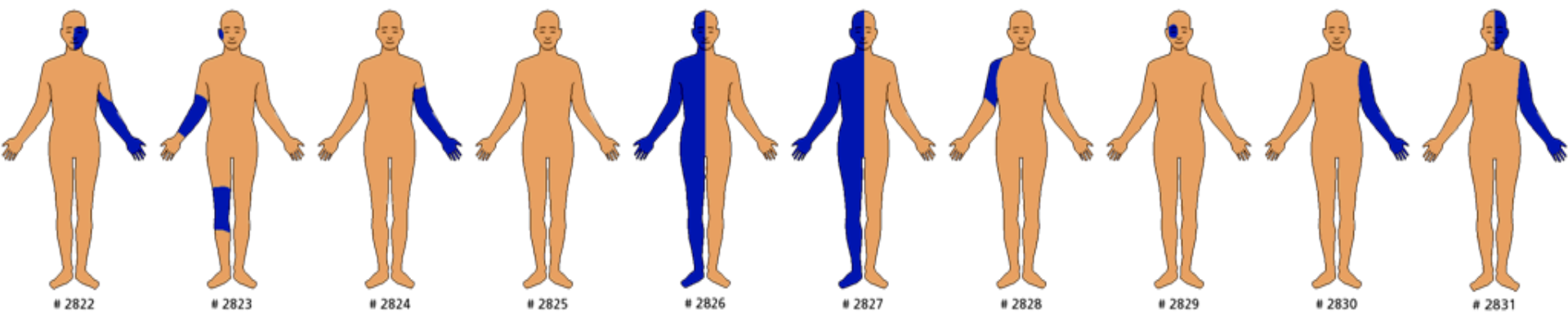
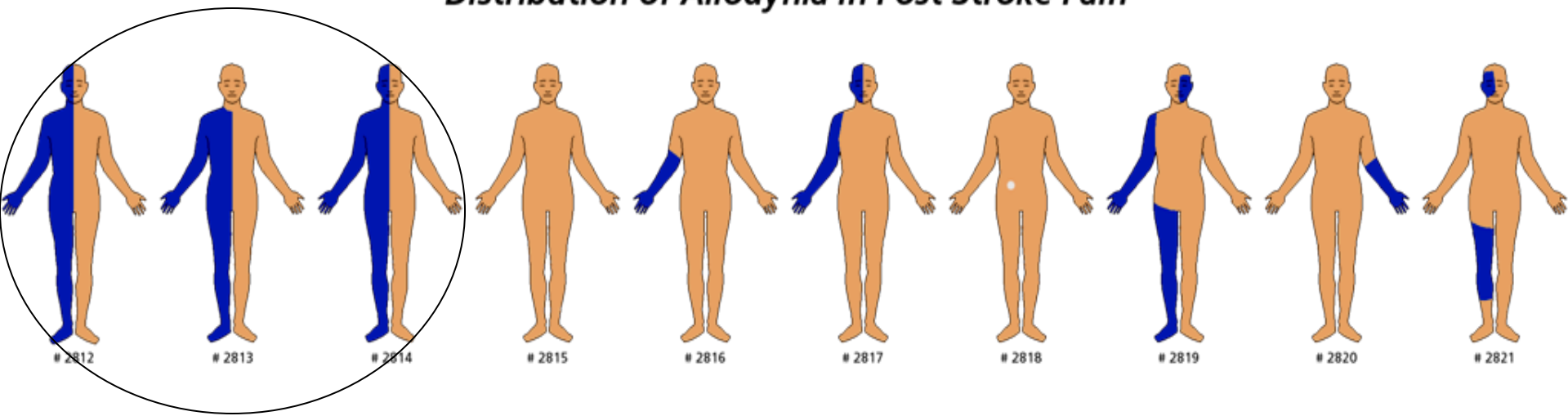


75 yr old M: L brainstem stroke

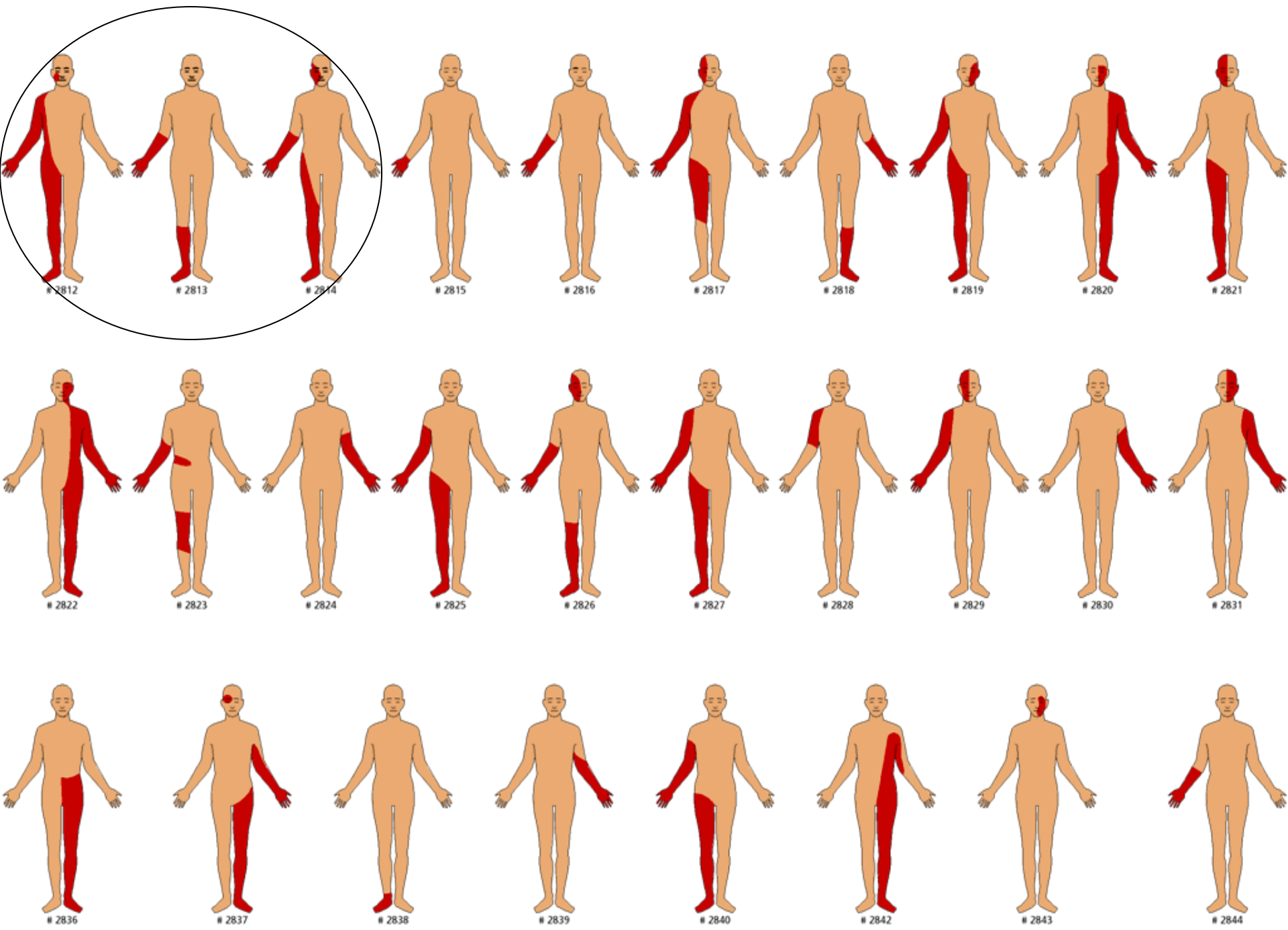
Crossed pain syndrome



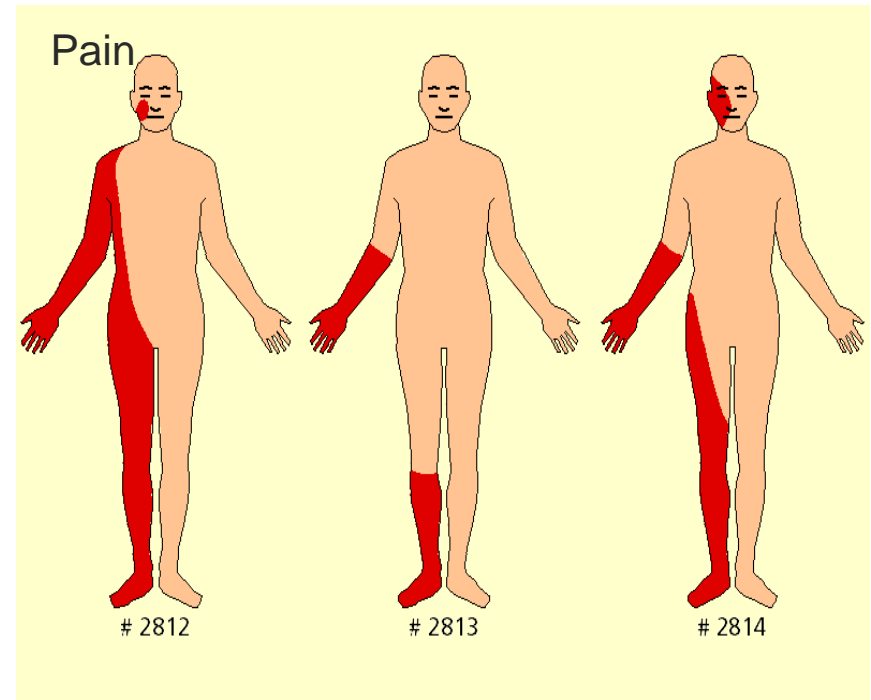
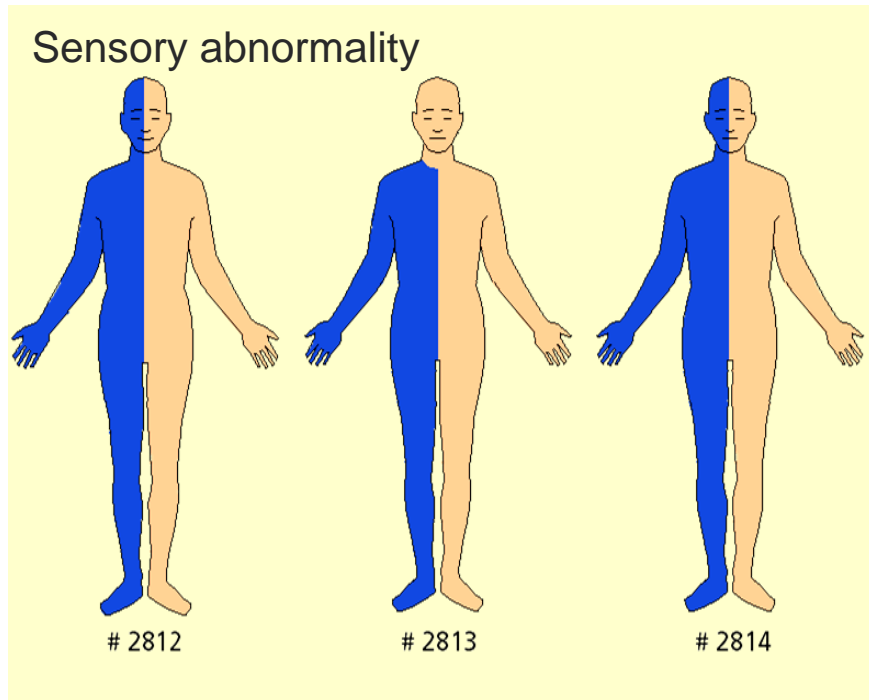
Distribution of Allodynia in Post Stroke Pain



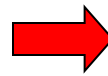
Distribution of Pain in Post Stroke Pain



Post Stroke: Central Pain and Sensory Abnormality



Neuropathic pain:
Pain distribution represent a
fraction of the deafferented
area



Combination of deafferentation and
clinical hypersensitivity suggest
hyperexcitability in neurons that
have lost their normal input

Central Post Stroke Pain:

Touch allodynia



Touch	No Pain N=71	Pain N=16	p
Normal	5(7%)	2(3%)	NS
Decreased	65(92%)	12(75%)	NS
Increased	1(1%)	1(16%)	NS
Allodynia	0	9(56%)	<0.001
Dysesthesia	0	8(50%)	<0.001
Allodynia or dysesthesia	0	12(75%)	<0.001

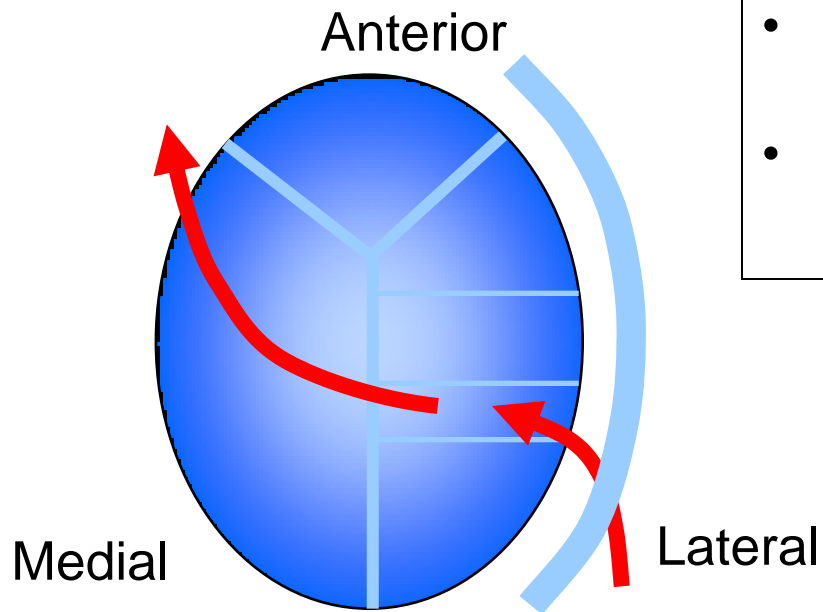
Central Post Stroke Pain: Cold Allodynia



Temp 20 °C	No Pain N=71	Pain N=16	p
Normal	28(39%)	1(6%)	NS
Decreased	37(52%)	8(50%)	NS
Increased	6(8%)	7(44%)	<0.001
Allodynia	0	9(56%)	<0.001
Dysesthesia	2(3%)	12(75%)	<0.001
Allodynia or dysesthesia	2(3%)	14(88%)	<0.001

Central post stroke Pain: Mechanisms

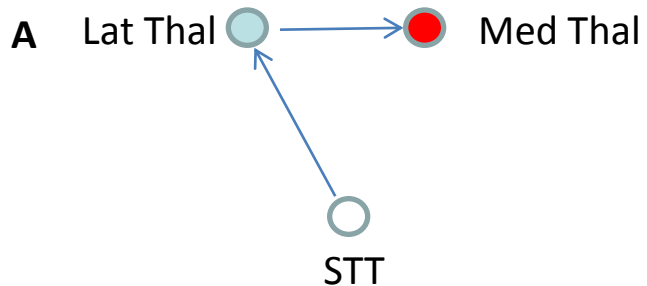
Thalamus



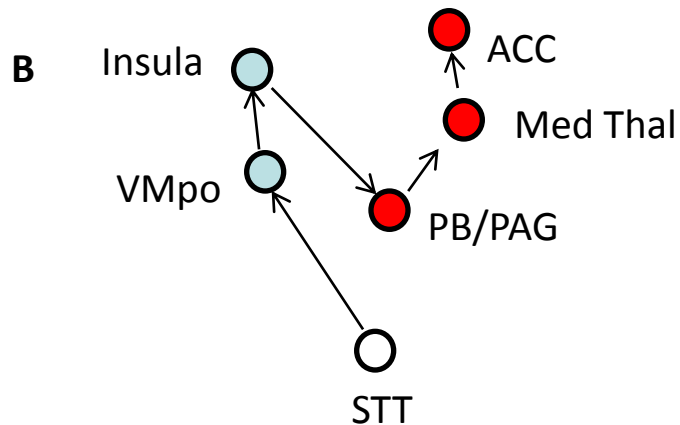
Reticular N

- Pain within area of sensory abnormality
- Pain area: Fraction of sensory loss
- Sensory loss and hypersensitivity.
- Loss of input to thalamus → Pain in corresponding body territory

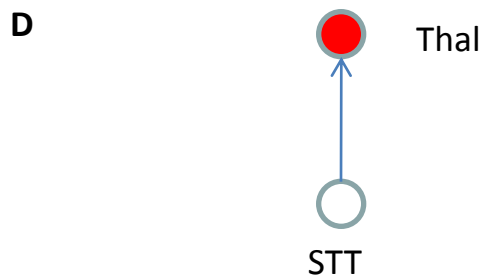
Loss of input disinhibition
 medial thalamus (Head and Holmes 1911)



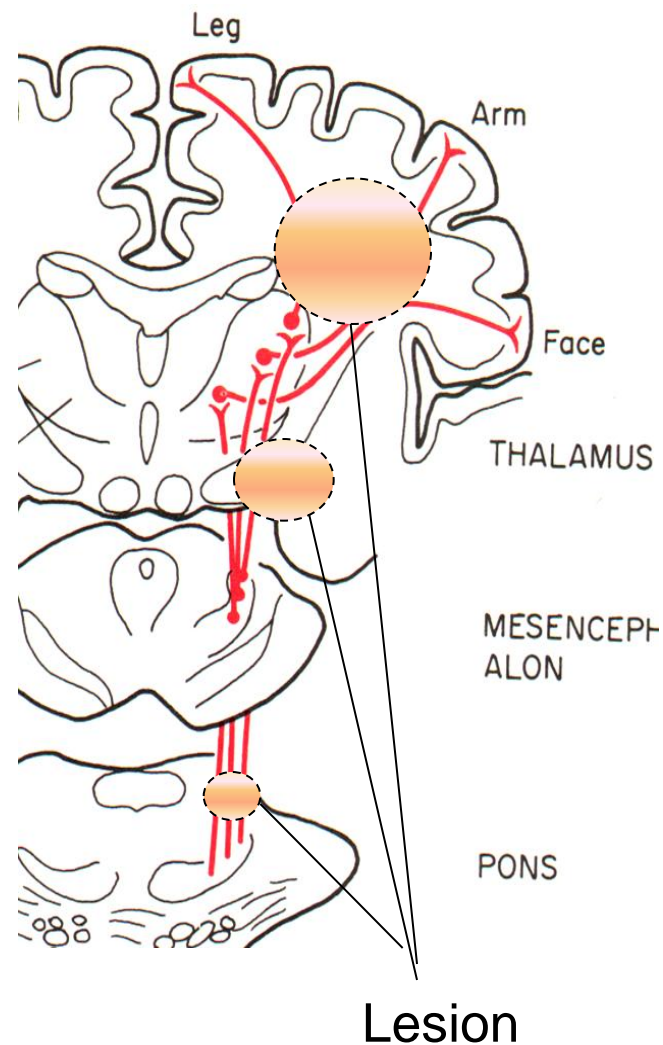
Loss of cold input to insula disinhibition
 medial thalamus (Craig et al., 2000)



Loss of ascending input to thalamus
 Bursting activity by low Ca spikes
 (Wang & Thompson 2008).

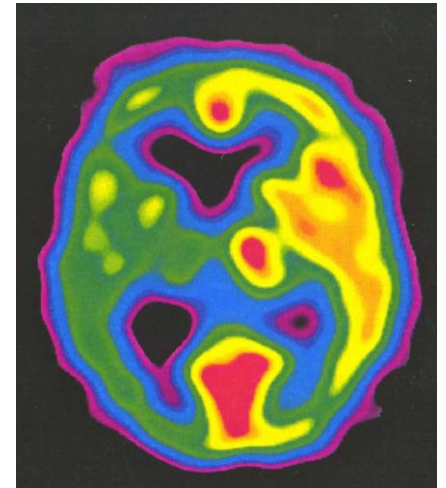
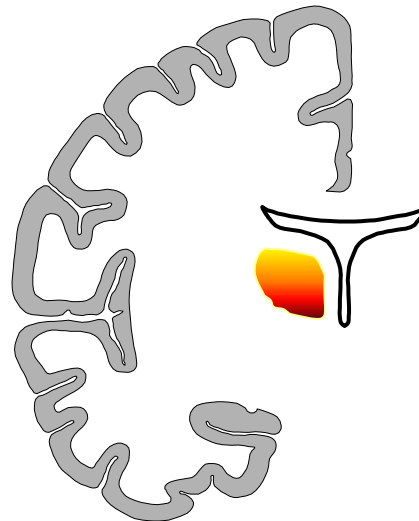


Central pain: Mechanisms



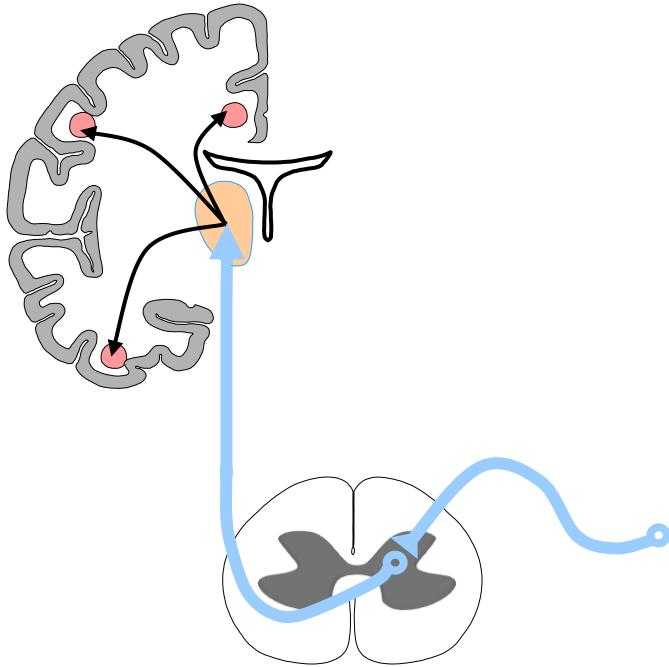
Central pain:

- Definition and causes
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Management of central pain

– reduce sensitization



Pharmacological treatment

Stimulation therapy

- TNS
- Deep brain stimulation
- Motor cortex stimulation

Psychological / other treatments

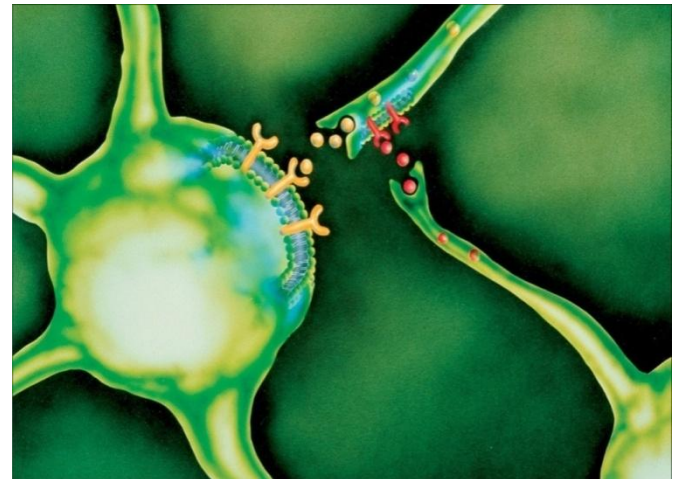
- Cognitive behavioural therapy
- Hypnosis *etc*
- Physiotherapy
- Educational programmes
- Other

Treatment Principles

- Reduce peripheral sensitisation
- Reduce activity in DRG
- Reduce ectopic activity
- Decrease central sensitisation
- Reduce central facilitation
- Increase central inhibition

Neuropathic Pain: Pharmacology

- **Antidepressants**
 - Tricyclic antidepressants
 - SSRI
 - SNRI
- **Anticonvulsants**
 - Gabapentin
 - Pregabalin
 - Valproic acid
 - Topiramate
 - Carbamazepine
 - Oxcarbazepine
 - Phenytoine
 - Lamotrigine
- **Opioids**
 - Morphine
 - Oxycodone
 - Tramadol
- **NMDA antagonists**
 - Memantine
 - Amantadine
 - Dextromethorphan
- **Cannabinoids**
- **Topicals**
 - Lidocaine
 - Capsaicin
- **Other**
 - Levetiracetam
 - Botulinum toxin



Central Pain Management :

Mechanisms of drugs

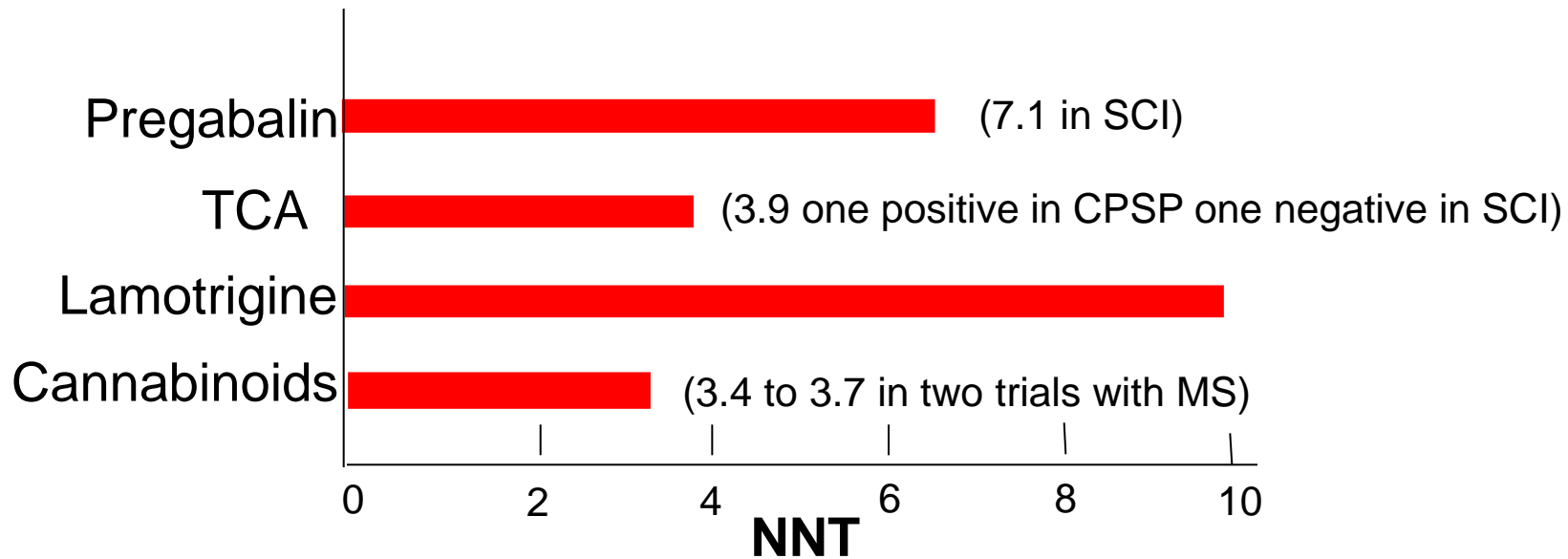
Pharmacological Agents

Lidocaine	Non-specific sodium channel blockade
Mexiletine	Non-specific sodium channel blockade
Oxcarbazepine	Non-specific sodium channel blockade
Lamotrigine	Specific sodium channel blockade
Gabapentin	Binding to $\alpha_2\delta$ -subunit calcium channel
Pregabalin	Binding to $\alpha_2\delta$ -subunit calcium channel
Valproic acid	GABAergic, sodium channel blockade
Dextromethorphan	NMDA-antagonist
Amitriptyline	NA and 5-HT reuptake inhib., NMDA-antagonist, Na block
Duloxetine	NA and 5-HT reuptake inhibitor
Morphine	μ -opioid receptor agonist
Cannabinoids	Cannabinoid receptor interaction

Central Post stroke Pain: Controlled clinical trials

Mechanism	Drug Dose	Study	Design N	Result	NNT (95% CI)
Na ⁺ Channel blocker	CBZ 800 mg	Leijon and Boivie 1989	Cross-over 15	Cbz= pla	3.4 (2-105)
5-HT and NA reuptake inhibitor	Amitriptyline 75	Leijon and Boivie 1989	Cross-over 15	Ami> PI	1.7 (1-3)
Na ⁺ Channel Blocker glutamate inhibitor	Lamotrigine > 200 mg	Vestergaard et al. 2001	Cross- over 30	Ltg>pla	NA
$\alpha_2\delta$ binding Ca ⁺⁺ channel	Pregabalin 300-600 mg	Vranken et al. 2007	Parallel 19	Preg > PI	3.3 (2-15)

Central Post stroke Pain: Evidence recommendation



Recommendation:

Level A: Pregabalin (SCI) Cannabinoid (MS)

Level B: Lamotrigine, Gabapentin

Level B no effect: Valproate and mexilitine (SCI)

Level C: Opioids



Pain 118 (2005) 289–305

PAIN

www.elsevier.com/locate/pain

Research papers

Algorithm for neuropathic pain treatment: An evidence based proposal

N.B. Finnerup^{a,*}, M. Otto^{b,1}, H.J. McQuay^{c,2}, T.S. Jensen^{a,3}, S.H. Sindrup^{b,4}

^aDepartment of Neurology, Danish Pain Research Centre, Aarhus University Hospital, Aarhus Sygehus, Noerrebrogade 44, Aarhus 8000, Denmark

^bDepartment of Neurology, Odense University Hospital, Sdr. Boulevard 29, Odense 5000, Denmark

^cPain Relief Unit, Churchill Hospital, Oxford OX3 7LJ, UK

Received 5 May 2005; received in revised form 14 July 2005; accepted 8 August 2005

1966-April 2005:

105 RCTs

59 (56%) cross-over

46 (44%) parallel

18th Jan 2010:

168 RCTs

79 (47%) cross-over

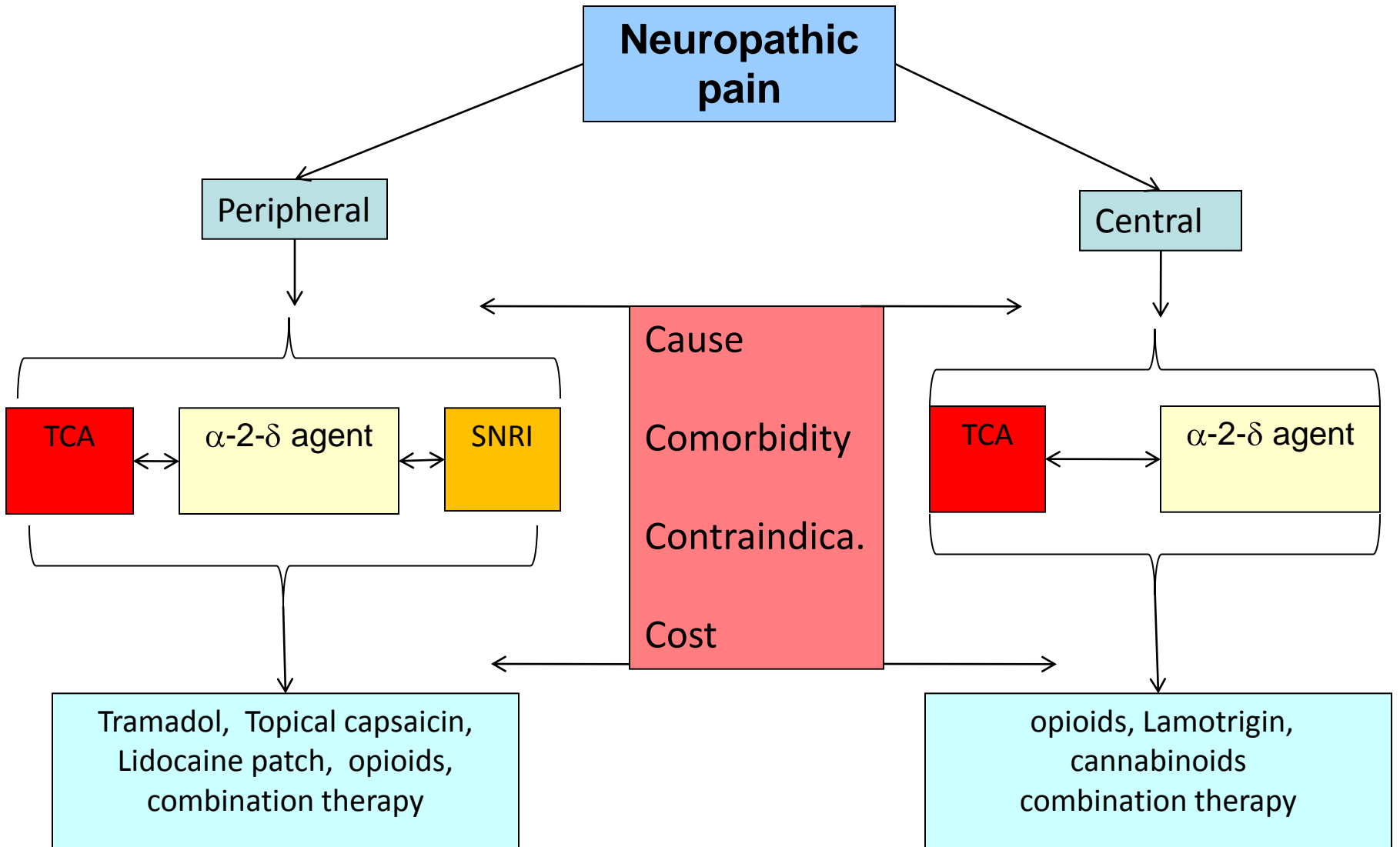
89 (53%) parallel

Increase:

60%

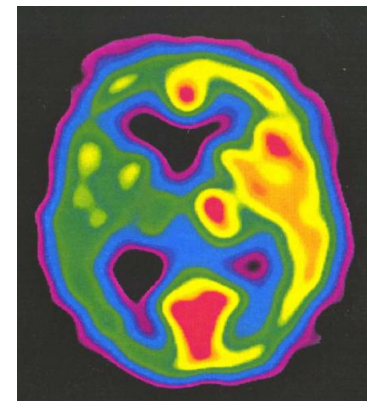
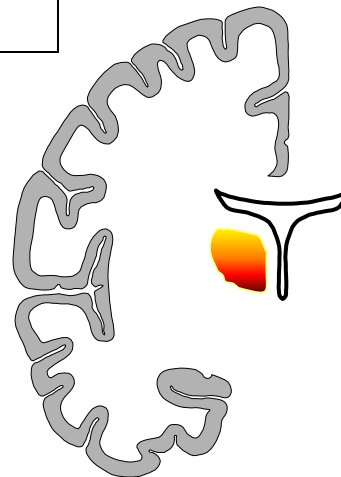
34%

93%



Conclusion: Post stroke Pain

- Post stroke pain different types of pain
- Central pain not uncommon.
- Clinical signs of neuronal hyperexcitability
- Pathophysiology hypothetical
- Pharmacological modulation with anti-hyperexcitable compounds may be useful



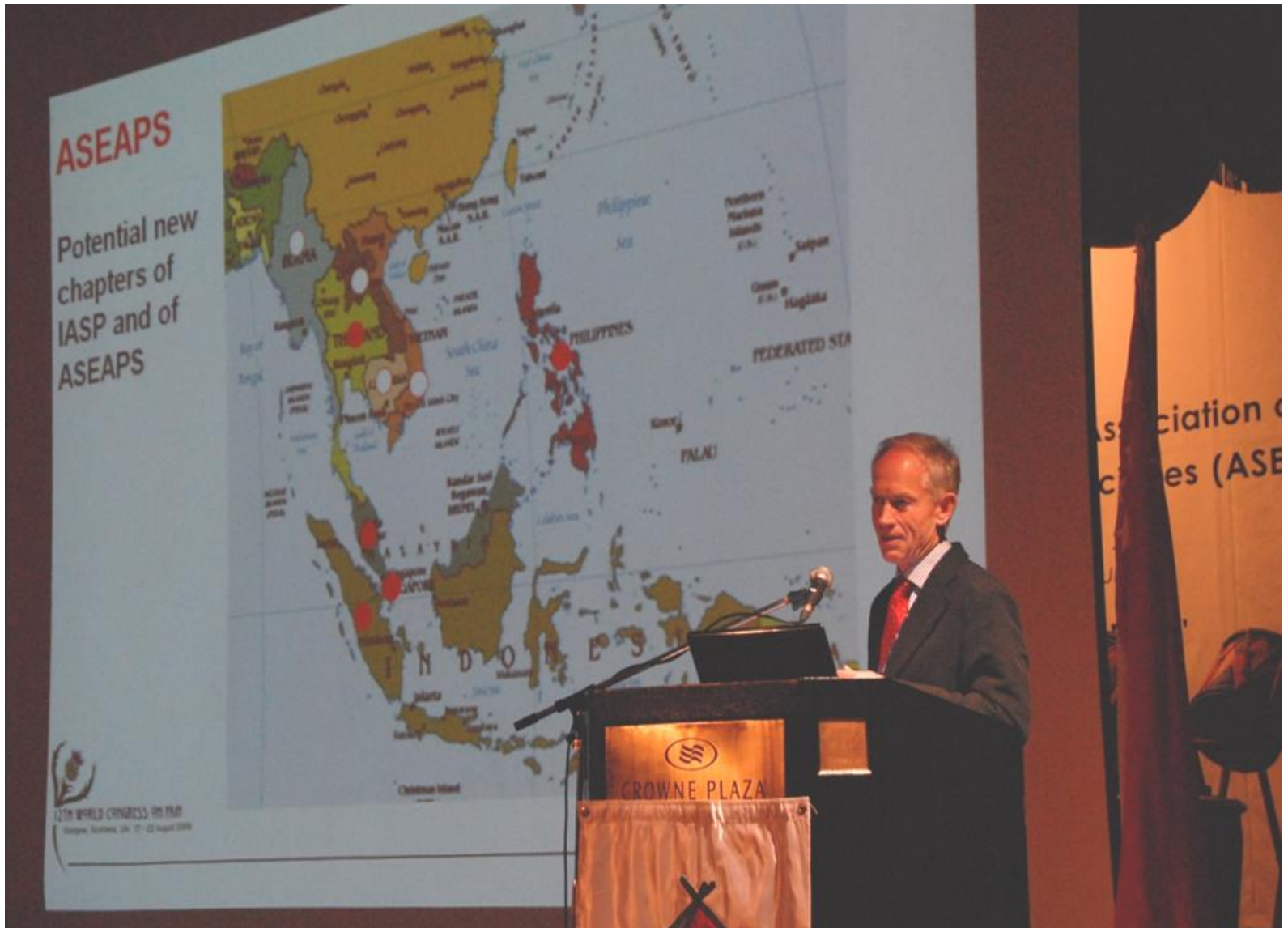


Thanks to all collaborators at DPRC:

Birgitte Brandsborg, Erisela Querama, Lene Vase, Lone Nikolajsen, Anders D Kristensen, Hanne Gottrup, **Nanna Finnerup**, **Cathrine Baastrup**, **Henriette Klit**, Lise Gormsen, Astrid Terkelsen, Annette T. Møller, Helle O. Andersen, Camilla Maersk-Møller, **Anne Hansen**, Lene Christensen, Casper Skau-Madsen, Kaare Brinck, Paal Karlsson



Opening speech from IASP President the 2nd ASEAPS congress Kuala Lumpur

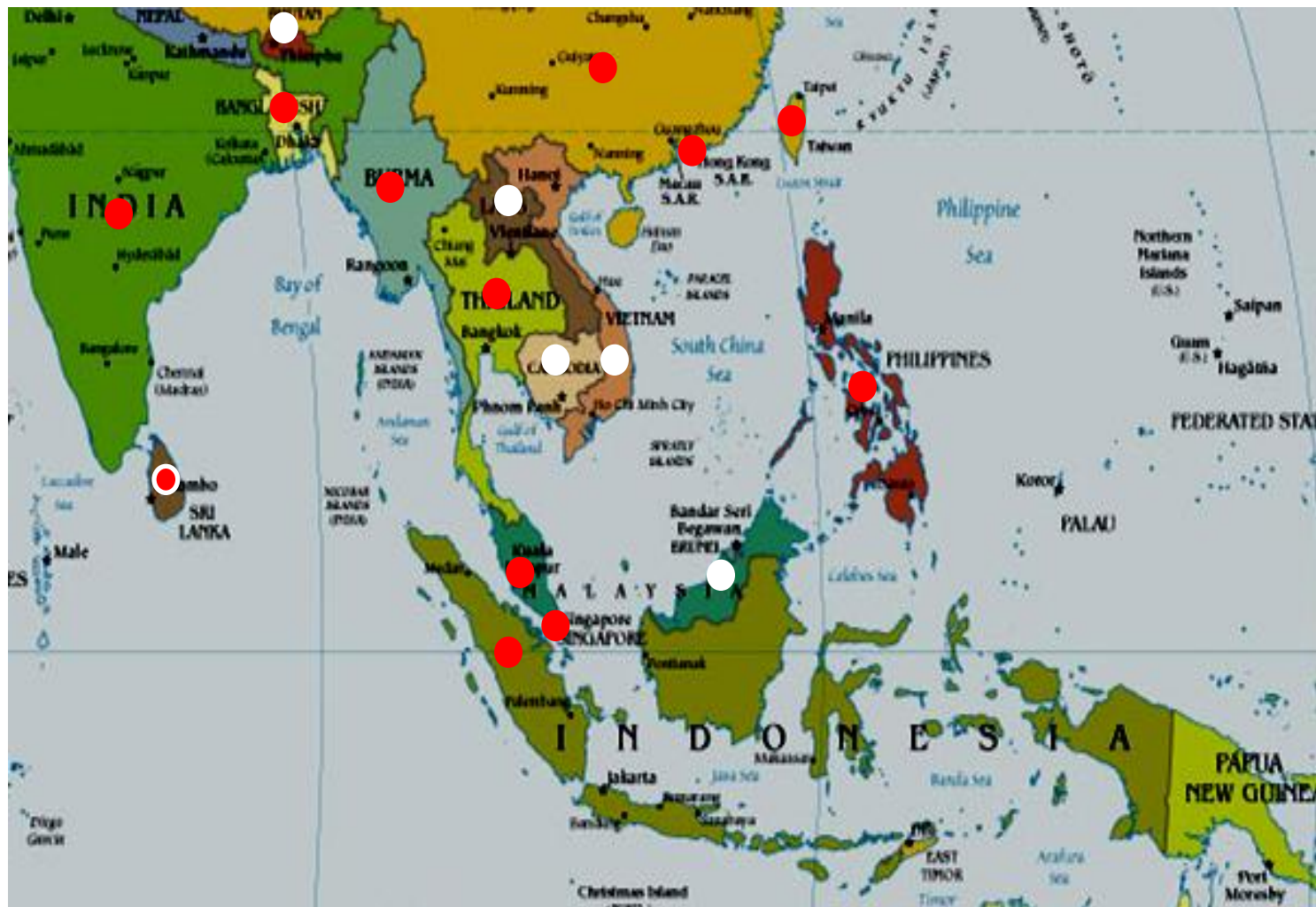


IASP and South East Asia

What can IASP do ?

Countries with IASP chapters ●

Countries without IASP chapters ○



**IASP send its warm wishes
to:**

Hong Kong Pain Society

Troels S. Jensen

www.iasp-pain.org

See You in Montréal August 2010





Thanks to all collaborators at DPRC:

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