CRPS: Clinical sub-typing and Precision Medicine

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Conflicts

- Chair, International Research
- Consortium for CRPS
- Chair, research committee of the RSDSA
- Consultant to St Pancras, London
- My funding comes from a private not-for profit foundations
- Patient Advocacy

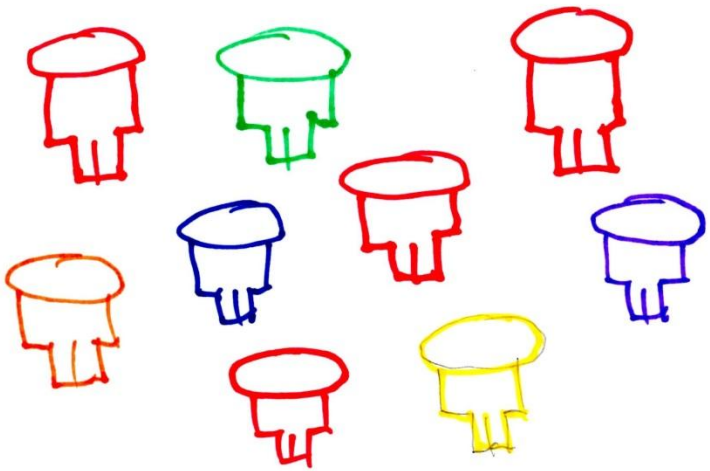
Precision Medicine

- A process where a diagnosis is based on an understanding of specific and (hopefully) objective mechanisms causing disease. These mechanistic sub-types are then targeted by (hopefully) RCT proven therapies.
- The reality is that often we must use less objective identifiers and empiric treatments

‘RSD’: Pain and Autonomic Dysfunction

Pre-Criteria

“I know it when I see it”



Diagnosis of CRPS: First IASP Criteria

Appendix A IASP diagnostic criteria for Complex Regional Pain Syndrome

(1) The presence of an initiating noxious event, or a cause of immobilization.

(2) Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.

(3) Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.

(4) This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Janig et al 1996

Solution:

- Survey
- Consensus
- Validate: Use statistically derived schemes using internal and external validation to improve specificity, while attempting to conserve as much sensitivity as possible.
- Re-Consensus, Re-Validate etc (15 yr)

Harden, Bruehl et al 1999
Harden et al 2010

IASP ‘CRPS’criteria v2

We set out to develop a logical, statistically derived criteria, based on signs and symptoms that were common to CRPS patients, that can be acquired in any clinic, by any physician, needing no special equipment or training

Harden, Bruehl et al 1999 *Pain*, 2010 *Pain Med*

The 'Budapest' Criteria

Table 4
Proposed experimental revision of CRPS diagnostic criteria

(1) Continuing pain which is disproportionate to any inciting event
(2) Must report at least one symptom in each of the four following categories
Sensory: reports of hyperesthesia
Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
(3) Must display at least one sign in two or more of the following categories:
Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)
Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry
Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

Harden et al, 1999, 2010

Statistically derived factors*:

Table 2
Factors (and factor loadings) resulting from PCA of diagnostic and associated signs and symptoms of CRPS[a]

Factor 1	Factor 2	Factor 3	Factor 4
Hyperalgesia signs (0.75)	Temperature asymmetry symptoms (0.68)	Edema signs (0.69)	Decreased range of motion signs (0.81)
Hyperesthesia symptoms (0.78)	Color change signs (0.67)	Sweating asymmetry signs (0.62)	Decreased range of motion symptoms (0.77)
	Color change symptoms (0.52)	Edema symptoms (0.61)	Motor dysfunction signs (0.77)
			Motor dysfunction symptoms (0.61)
			Trophic symptoms (0.52)
			Trophic signs (0.51)

[a] Note: PCA, Principal components analysis. As expected, allodynic signs loaded most strongly on Factor 1 (0.44), but did not meet the criteria for inclusion in the factor (>0.50).

Harden. Bruehl et a very large International Research Group 1999, 2010
*Factor Analysis

• Diagnostic criteria (Budapest)

Clinical

Symptoms

- Factor 1 — Positive sensory symptoms
- Factor 2 — Vascular symptoms
- Factor 3 — Edema, sweating abnormalities
- Factor 4 — Motor, trophic changes

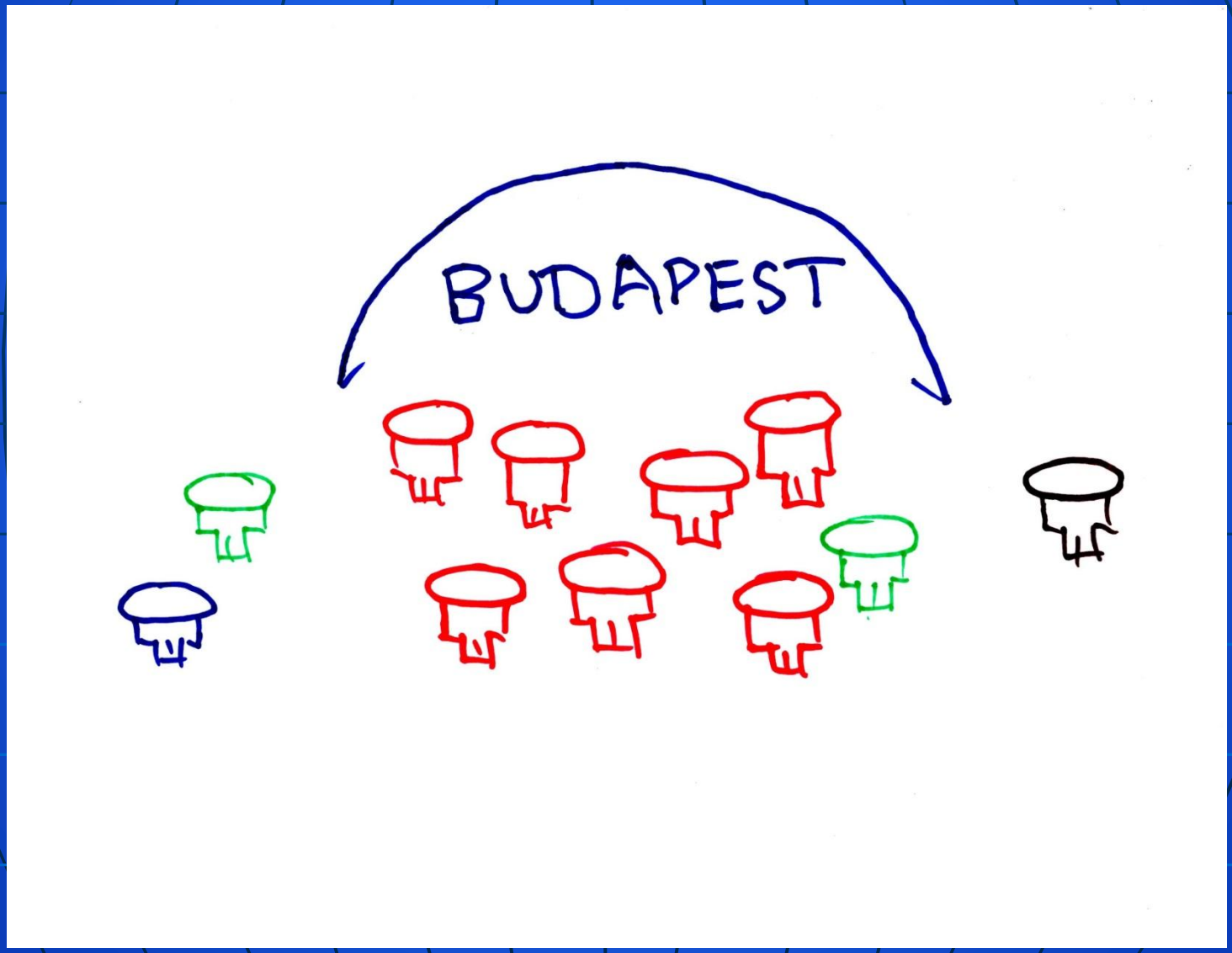
Signs

- Factor 1 — Positive sensory signs
- Factor 2 — Vascular signs
- Factor 3 — Edema, sweating abnormalities
- Factor 4 — Motor, trophic changes

≥ 3 symptoms Sens. 0.85 Spec. 0.69
≥ 2 signs

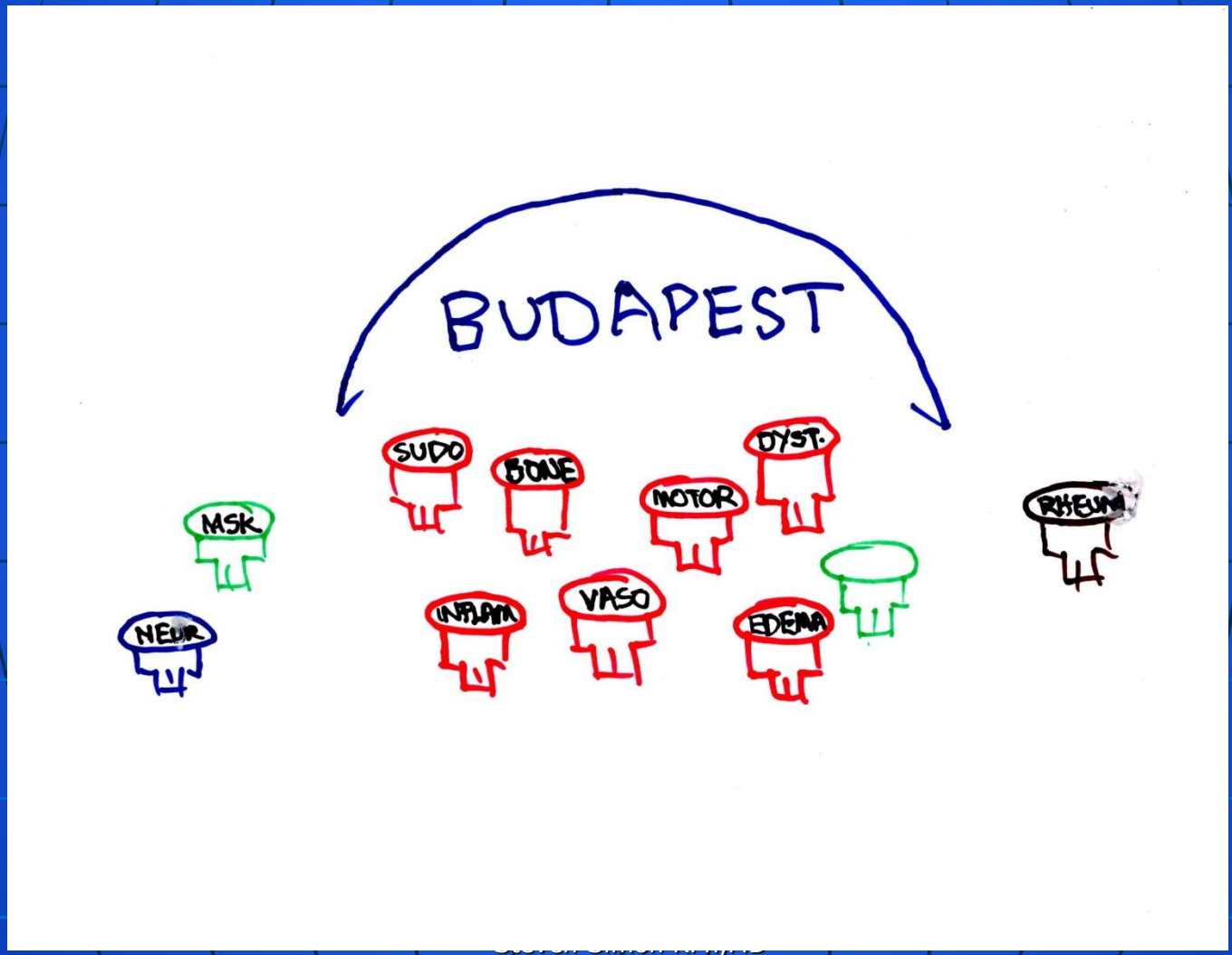
Positive sensory sx: allodynia, hyperalgesia,deep somatic allodynia
Signs at time of diagnosis

IASP II ‘Budapest Criteria’



Unfortunately, Researchers proceeded to use the Budapest criteria to identify subjects (inclusion criteria) for research *which failed for two decades to yield statistically significant results,* yet there was usually a subset/subtype that responded

Subsets: Research significant! Clinically significant!



Toronto and Valencia subtype meetings

Subtype/Subset Selected:

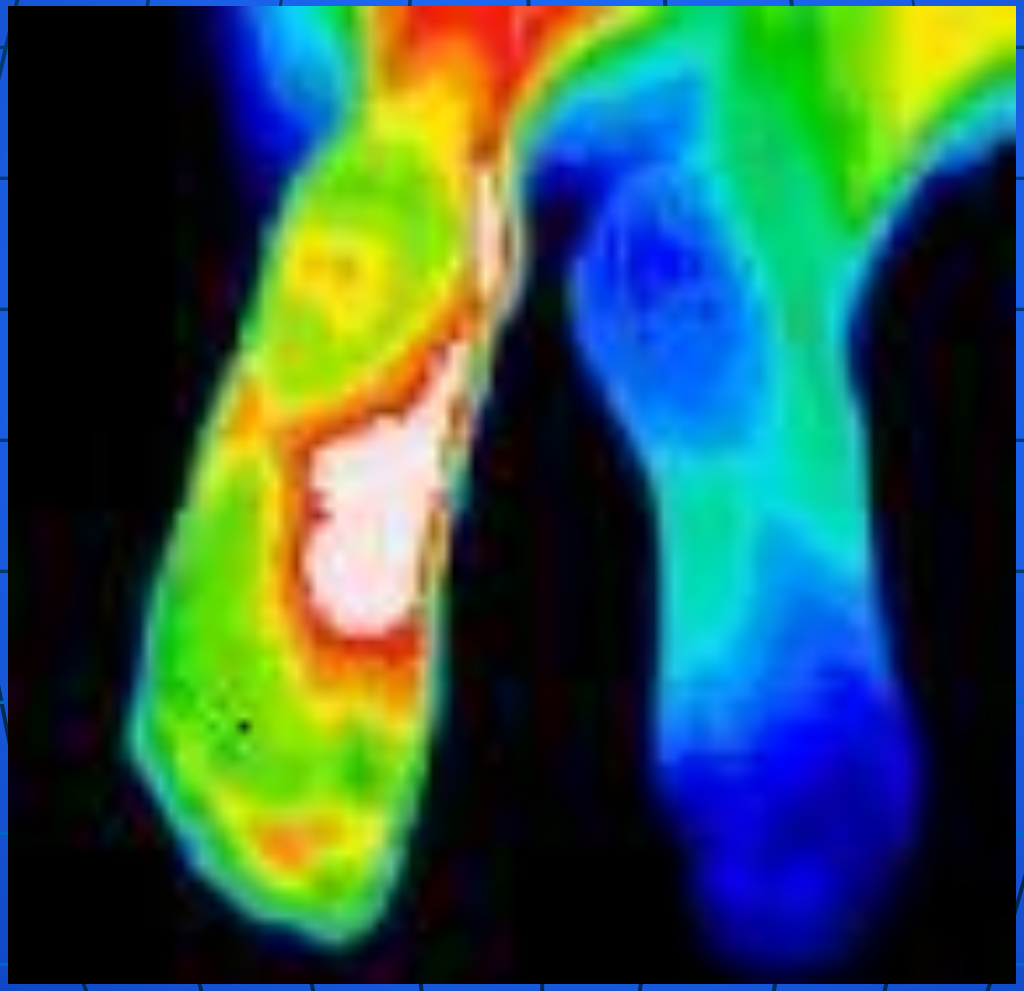
Cold versus Hot CRPS

for formal study> ongoing large International trial sponsored by RSDSA

Goebel et al 2017

Vasomotor changes

qThermography; ‘Fully Objective’



Proposed Clinically Significant Subtypes (usually more than one)

Examples:{mechanism} [identification, quantification] (empirical rx)

Hot Subset {e.g. inflammatory, SNS dysfunction} [qIRT] (steroids)

Cold {e.g. SNS dysfunction, periph sensitization [qIRT] (blocks, Ca+ blocker, etc)

4 PCA factors high pain; vasomotor; edematous, sudomotor ; dystrophic, motor abn.

Central Sensitization [fMRI, DTI]

Peripheral Sensitization [QST]

Limb Dysmorphic (mirror)

Auto-Immune

Abnormal response to 3phase Bone Scan(bisphosphonates)

Pronounced Affective Diseases

Specific Etiologies

Syndromes

Causalgia v RSD, NOS, "Spreading" etc etc

"Chronic Low Back Pain"

Radiculopathy
Discogenic
Myofascial
etc

Thus, Sub-typing not just relevant and important for research but

critical for 'precise' diagnosis clinically!

Objectify! Quantify!

fMRI*

Magnetoencephalography*

Dense Array Quantitative EEG*

Quantitative Telethermography*

Neurometry*

QST*

PET

SPECT

etc, etc…

Identify subtypes AND monitor therapy

Biomarkers, Objective tests….

Ultimately gold standard tests for identification of different clinical sets and subsets and measuring efficacy of tailored interventions=

"Precision Medicine"

Sudeck's atrophy

Figure 1. Fine-detail roentgenograms of the hands of a patient with the RSDS, showing the normal left hand (**left**) and characteristic patchy demineralization in the affected right hand (**right**).

Volumeter; ‘fully objective’

Measure Cytokines in Cutaneous Blisters

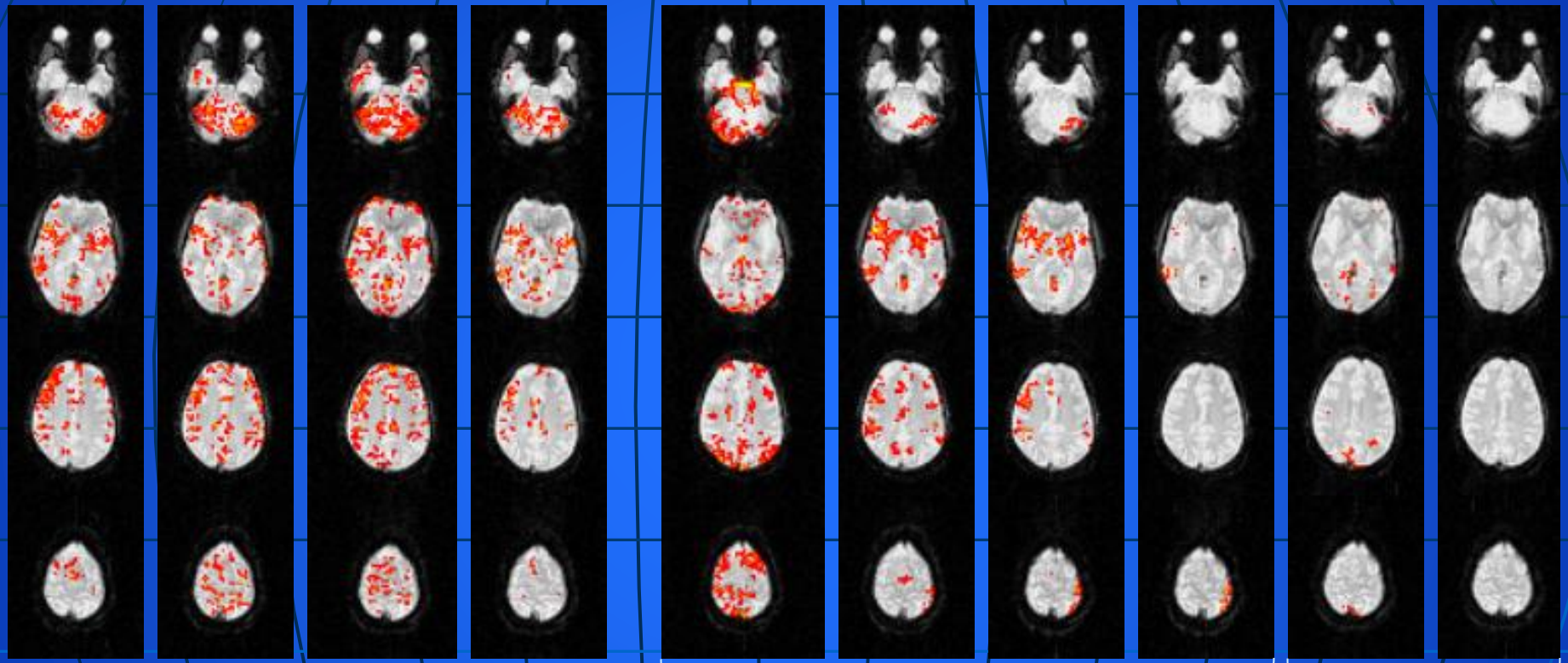
- Blister formation to measure
- mediators of inflammation

Huygen et al

3 Phase Bone Scan? How about Bone Densitometry

Using fMRI to 'Quantitate and Objectify Pain (?), study outcome

VAS: 7 8 9 8.5 3 2 2.5 1 1.5 1

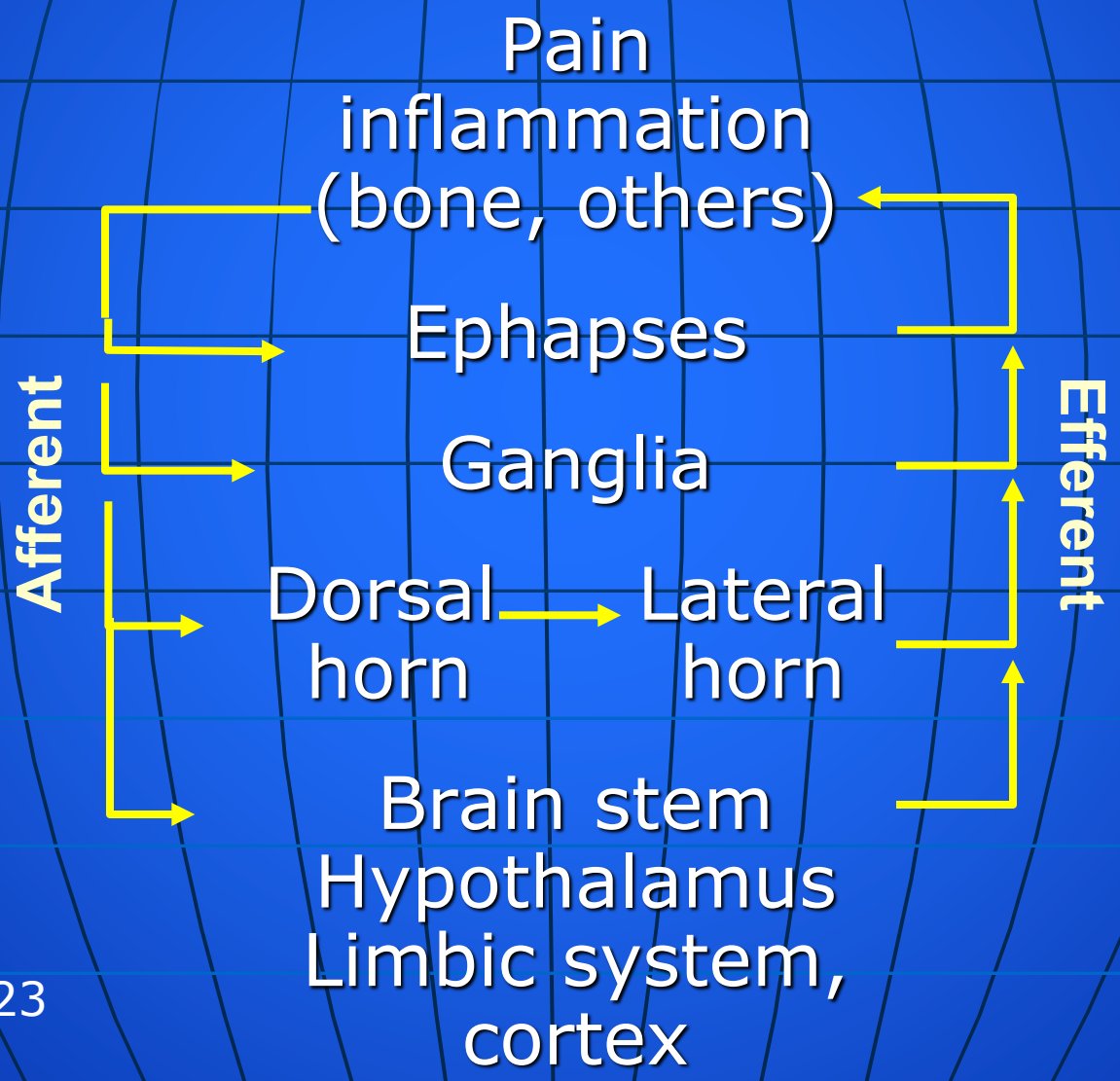


200 mg 'drug'

1 hour post-drug

3 hour post-drug

Hypothesis: CRPS maintained and reinforced by nested positive feed forward (afferent nociceptors), central nociplasticity and feed back (efferent motor and sympathetic nerves) loops*



*Harden 2023

Motor Disturbance

Bradykinesia

Hypothesis: CRPS maintained and reinforced by nested positive feed forward (afferent nociceptors) and feed back (efferent sympathetic nerves) loops

Today's dogma will be tomorrow's heresy…

D.J.Dalessio