The role of QST and skin biopsy in accelerating analgesic drug development: IMMPACT considerations

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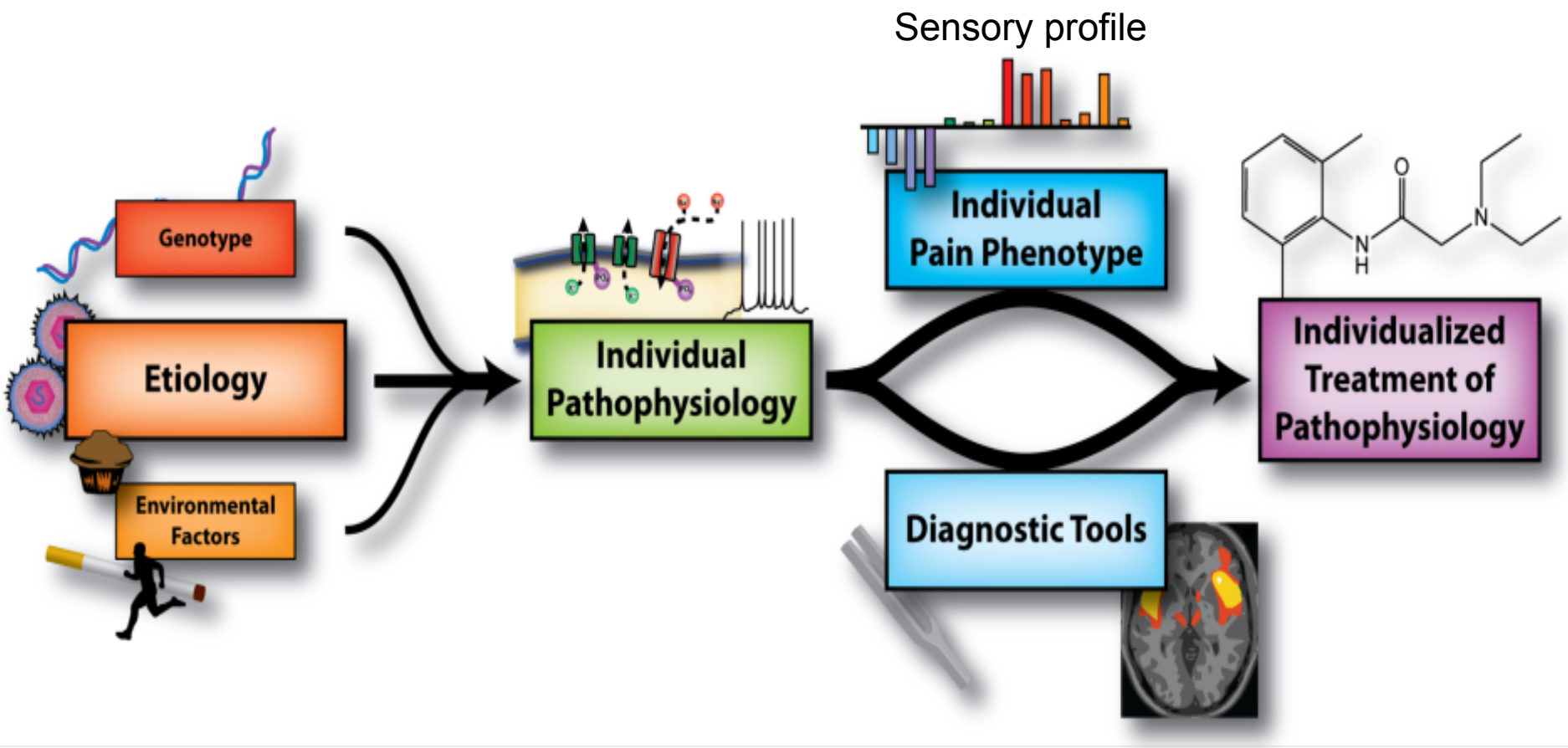
Mechanism / profile-based therapy



Von Hehn, Baron and Woolf 2012

Agenda

The sensory phenotype:
not a true biomarker - indirect clinical assessment

1. The sensory phenotype allows to subgroup patients

2. Sensory phenotypes reveal novel “druggable” targets

3. Sensory phenotypes show predictive validity in trials
   Clinical assessment tools for prediction

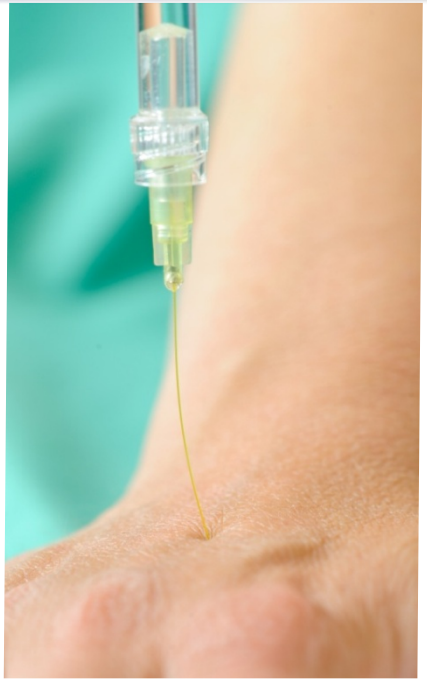
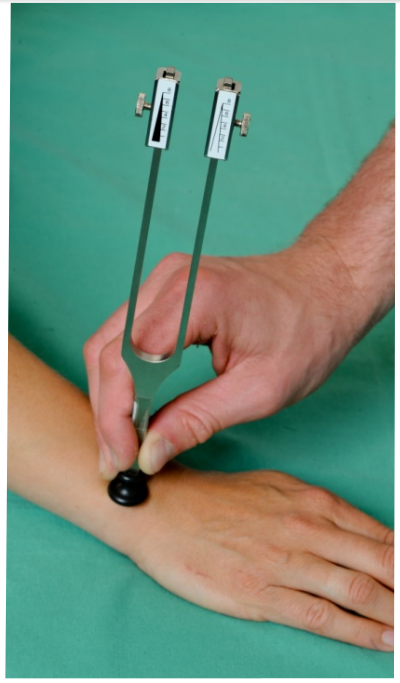
4. Sensory phenotype can be used as endpoints
   Clinical assessment tool for efficacy – response (surrogate endpoint)

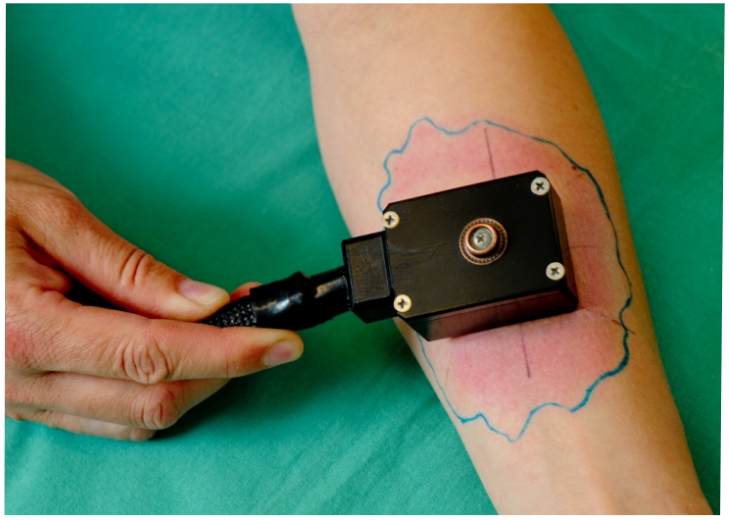
Agenda 1

The sensory phenotype allows to subgroup patients

Segmentation methods to subgroup patients using QST and/or PRO AT BASELINE

Profiling of signs: QST protocol / 13 parameters



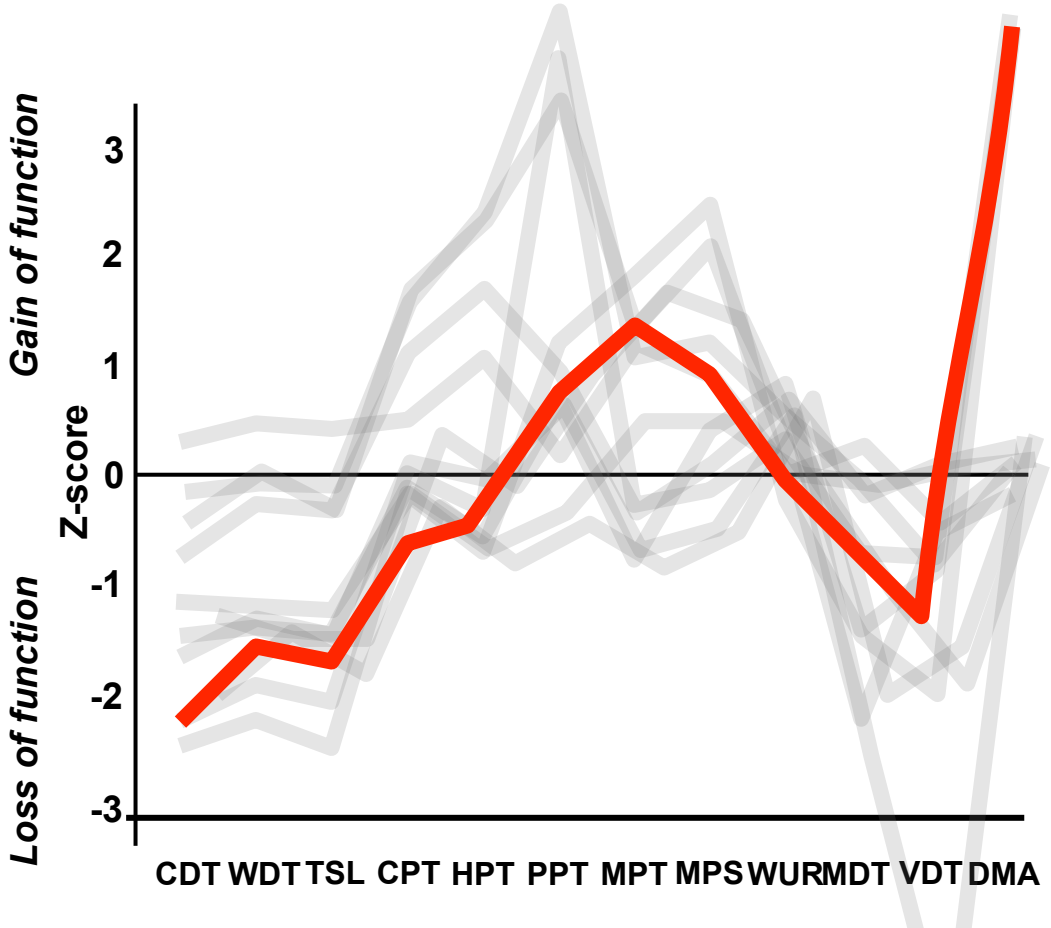
What is a sensory QST-profile?

Combination of sensory signs at baseline

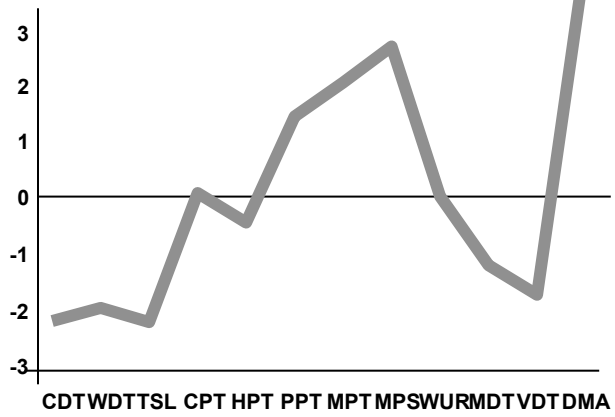
Hierarchical cluster analysis

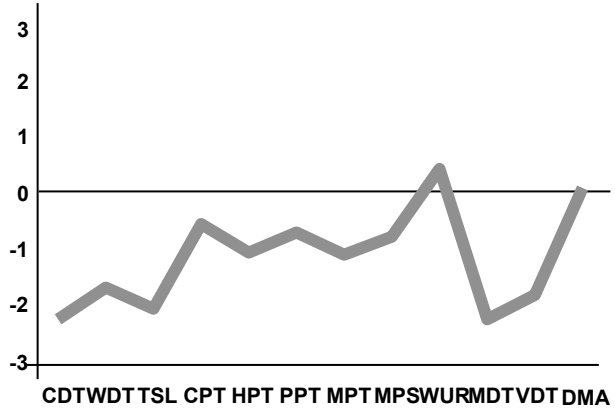
Many neuropathic etiologies

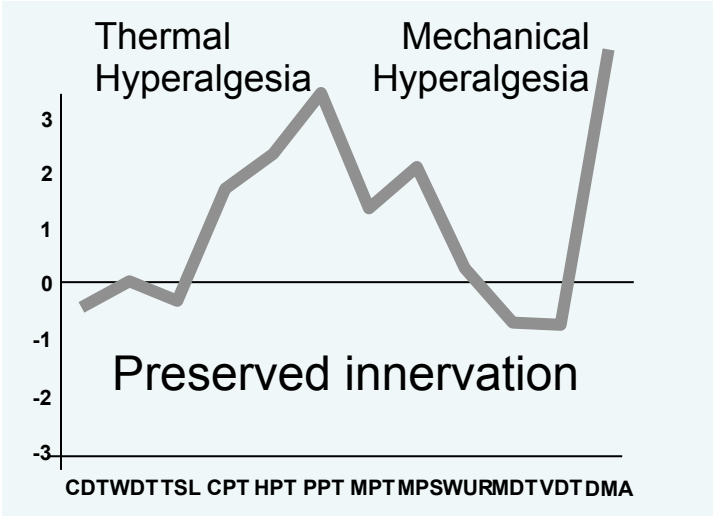
N>3500

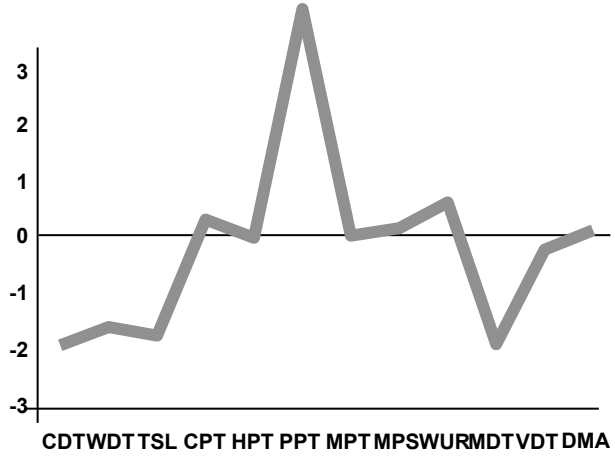


Subgroups





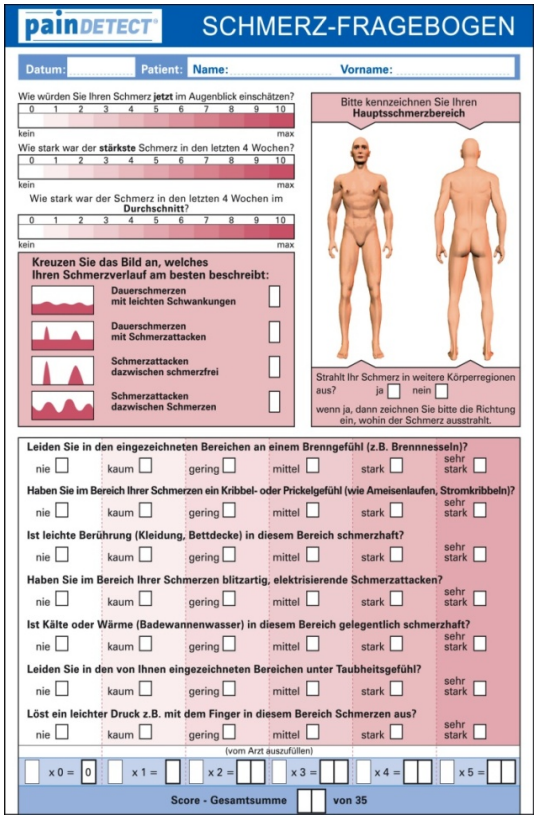




Heterogeneous sensory profiles = heterogeneous mechanisms

Profiling of symptoms: PRO / questionnaires

painDETECT™



painDETECT SCHMERZ-FRAGEBOGEN

Datum: Patient: Name: Vorname:

Wie würden Sie Ihren Schmerz **jetzt** im Augenblick einschätzen?
0 1 2 3 4 5 6 7 8 9 10
kein max

Wie stark war der **stärkste** Schmerz in den letzten 4 Wochen?
0 1 2 3 4 5 6 7 8 9 10
kein max

Wie stark war der Schmerz in den letzten 4 Wochen im **Durchschnitt?**
0 1 2 3 4 5 6 7 8 9 10
kein max

Kreuzen Sie das Bild an, welches Ihren Schmerzverlauf am besten beschreibt:

- Dauerschmerzen mit leichten Schwankungen
- Dauerschmerzen mit Schmerzattacken
- Schmerzattacken dazwischen schmerzfrei
- Schmerzattacken dazwischen Schmerzen

Bitte kennzeichnen Sie Ihren **Hauptsschmerzbereich**

Strahlt Ihr Schmerz in weitere Körperregionen aus? ja nein

wenn ja, dann zeichnen Sie bitte die Richtung ein, wohin der Schmerz ausstrahlt.

Leiden Sie in den eingezeichneten Bereichen an einem Brenngefühl (z.B. Brennnesseln)?
nie kaum gering mittel stark sehr stark

Haben Sie im Bereich Ihrer Schmerzen ein Kribbel- oder Prickelgefühl (wie Ameisenlaufen, Stromkribbeln)?
nie kaum gering mittel stark sehr stark

Ist leichte Berührung (Kleidung, Bettdecke) in diesem Bereich schmerzhaft?
nie kaum gering mittel stark sehr stark

Haben Sie im Bereich Ihrer Schmerzen blitzartig, elektrisierende Schmerzattacken?
nie kaum gering mittel stark sehr stark

Ist Kälte oder Wärme (Badewannenwasser) in diesem Bereich gelegentlich schmerzhaft?
nie kaum gering mittel stark sehr stark

Leiden Sie in den von Ihnen eingezeichneten Bereichen unter Taubheitsgefühl?
nie kaum gering mittel stark sehr stark

Löst ein leichter Druck z.B. mit dem Finger in diesem Bereich Schmerzen aus?
nie kaum gering mittel stark sehr stark

(vom Arzt auszufüllen)

x 0 = 0 | x 1 = | x 2 = | x 3 = | x 4 = | x 5 =

Score - Gesamtsumme von 35

NPSI

Neuropathic
Pain
Symptom
Inventory

Freynhagen et al. 2006, Bouhassira et al. 2004

Profiling of symptoms: PRO / questionnaires

1. Burning pain?
2. Tingling or prickling (electricity)?
3. Sensitivity to touch (clothes, blanket)?
4. Occasionally painful cold or heat (e.g. bath tub)?
5. Shooting pain, electric shock like?
6. Numbness?
7. Can pain be caused by light pressure (e.g. with finger)?

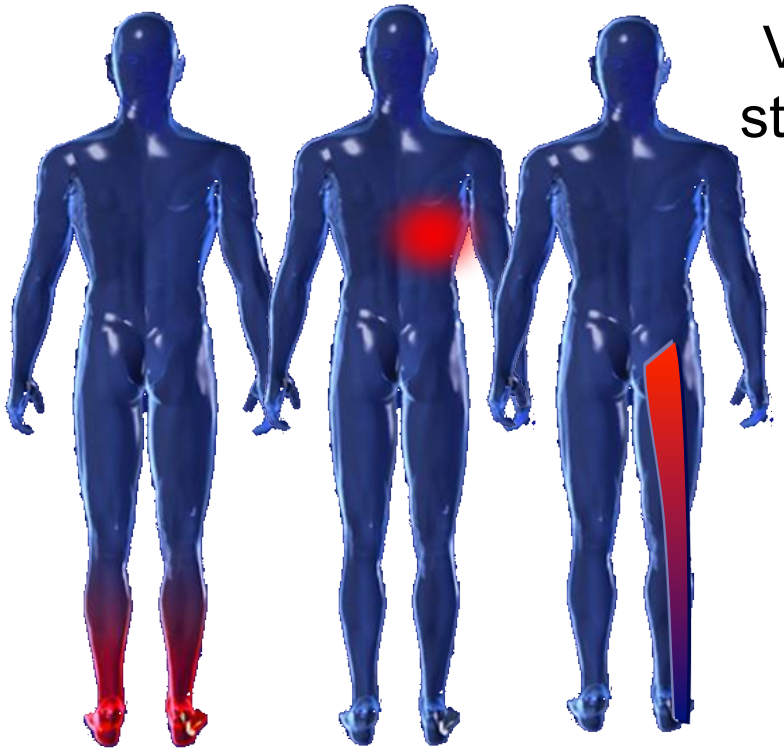
Very strong	=	5
Strong	=	4
Moderate	=	3
Slight	=	2
Hardly noticed	=	1
Never	=	0

Freynhagen et al. 2006

What is a sensory PRO-profile?

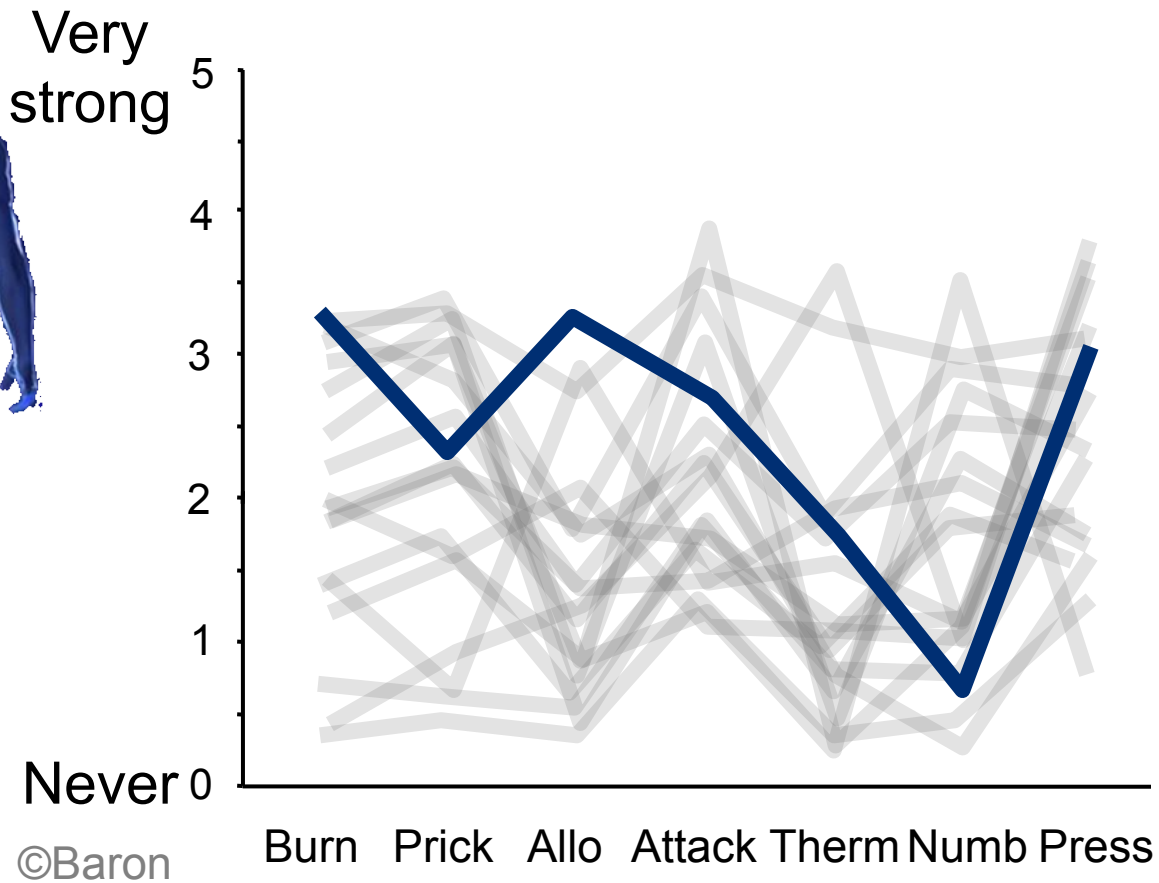
Combination of sensory symptoms at baseline

Hierarchical cluster analysis



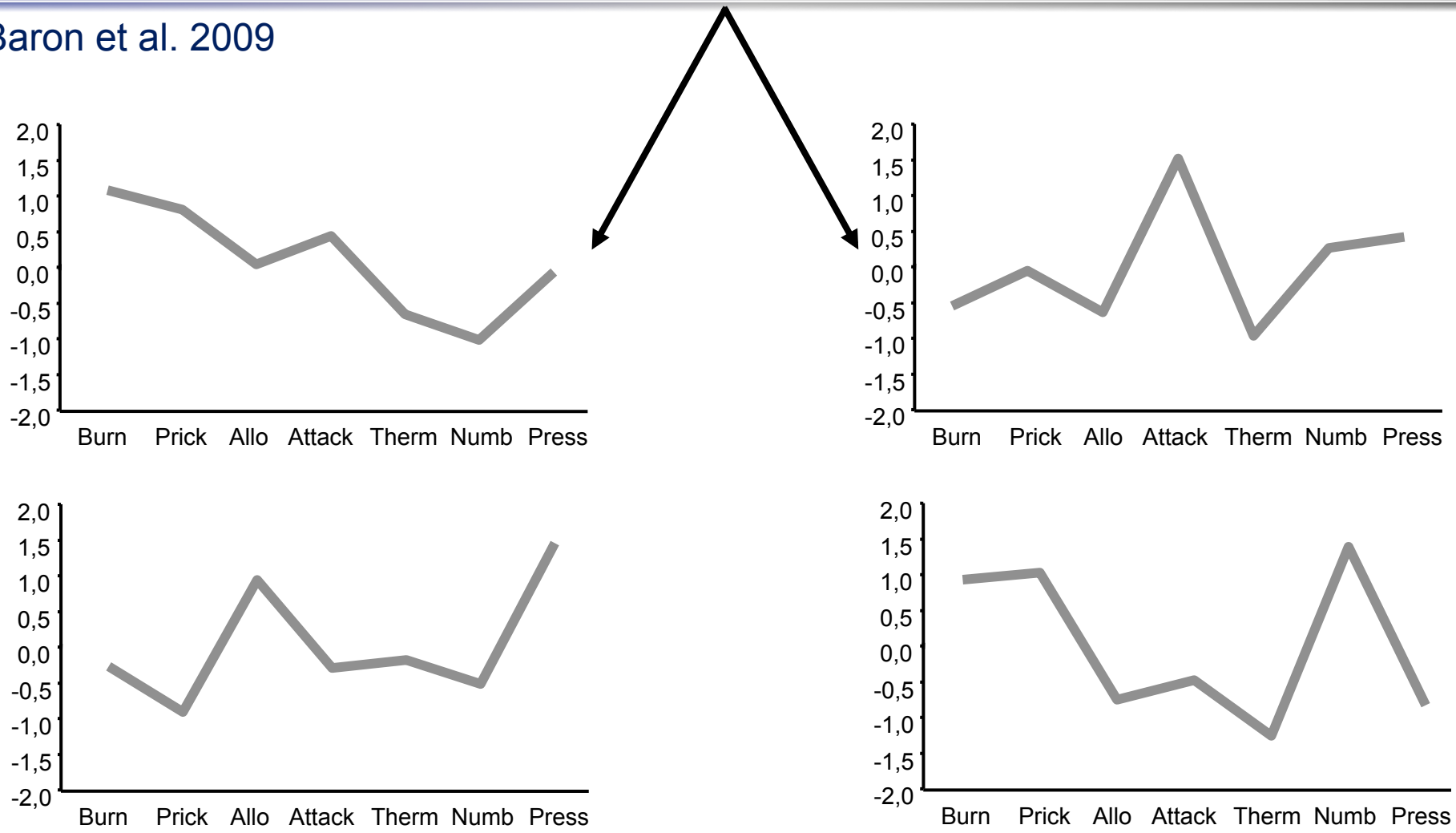
DPN, PHN, RAD

N=4200



Subgroups

Baron et al. 2009



Heterogeneous sensory profiles = heterogeneous mechanisms

Agenda 2

Sensory phenotype reveals

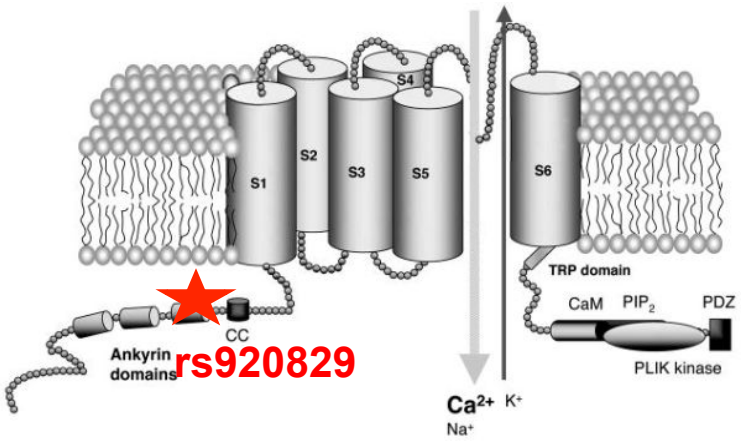
new “druggable” targets

Example:

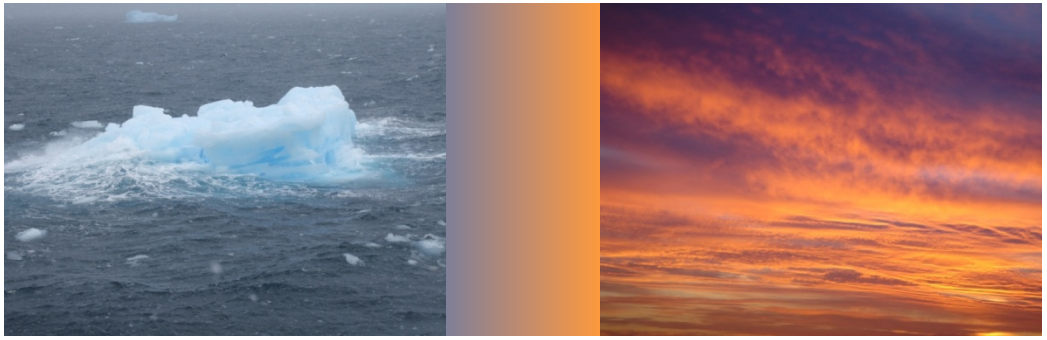
Genotyping of TRPA1

Painful vs. painless neuropathies

Genetic profiling – association with QST



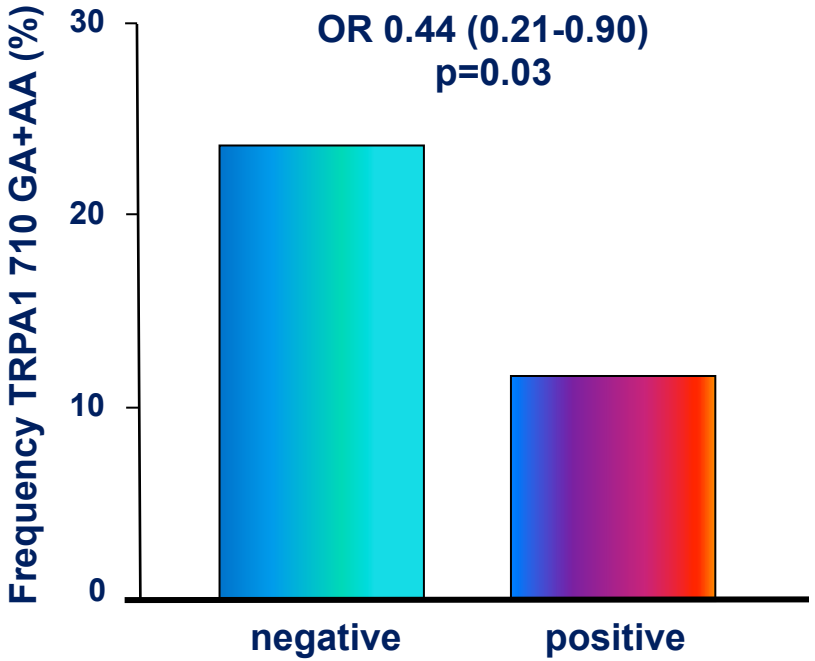
Paradoxical heat



TRP A1

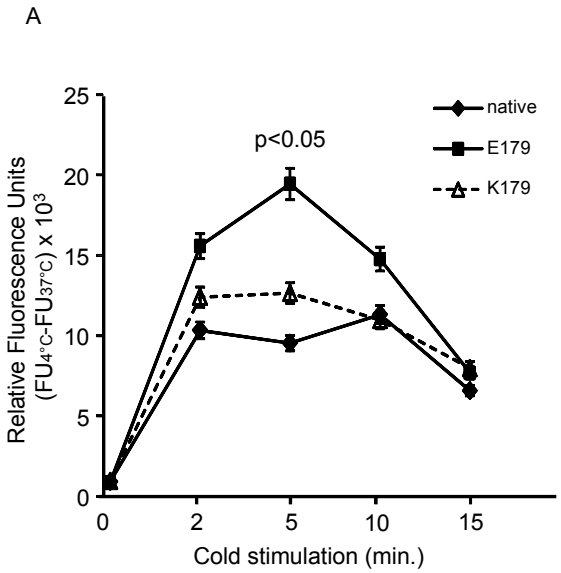
80% GG polymorphism

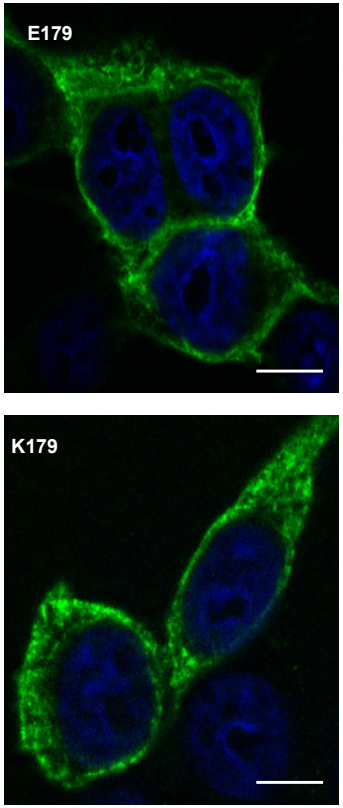
20% AA/GA polymorphism (protecting factor)



Binder et al. 2011

The SNP is functional





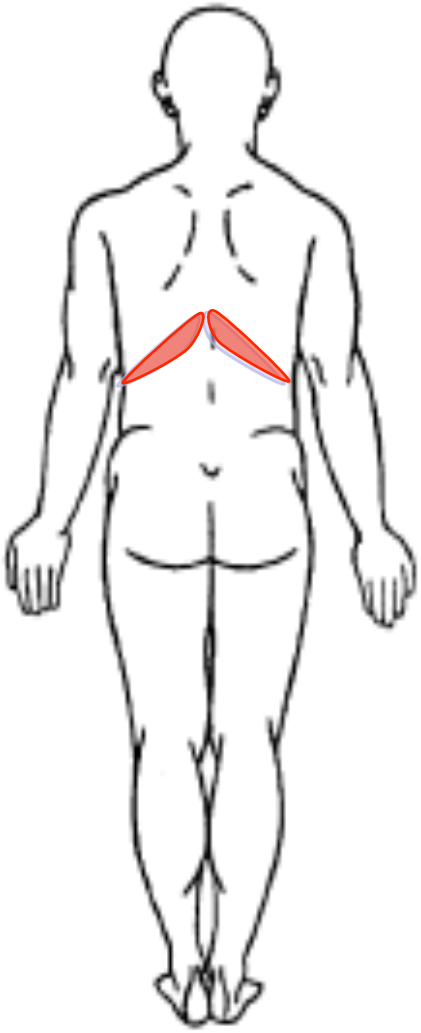
May et al. 2012

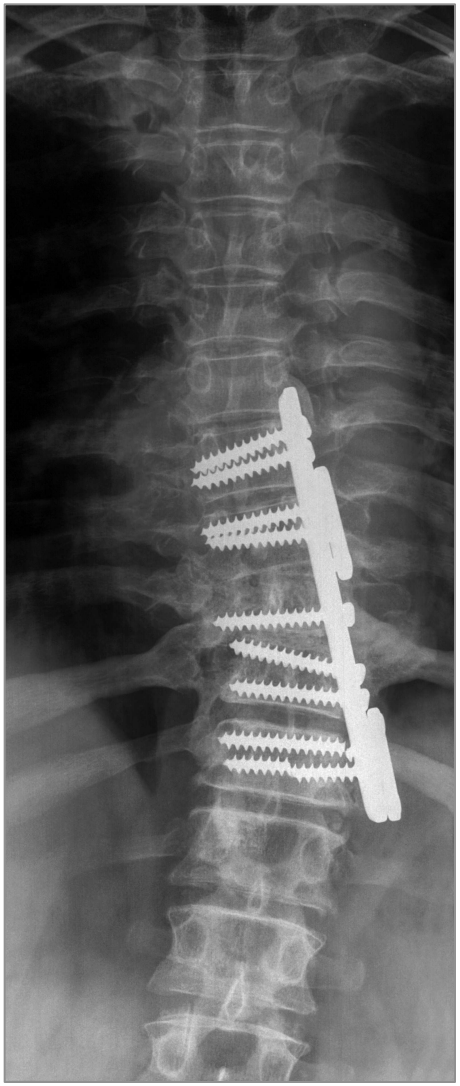
Agenda 3

The sensory phenotype shows predictive validity in treatment trials

Segmentation methods identify differential response

QST identifies responders





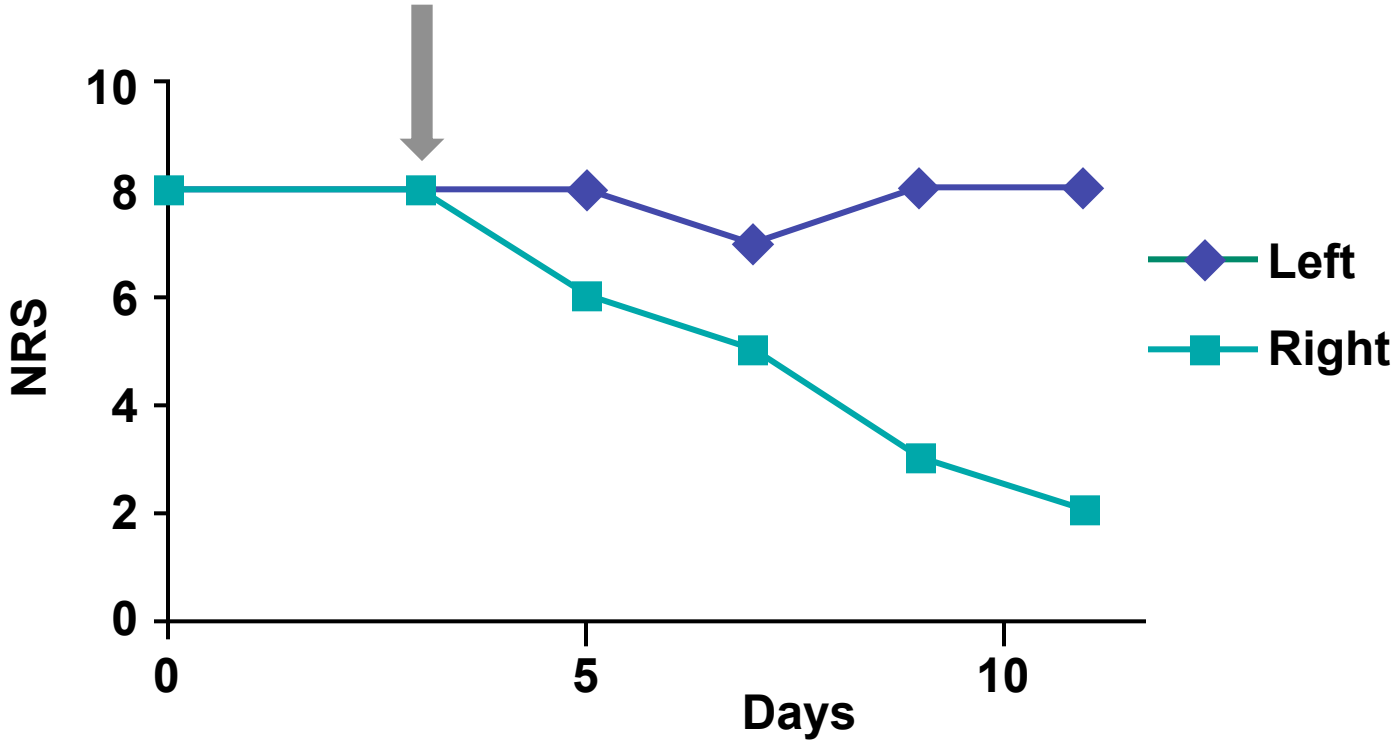
Spinal column trauma 1999
With partial lesion of spinal nerves on both sides

Severe pain
Th9 both sides
(peripheral neuropathic pain)

Westermann et al. 2012

QST identifies responders

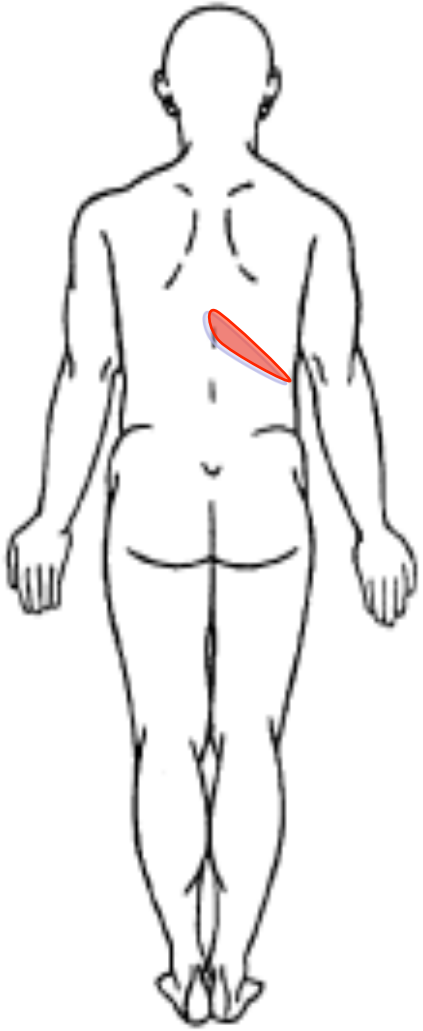
- Titration of Pregabalin
  - ⇒ End dose 450mg/d
  - ⇒ Pain reduction to Ø NRS 2 only on right side
  - ⇒ Sitting and leaning in wheel chair much improved



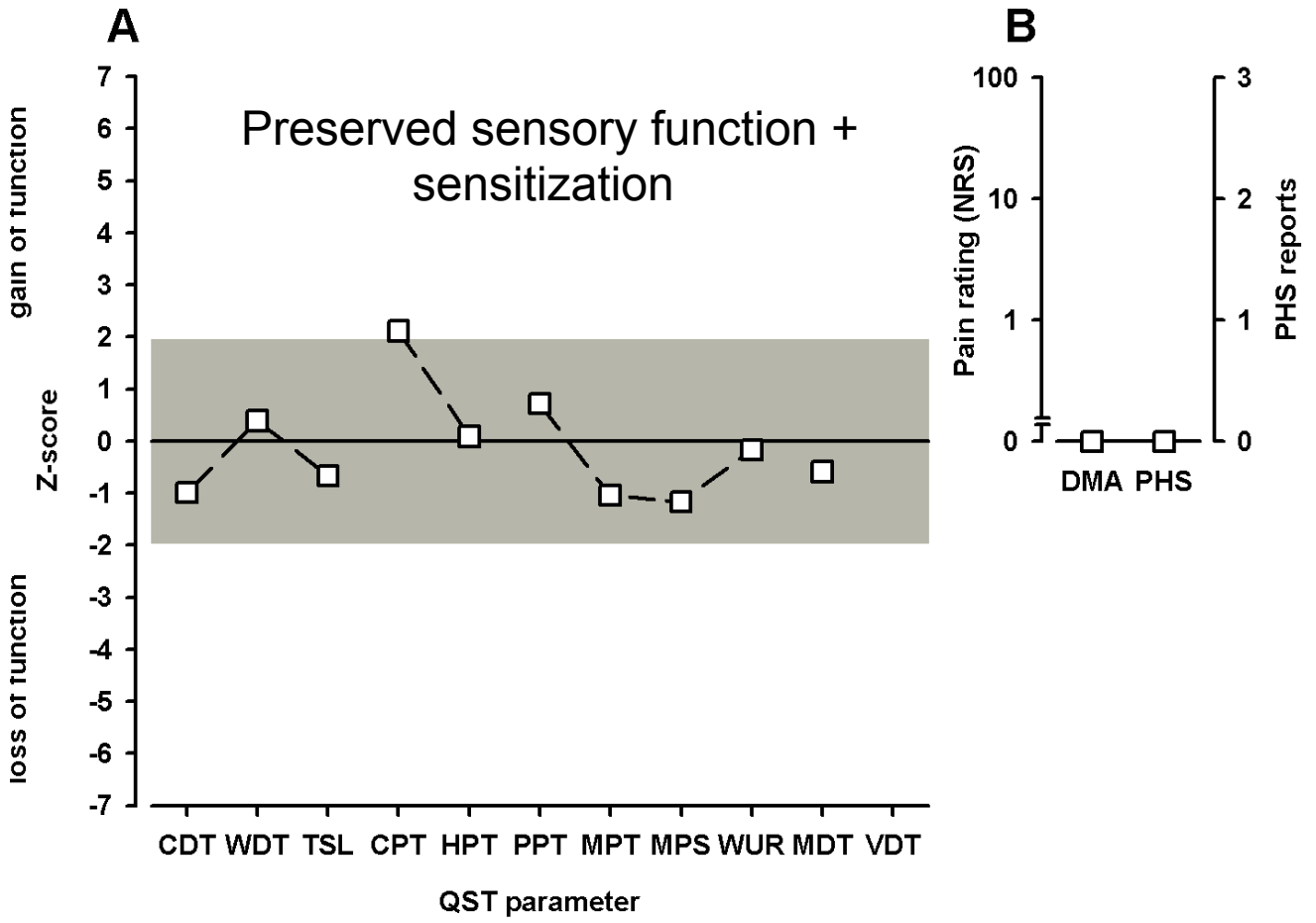
Westermann et al. 2012

QST identifies responders

Peripheral nerve injury



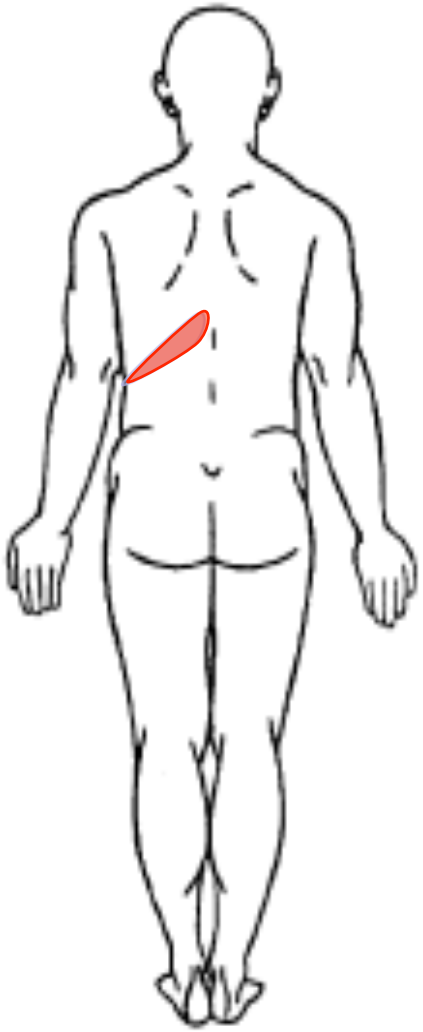
QST on right side



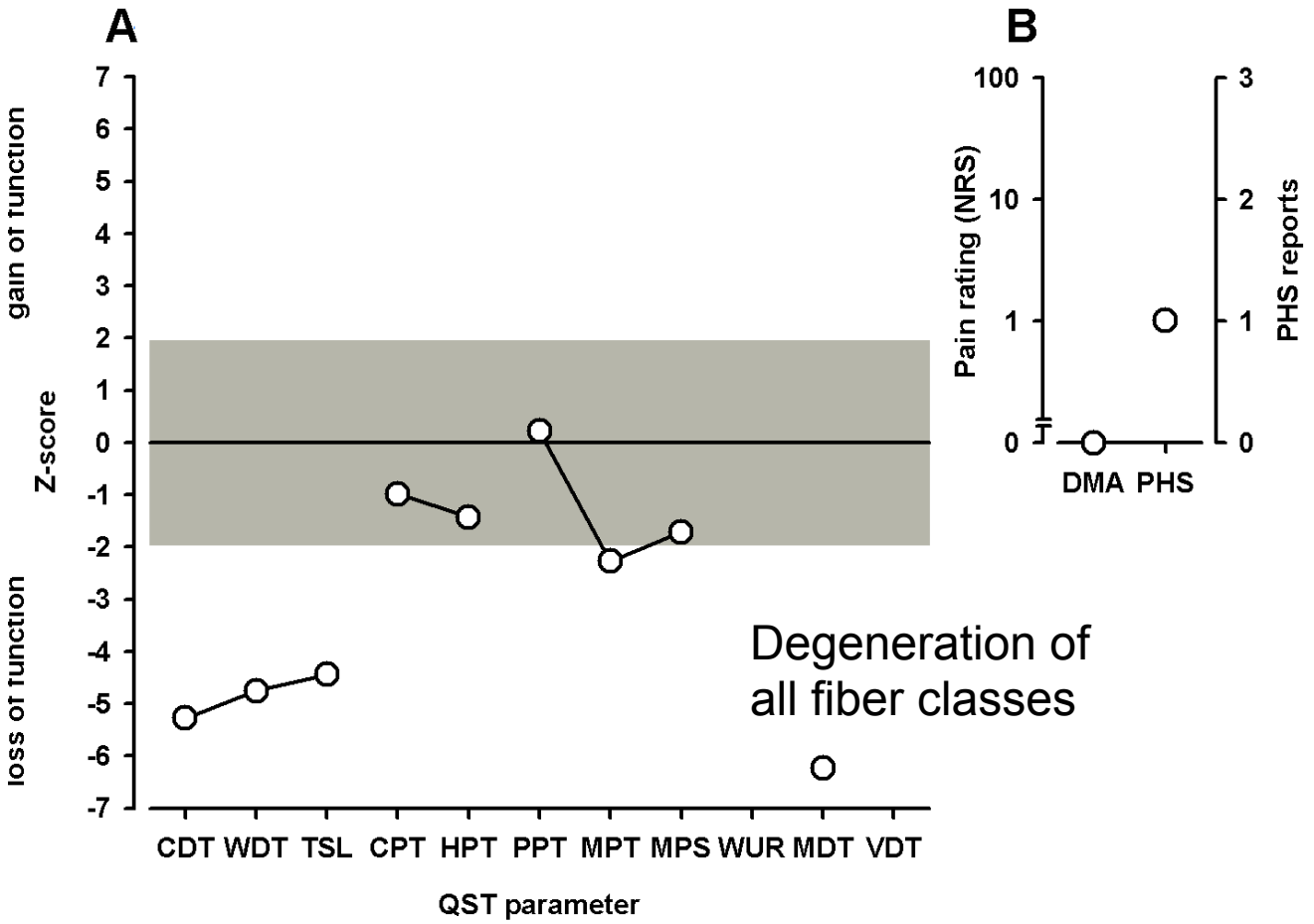
Westermann et al. 2012

Example: treatment effect depends on subgroup

Peripheral nerve injury



QST on left side



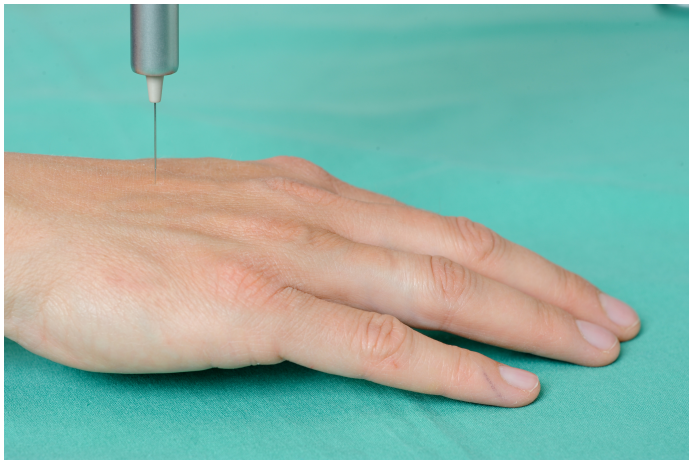
Westermann et al. 2012

QST identifies responders

Randomized, double-blind, placebo-controlled trial in HIV neuropathy

– Pain difference:

VAS -0.25, P = 0.4



Severe pinprick hyperalgesia at baseline (1/3)

- Pain difference VAS -2.14 (P<0.01)

Low-to-moderate pinprick hyperalgesia (2/3)

- Pain differende VAS -0.06 (P=0.88)

Simpson et al. 2008

NPSI identifies responders

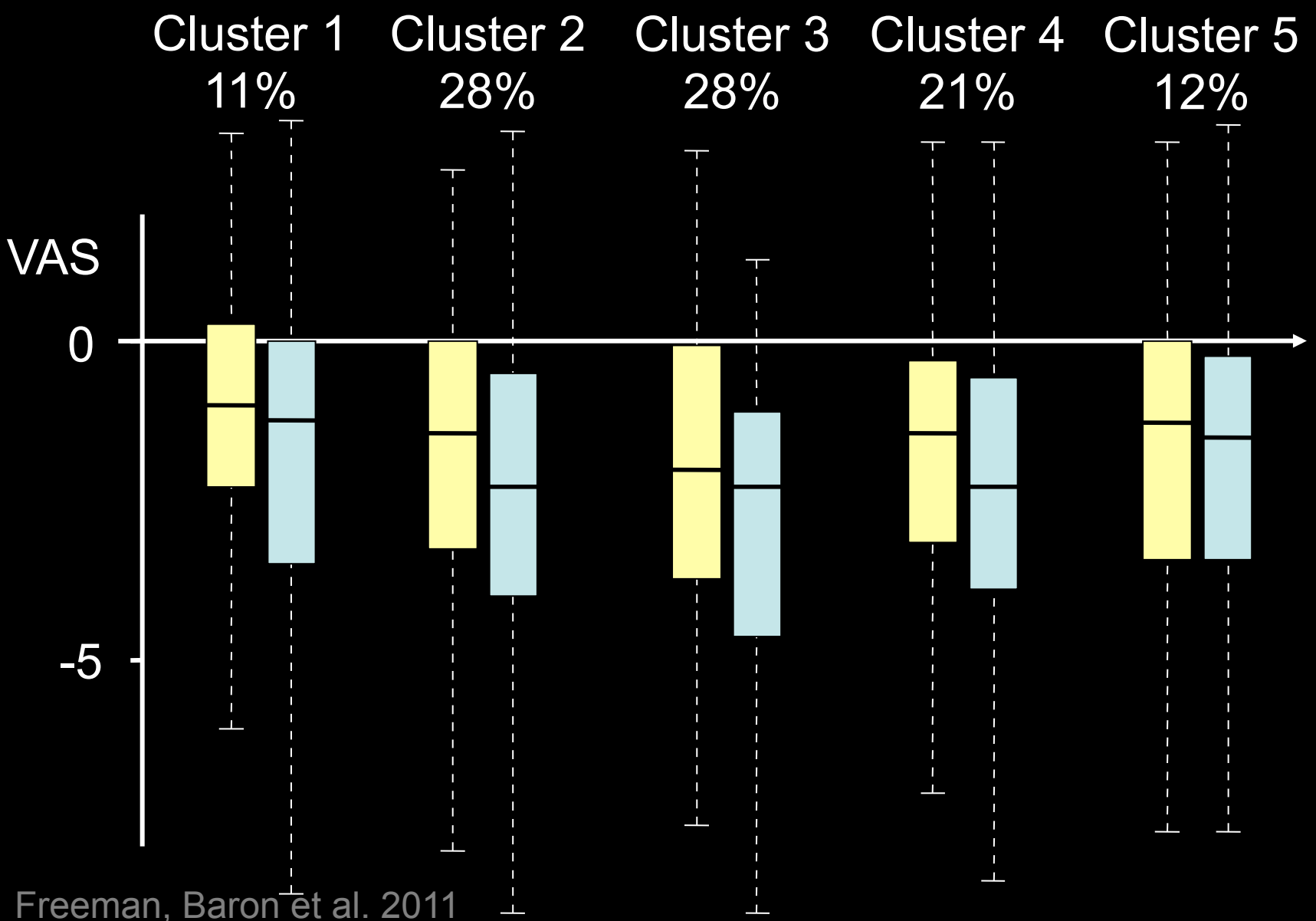
Recent Pregabalin studies:
Three out of four double-blind placebo controlled trials were negative

HIV, PostStroke, DPN, PostTrauma

Segmentation methods to subgroup patients using NPSI AT BASELINE

Pregabalin is effective in subgroups !!!

NPSI identifies responders



Freeman, Baron et al. 2011

PQAS identifies responders

Pregabalin in 50 patients with peripheral neuropathic pain

Pain Quality assessment scale (PQAS) at baseline

Seven items were associated with response:

- Intense
- Electrical
- Tingling
- Cramping
- Radiating
- Throbbing
- Deep

PQAS Scale or Item	Treatment Group: Pregabalin N = 50	Treatment Group: Placebo N = 49
PQAS scale		
PQAS paroxysmal	0.42**	0.14
PQAS surface	0.09	−0.09
PQAS deep	0.29*	0.08
PQAS item		
Intense	0.43**	−0.03
Sharp	0.28	0.27
Hot	0.28	0.24
Dull	0.15	0.14
		.09
		.10
		.11
		.13
		.05
		.21
		.01
		.02
		.00
		.01
		.17
		.09
		.17
		.09
		.15
		.04

* $P < 0.05$; ** $P < 0.01$

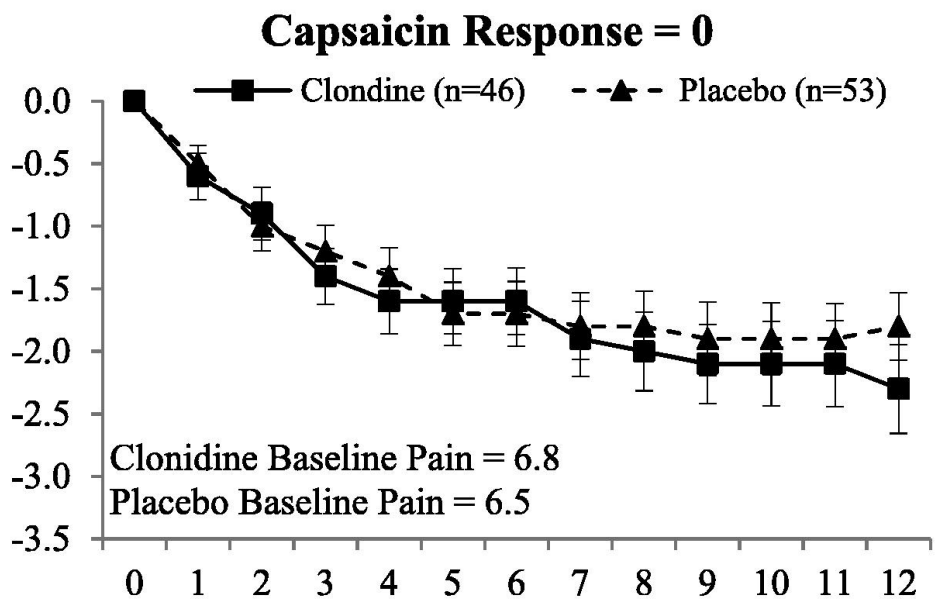
Observed Response	Predicted Response: Nonresponse	Predicted Response: Response	Percentage Correct
Nonresponse	17	7	70.8
Response	4	22	84.6
Overall percentage			78.0

Gammaitoni et al. 2012

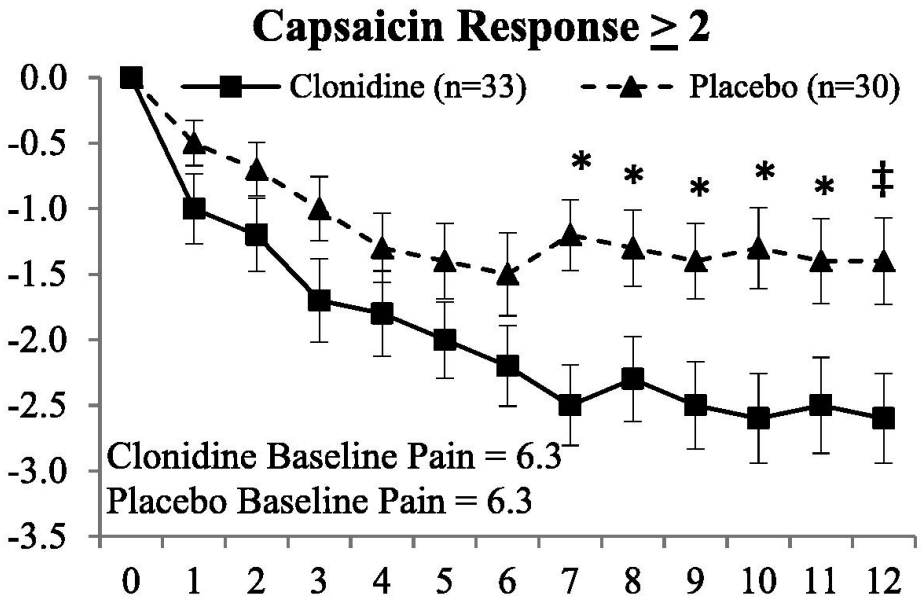
Capsaicin identifies responders

Painful diabetic neuropathy – topical clonidine

Fibers degenerated, no function



Fibers sensitized, overactive



Campbell et al. 2012

Agenda 4

QST and questionnaires are reliable

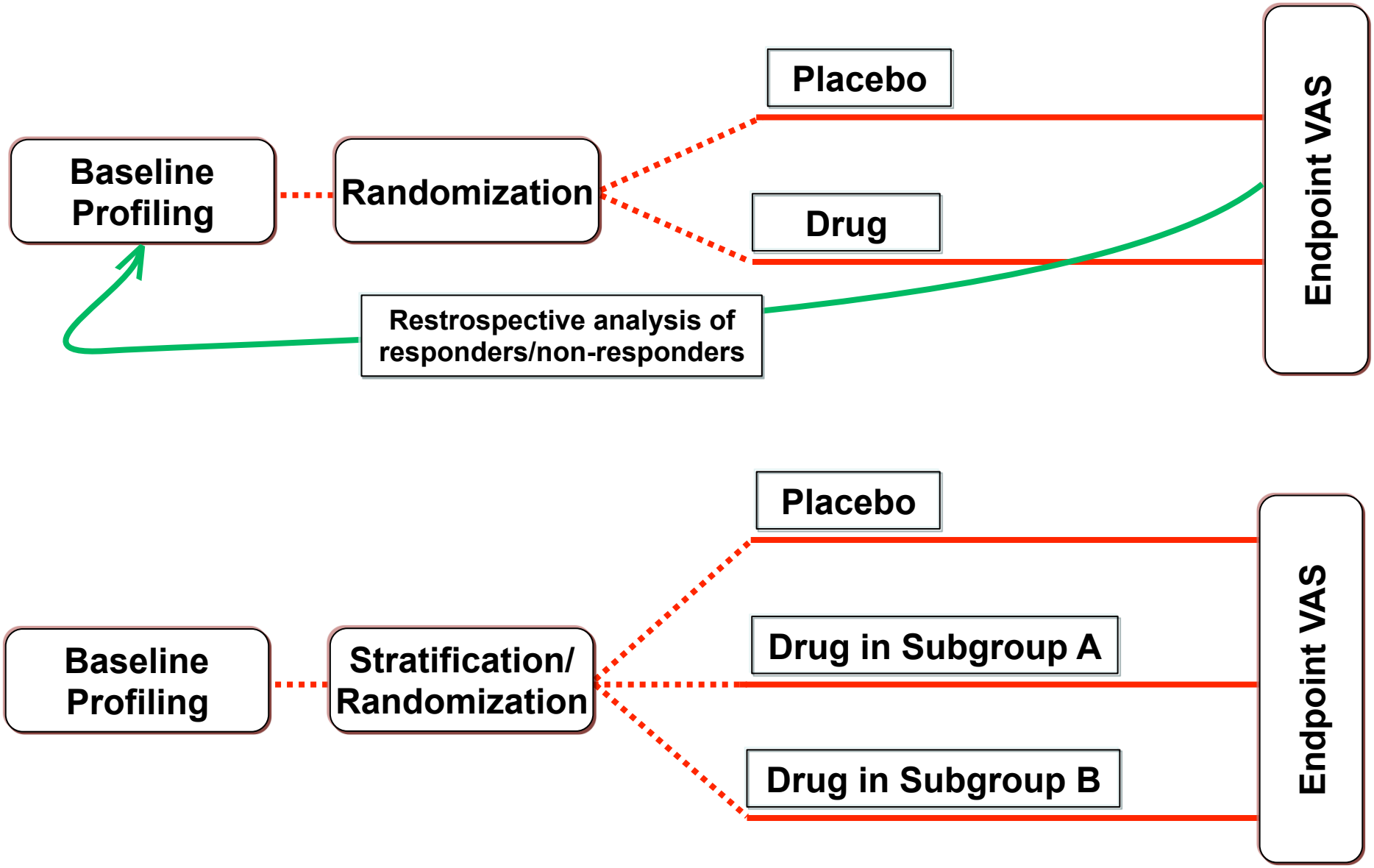
Sensory phenotype can be used as endpoints

Clinical assessment tool for efficacy – response
(surrogate endpoint)

IMMPACT considerations

	SENSORY PROFILES QST / PRO	CAPSAICIN RESPONSE	SKIN BIOPSY
PROGNOSTIC	?	?	+ Regeneration capacity
PREDICTIVE	++	+	+
PHARMACODYNAMIC	++	?	-
EFFICACY RESPONSE / SURROGATE ENDPOINT	++	?	+

Modern profile-based trial design



Sub-grouping of patients with neuropathic pain according to pain-related sensory abnormalities: a first step to a stratified treatment approach

Ralf Baron, Matti Förster, Andreas Binder

The Lancet Neurology Nov 2012

Different assessment tools - A critical evaluation

	PainDETECT 7 items		NPSI 10 items		SteP 16 items		QST 13 items	
Symptoms percieved by patients	Burning pain	S	Burning	S	Both superficial and deep pain present	S		
	Prickling pain	S	Squeezing	S	Intermittent pain episodes (1 min – several hours)	S		
	Allodynia	Ep	Pressure	S	Quality	S		
	Pain attacks	S	Electric shocks	S	Pain evoked by activity or body position	Ep		
	Thermally evoked pain	Ep	Stabbing	S	Nonpainful sensations (e.g., dysesthesias)	S		
	Numbness	En	Provoked by Brushing	Ep	Current pain	S		
	Pressure evoked	Ep	Provoked by pressure	Ep				
			Provoked by cold	Ep				
			Pins and needles	S				
			Tingling	S				
Signs/Physical examination					Trophic skin changes	S	Warm perception	En
					Decreased touch and and touch evoked pain	Epn	Cold perception	En
					Blunt pressure	Ep	Warm/cold limen	En
					Decreased brush sensation Brush evoked pain	Epn	Heat pain threshold	Epn
					Decreased vibration sensation	En	Cold pain threshold	Epn
					Decreased pinprick sensation Pinprick evoked pain	Epn	Pressure pain threshold	Epn
					Warm perception	Epn	MPT	Epn
					Cold sensation	Epn	MPS	Ep
					Temporal summation	Epn	MDT	En
					Straight-leg-raising test	Ep	Vibration	En
							WUR	Ep
							PHS	Ep
							DMA	Ep

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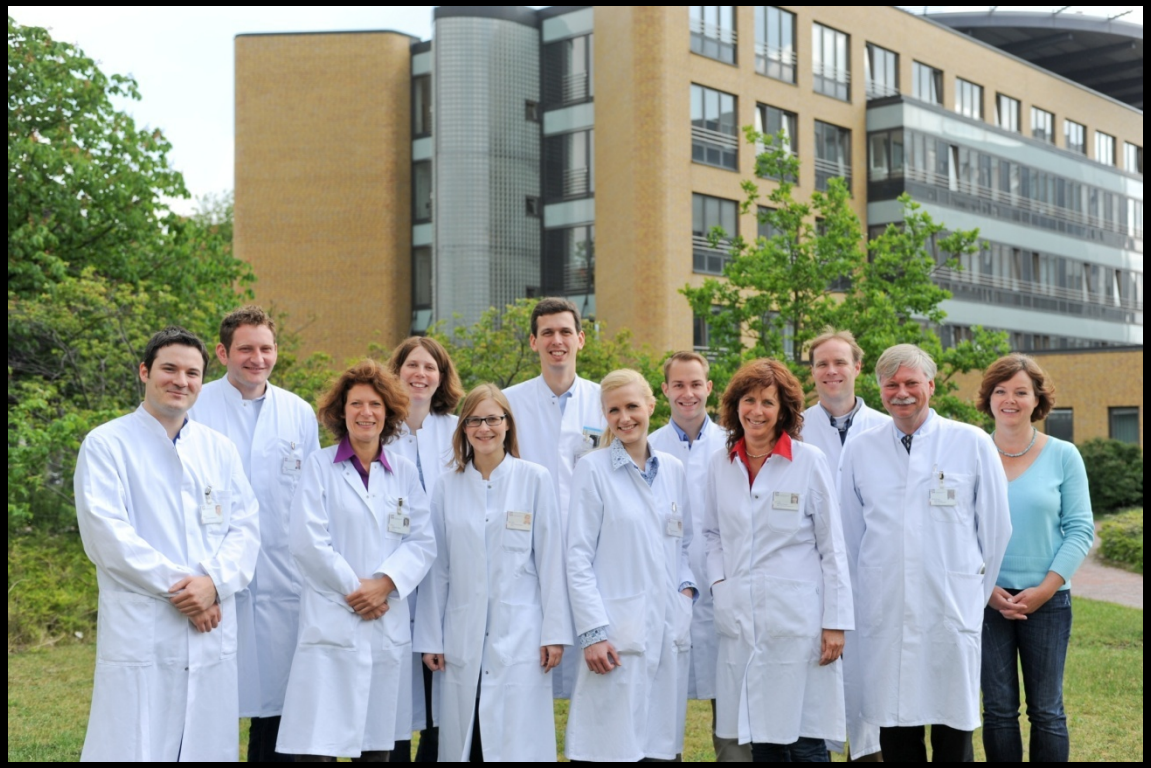

Conflicts of interest

Grant / Research Support:
Pfizer, Genzyme, Grünenthal,
Member of the IMI „Europain“ collaboration
and industry members of this are: Astra Zeneca, Pfizer, Esteve, UCB-Pharma, Sanofi Aventis, Grünenthal, Eli Lilly, Boehringer Ingelheim
German Federal Ministry of Education and Research:
German Research Network on Neuropathic Pain (01EM0903)
Modelling Pain Switches (0315449B)
German Research Foundation (DFG): BA1921/2-2, JA240/19-1

Consultant / Speakers Bureau:
Pfizer, Genzyme, Grünenthal, Mundipharma, Allergan, Sanofi Pasteur, Medtronic, Eisai, UCB BioSciences, Eli Lilly, Boehringer Ingelheim, Astellas, Novartis, Biogen Idec, Astra Zeneca, Bristol-Myers Squibb