

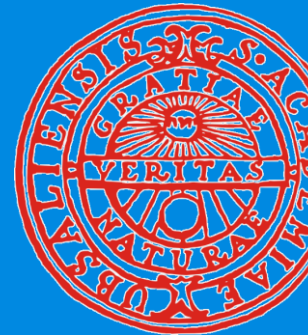
# Phantomschmerz – kortikale Reorganisation

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Faculty of Medicine Mannheim

Dept. Anesthesiology



# Schmerzverarbeitung und Schmerzentstehung im Gehirn

- Verarbeitungswege
- Phantomschmerz:  
maladaptive kortikale Reorganisation vs.  
unterbrochene funktionelle Verbindung
- Strukturelle Basis des „Schmerzgedächtnis“

Adverse event(s) affect

Epigenetics

Cell biology

Systems and neural networks

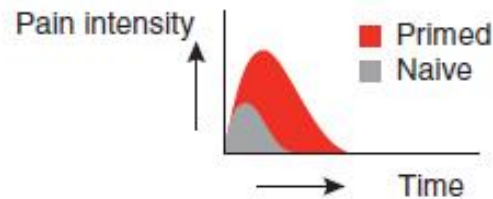
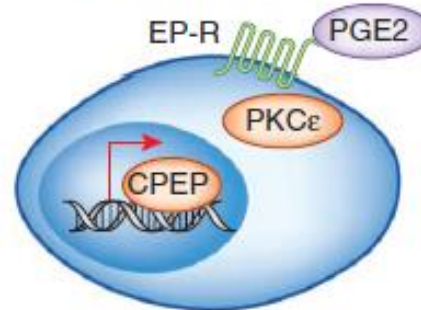
Example:  
Depression

- Persistent alterations in histone methylation at the *BDNF* promoter



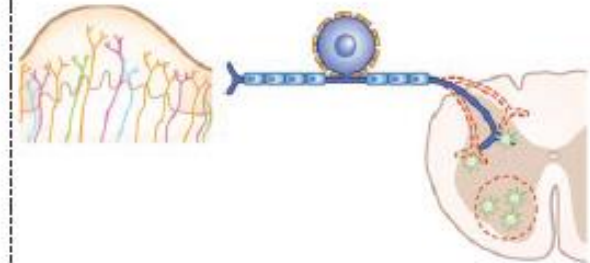
Long-term molecular memory:  
risk factor for recurring  
depression or other conditions  
like chronic pain?

- Example:  
Repeated challenge with  
inflammatory mediator  
- Changes to cellular processes

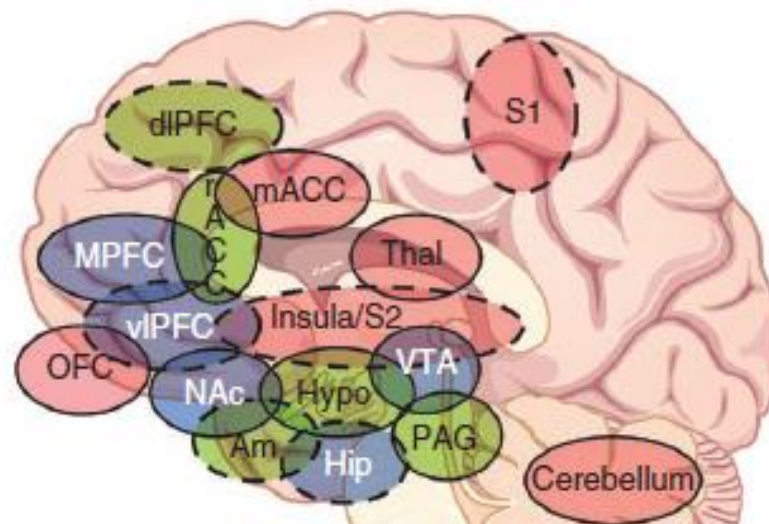


Primed state, leading to increased  
and longer lasting pain in  
animal models

- Example:  
Neonatal skin incision  
- Altered innervation of skin and  
spinal cord; altered glial responses



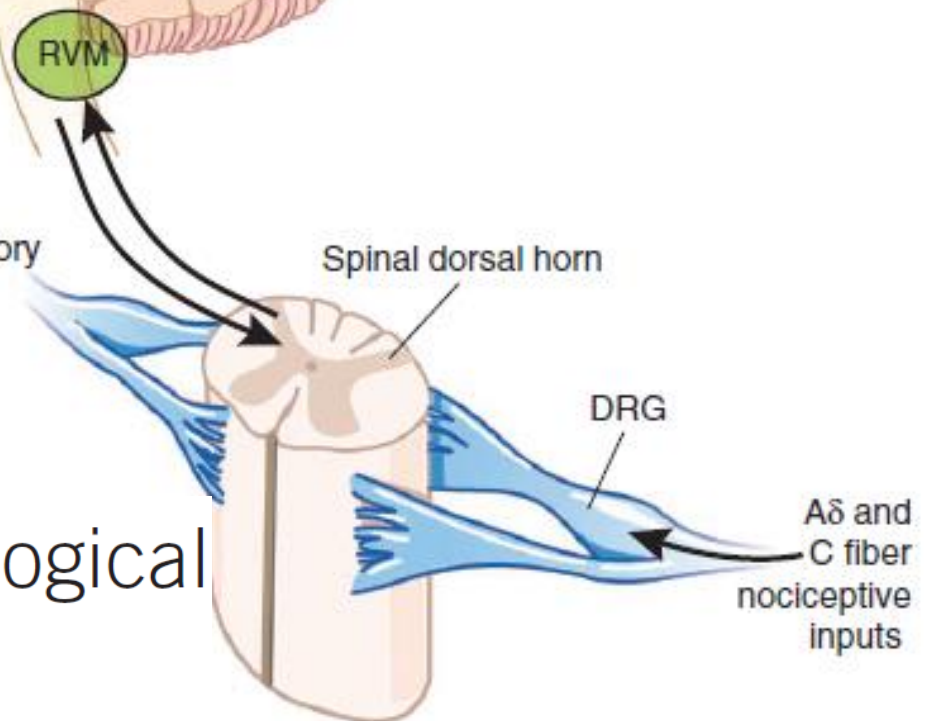
Altered pain sensitivity in adulthood



Networks with potential to affect risk for chronic pain

- Reward network Belohnungsnetzwerk
- DPMS „absteigende Hemmung“
- Areas also relevant to pain percept but that might not affect risk

Descending inhibitory and facilitatory influences



# Pain vulnerability: a neurobiological perspective

# Schmerzverarbeitung und Schmerzentstehung im Gehirn

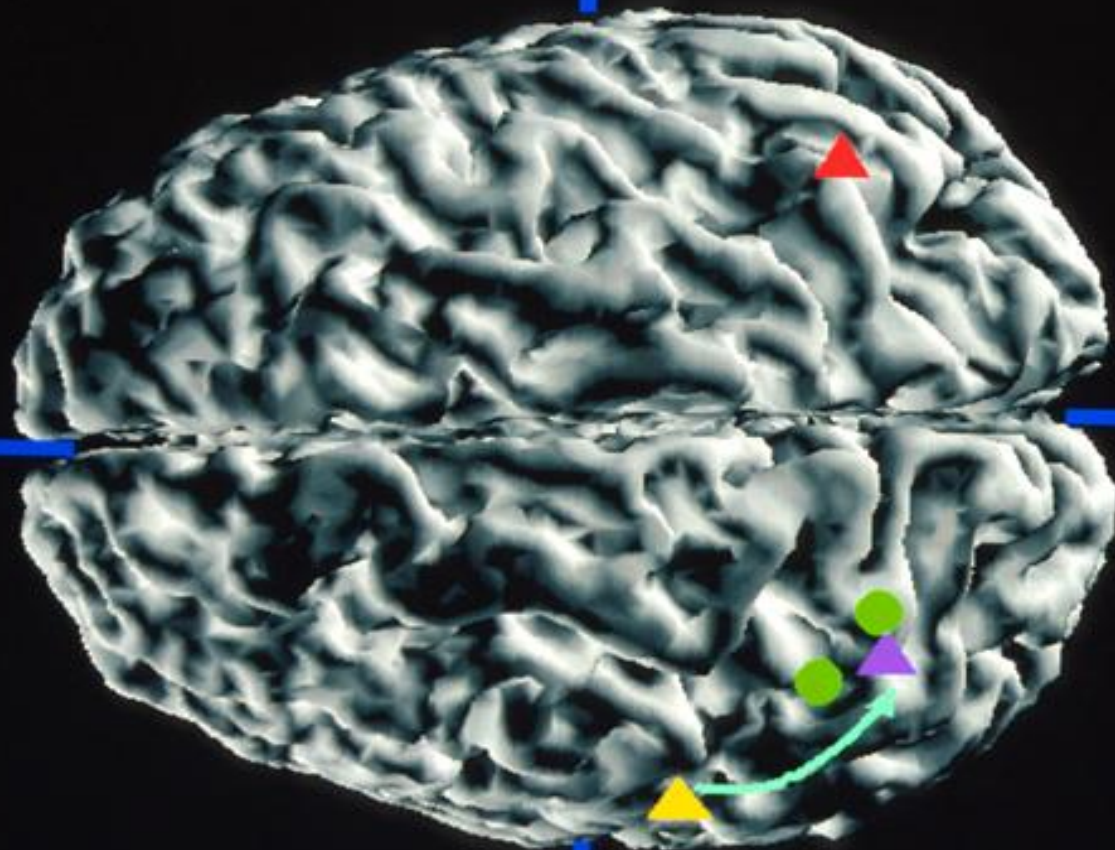
- Beispiel Phantomschmerz:  
maladaptive kortikale Reorganisation vs.  
unterbrochene funktionelle Verbindung
- Rolle der funktionellen zentralen Bildgebung

# Phantomschmerz – traditionelles Konzept: maladaptive kortikale Reorganisation

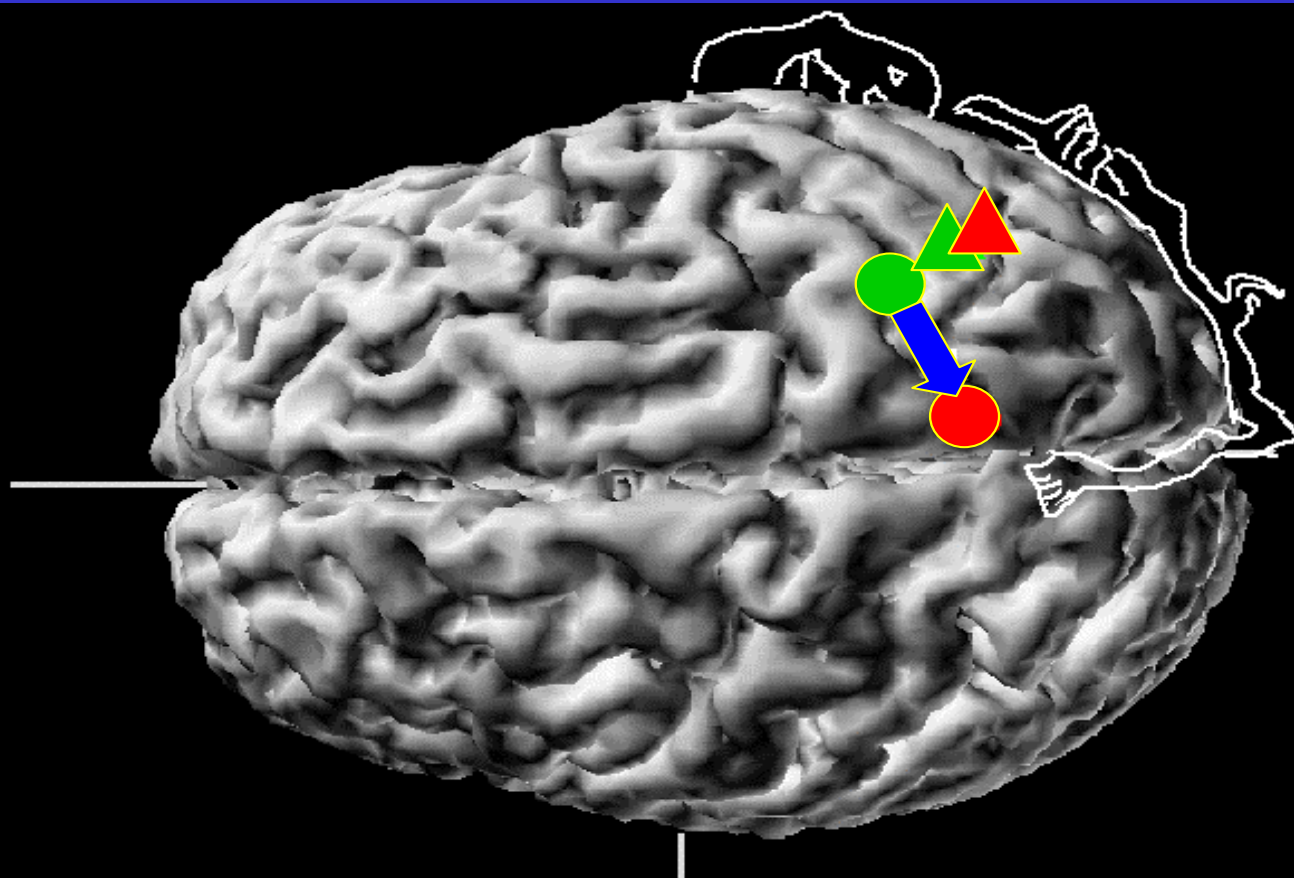
- Verlust von peripherem Eingang nach Amputation
- Funktionale Bildgebung der kortikalen Repräsentation
- „Schrumpfen“ der kortikalen Repräsentation und „Invasion“ durch benachbarte Areale
- Korrelation der Schmerzintensität mit Ausmaß dieser „Invasion“



# Cortical Reorganization



- digits of the intact side
- ▲ mouth of the intact side
- ▲ mouth of the amputation side
- ▲ mirrored mouth of the amputation side
- reorganization



**chronic back pain**

● **back**

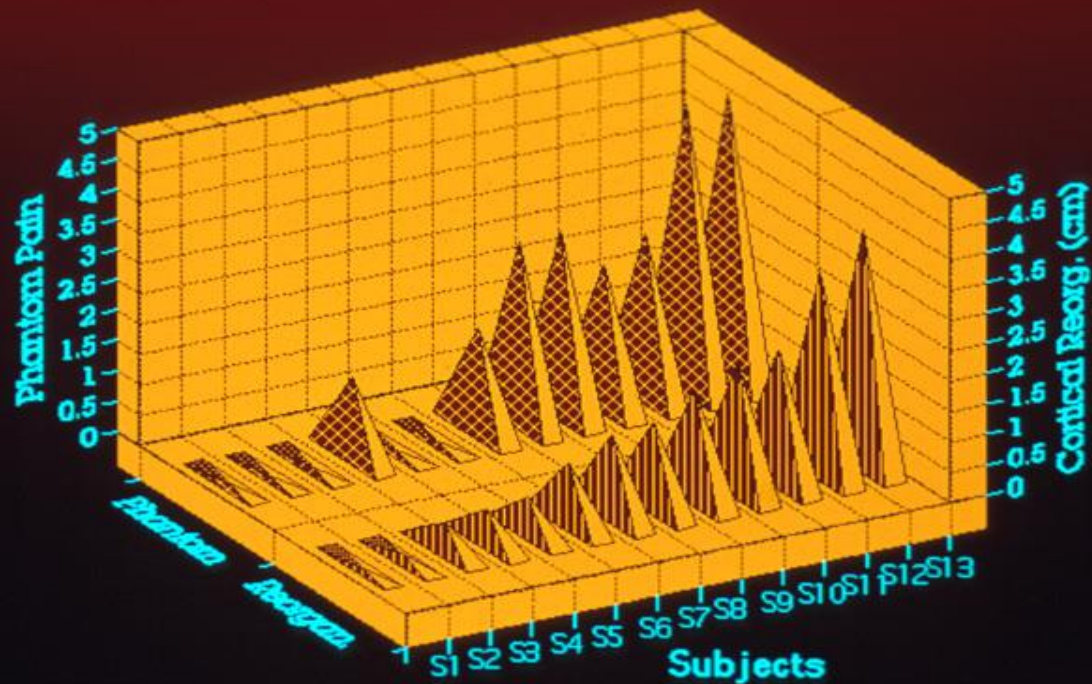
▲ **digit**

**control group**

● **back**

▲ **digit**





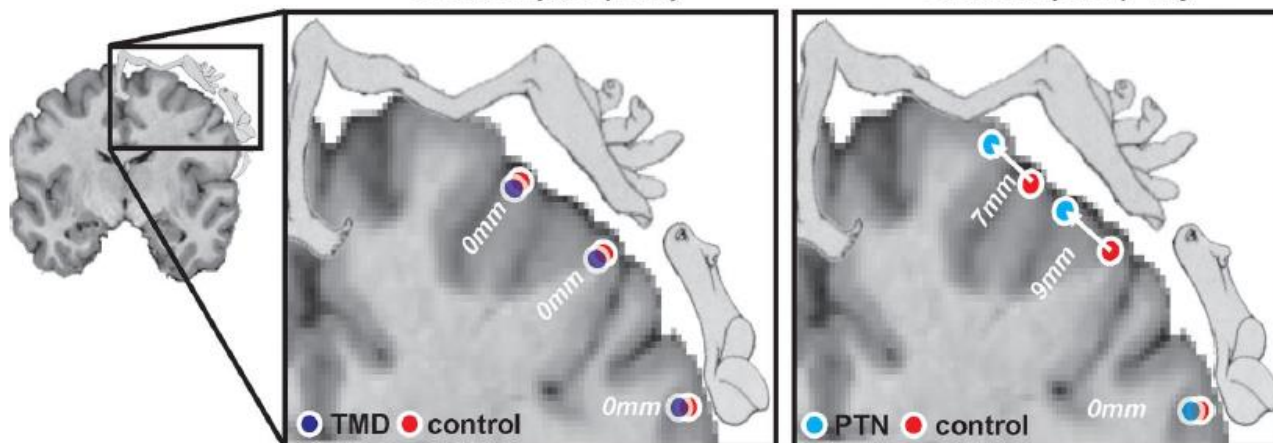
Gustlin et al. J Neurosci, 2012

Flor et al. Nature 1995

SI organization and chronic pain

control versus nociceptive orofacial pain (TMD)

control versus neuropathic orofacial pain (PTN)



# Kortikale Reorganisation

- **Ausmaß**  
der maladaptiven **kortikalen Reorganization**  
durch die **Deafferenzierung**

bestimmt

die **Stärke des Schmerzes**

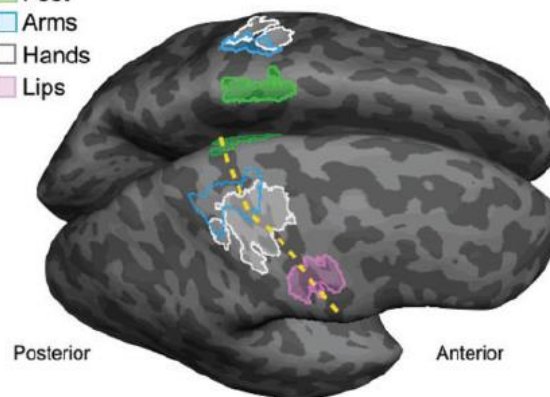
## REPORT

# Reassessing cortical reorganization in the primary sensorimotor cortex following arm amputation

Tamar R. Makin,<sup>1,\*</sup> Jan Scholz,<sup>1,2,\*</sup> David Henderson Slater,<sup>1,3</sup> Heidi Iohansen-Berg<sup>1</sup> and Irene Tracey<sup>1,4</sup>

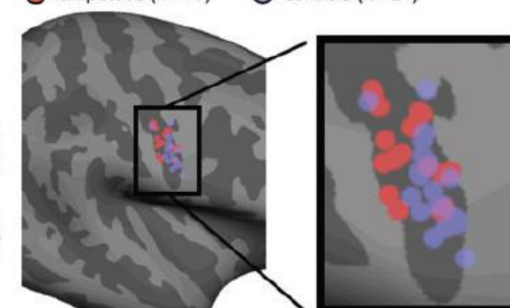
### A The sensorimotor homunculus

- Feet
- Arms
- Hands
- Lips



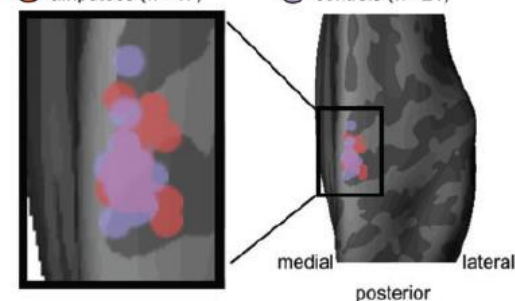
### B Lip centre of gravity - surface-based

- amputees ( $n=17$ )
- controls ( $n=21$ )

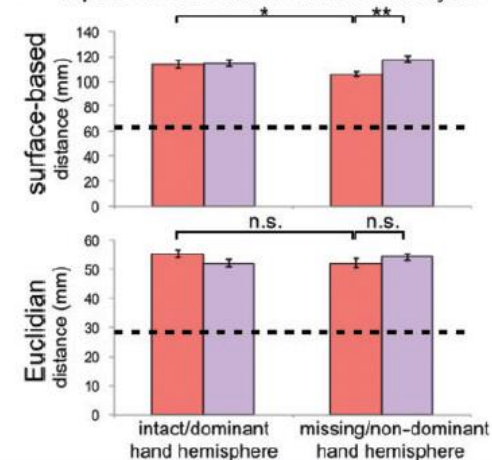


### C Feet centre of gravity- surface-based

- amputees ( $n=17$ )
- controls ( $n=21$ )



### D Lips-to-feet cortical distance analysis



Contrary to previous studies and despite our relatively large sample size, we were unable to identify any statistical relationship between cortical reorganization and phantom sensations or pain. This could be attributed to differences

ARTICLE

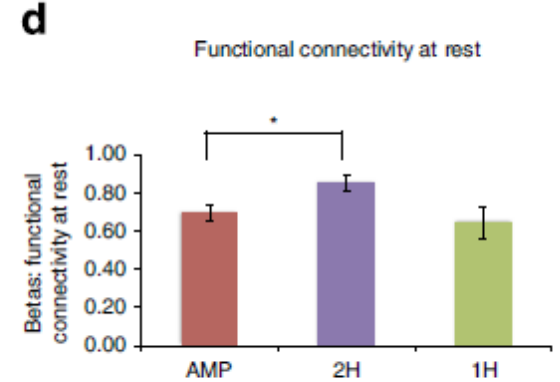
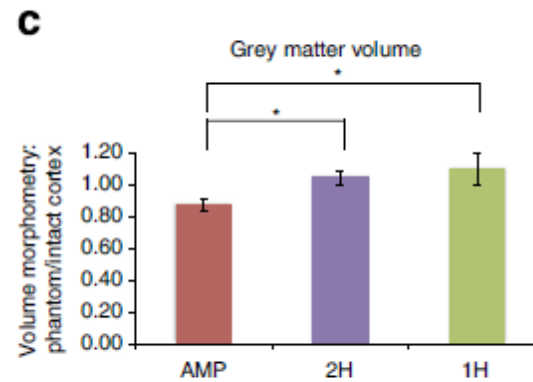
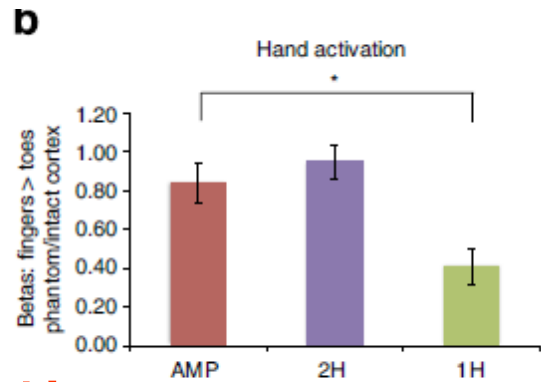
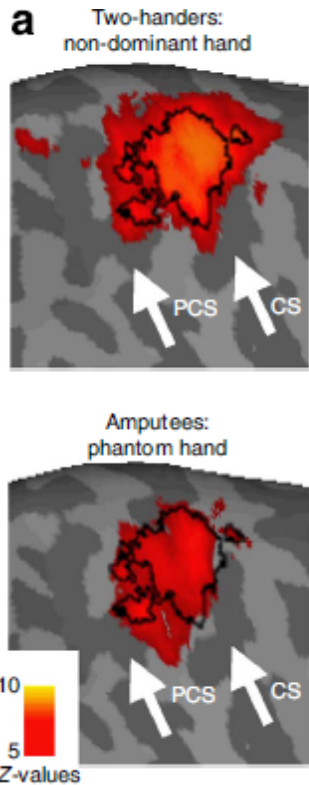
Received 22 Oct 2012 | Accepted 1 Feb 2013 | Published 5 Mar 2013

DOI: 10.1038/ncomms2571

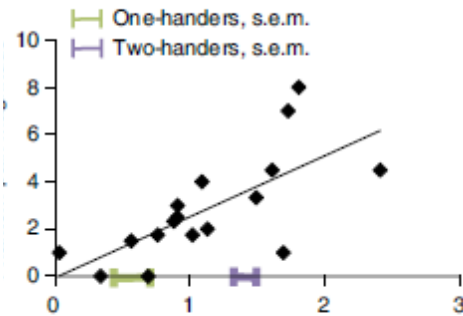
OPEN

# Phantom pain is associated with preserved structure and function in the former hand area

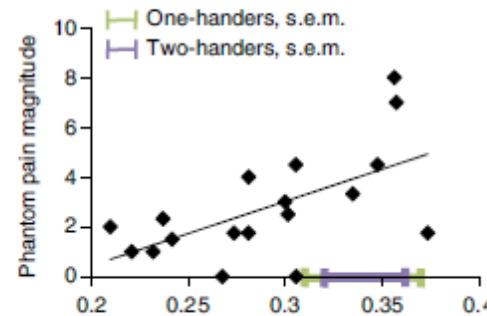
Tamar R. Makin<sup>1</sup>, Jan Scholz<sup>1,2</sup>, Nicola Filippini<sup>1,3</sup>, David Henderson Slater<sup>4</sup>, Irene Tracey<sup>1,5</sup>  
& Heidi Johansen-Berg<sup>1</sup>



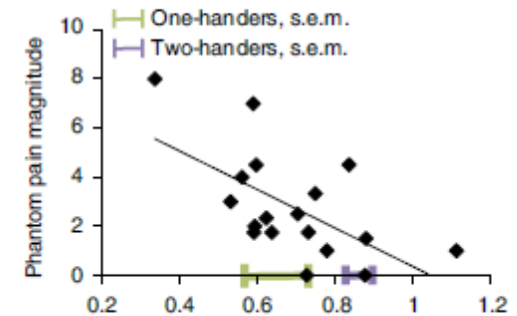
Phantomschmerz



Hand Aktivierung



Volumen graue Subst. Funkt. Konnektiv.



# Erhaltende Repräsentation, aber reduzierte Konnektivität

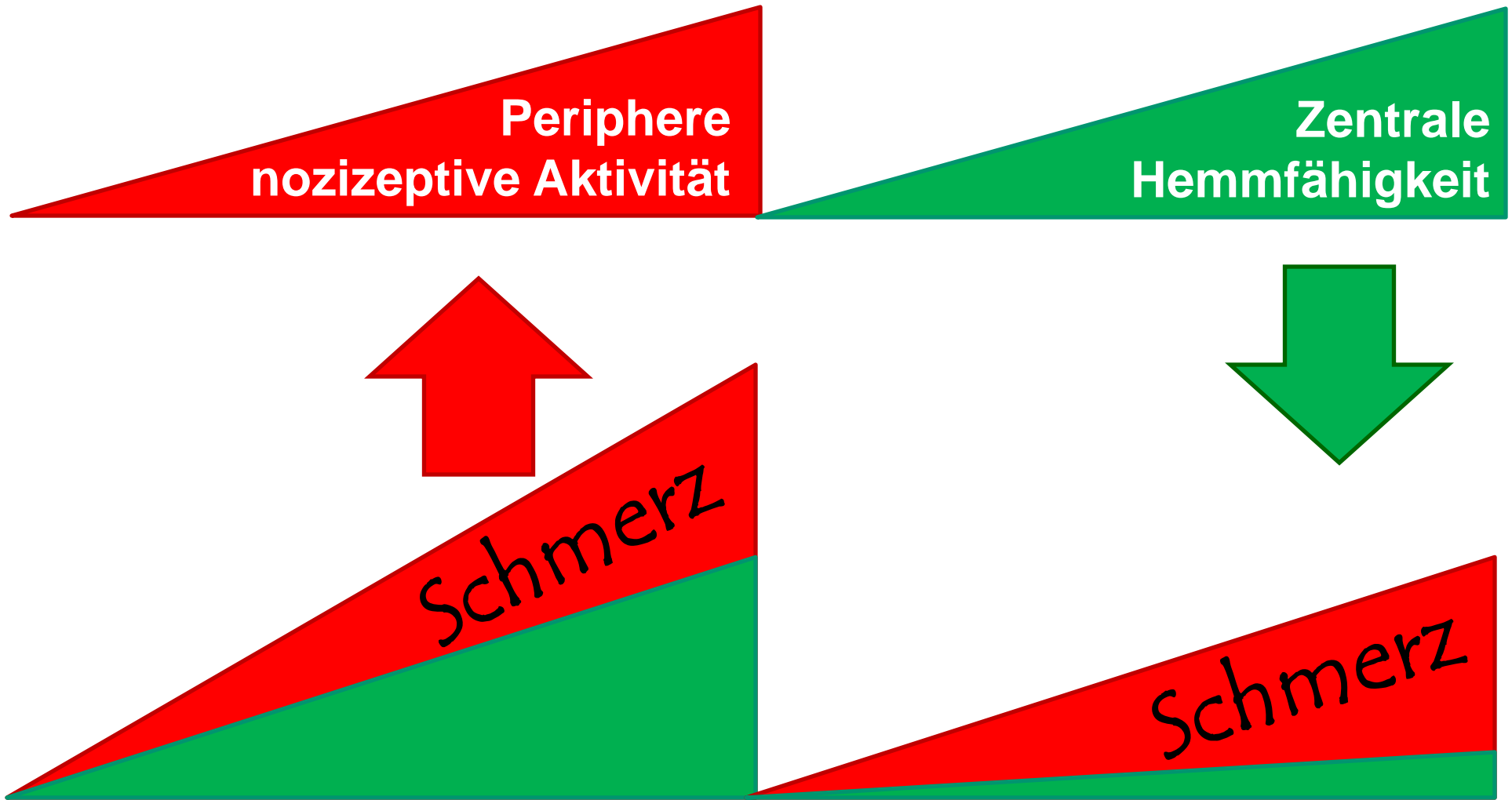
- Reduzierte Konnektivität kombiniert mit erhaltener Repräsentation bestimmt die Schmerzstärke
- Erhaltene Repräsentation erfordert sensorischen Eingang!

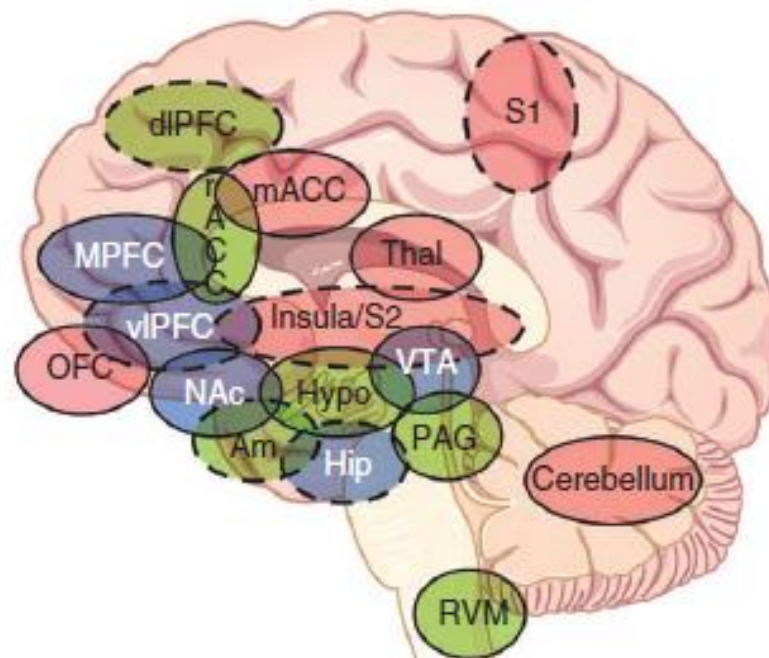


# Erhaltende Repräsentation, aber reduzierte Konnektivität

- „sinnlose“ neuronale Aktivität aus dem Stumpf führt zu besser erhaltener zentraler Repräsentation
- allerdings kann diese Aktivität nicht mit der regulären Aktivität in Einklang gebracht werden – die Konnektivität des zentralen Repräsentationsareals ist also gering
- Bei Phantomschmerz gelingt es nicht, das „Unsinnssignal“ vollständig zu unterdrücken

# Gleichgewicht zwischen peripherem nozizeptivem Input und Zentralen Hemmmechanismen

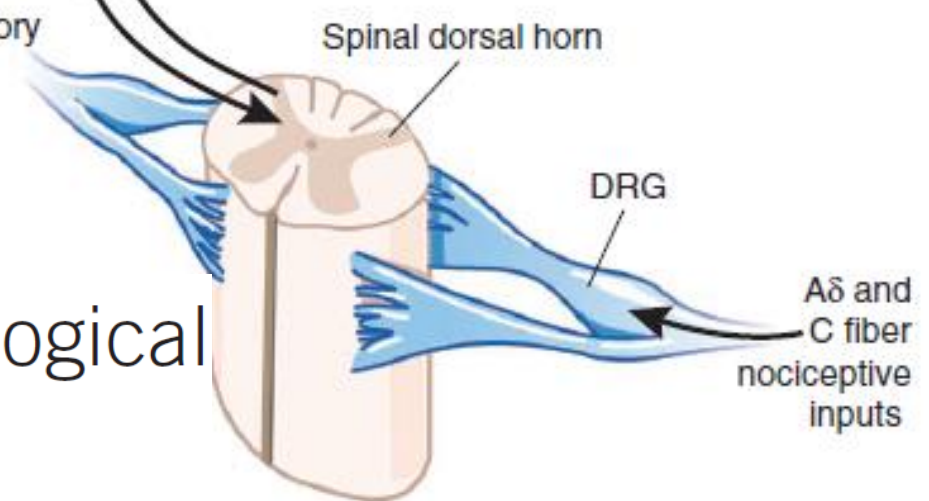




Networks with potential to affect risk for chronic pain

- Reward network
- DPMS
- Areas also relevant to pain percept but that might not affect risk

Descending inhibitory and facilitatory influences



# Pain vulnerability: a neurobiological perspective

# Phantomschmerz nach Amputation

**Table 6** Patients' Current Age, Time Postamputation, and Patients' Age at Time of Amputation (Mean  $\pm$  SD)

	Yes (SD)	No (SD)	<i>p</i>
Phantom pain	n = 29	n = 36	
Age (yr)	48 (15.4)	43 (14.9)	0.51
Follow-up (yr)	3 (0.9)	2 (0.9)	0.69
Age of amputation (yr)	44 (15.6)	41 (15)	0.71
Phantom sensation	n = 35	n = 30	
Age (yr)	44 (14.6)	47 (15.8)	0.48
Follow-up (yr)	3 (0.9)	2 (0.9)	0.55
Age of amputation (yr)	41 (14.7)	44 (16)	0.19
Stump pain	n = 40	n = 25	
Age (yr)	42 (15.8)	50 (13.2)	0.22
Follow-up (yr)	3 (0.9)	3 (1)	0.69
Age of amputation (yr)	40 (15.7)	47 (13.6)	0.48
Stump sensation	n = 51	n = 14	
Age (yr)	43 (15)	52 (14.4)	0.19

**Table 4** Number and Percentage of Subjects Reporting Phantom Pain, Phantom Sensation, Stump Pain, and Stump Sensation (n = 65)

	Phantom Pain (%)	Phantom Sensation (%)	Stump Pain (%)	Stump Sensation (%)
Prevalence	29 (45)	35 (54)	40 (62)	51 (79)
95% CI*	31–45	55–63	41–56	55–61

\* 95% confidence interval.

## Painful and Nonpainful Phantom and Stump Sensations in Acute Traumatic Amputees

Marcus T. Schley, MD, Petra Wilms, MD, Stephanie Toepfner, MD, Hanns-Peter Schaller, MD, PhD, Martin Schmelz, MD, PhD, Christoph J. Konrad, MD, PhD, and Niels Birbaumer, MD, PhD

*The Journal of* **TRAUMA**<sup>®</sup> *Injury, Infection, and Critical Care*

# Phantomschmerz nach Amputation

**Table 7** Percentage and Number of Patients With Respect to the First Experience of Phantom Pain and Amputation Level

Amputation Level	Phantom Pain (%)			<i>p</i>
	Early* (n)	Late† (n)	Never (n)	
Part of finger (n = 27)	7 (2)	19 (5)	74 (20)	<0.01
Finger basic (n = 16)	31 (5)	25 (4)	44 (7)	0.69
More than one finger (n = 22)	14 (3)	46 (10)	41 (9)	<0.01

\* First occurrence within 3 months after amputation.

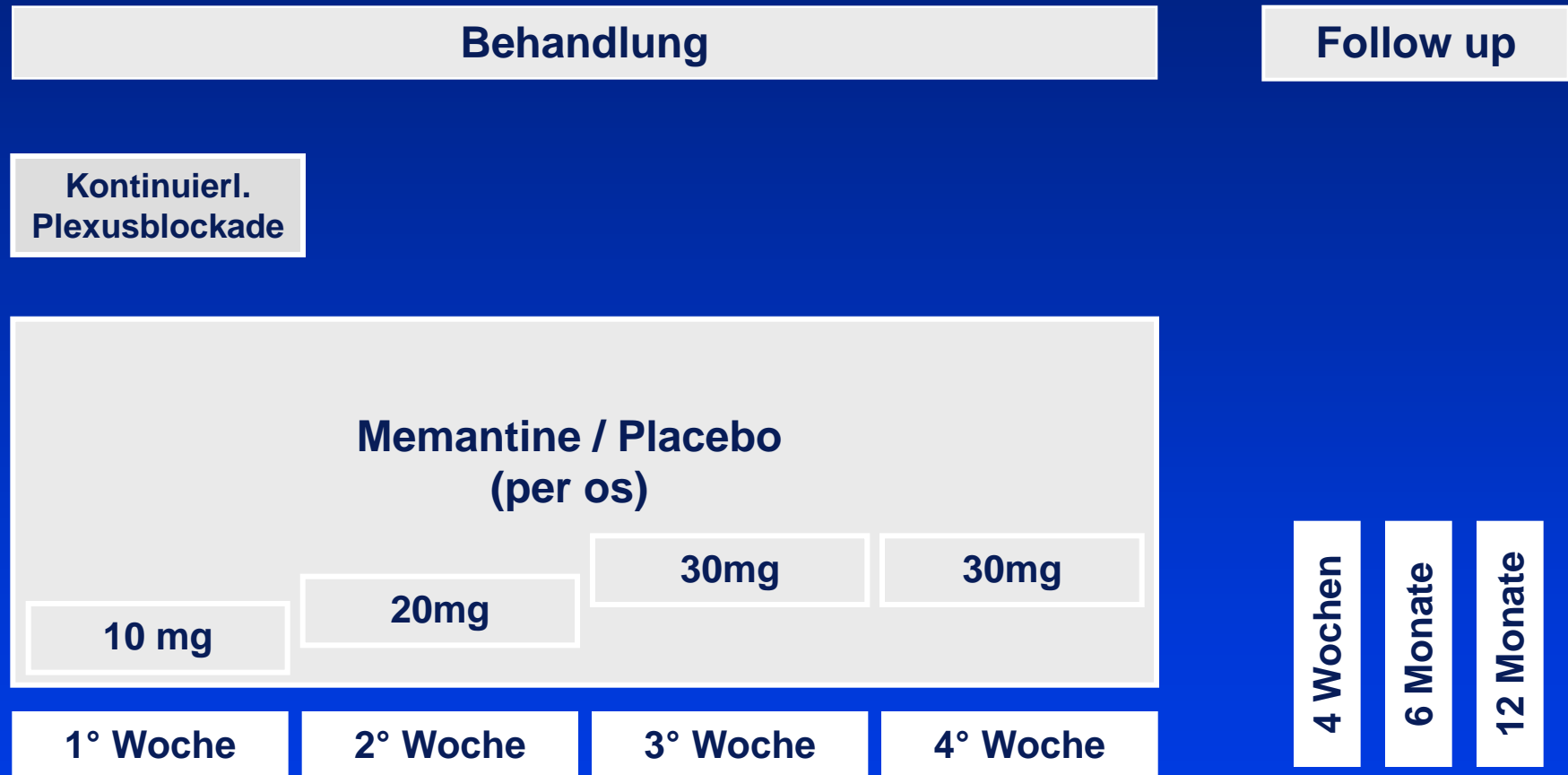
† After 12 months.

**Table 5** Frequency, Dynamics, First Appearance, and Intensity of Phantom and Stump Pain Sensations

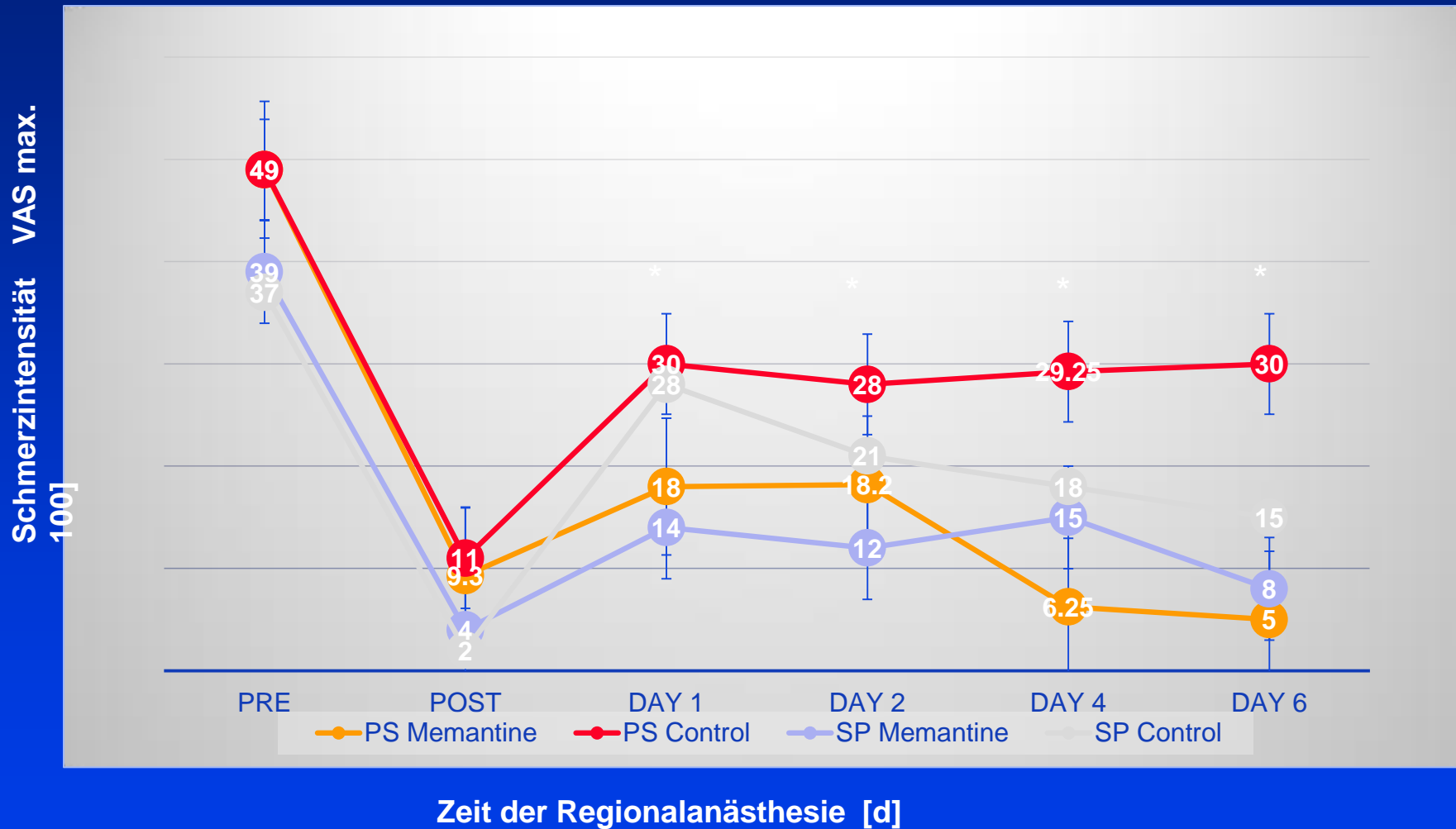
	Phantom Pain (%)	Phantom Sensation (%)	Stump Pain (%)	Stump Sensation (%)
Frequency of pain or sensation (after amputation)	n = 29	n = 35	n = 40	n = 51
Time of first appearance				
At once	8 (28)	5 (14)	12 (30)	9 (18)
1 wk later	1 (3)	2 (6)	4 (10)	2 (4)
1 month later	2 (7)	3 (9)	5 (13)	6 (12)
6 months later	3 (10)	3 (9)	2 (5)	7 (14)
More than 12 months later	12 (41)	19 (54)	16 (40)	22 (43)
Unknown	3 (10)	3 (9)	1 (3)	5 (10)



# Verhindert NMDA – Blockade die Entstehung von Phantomschmerz?

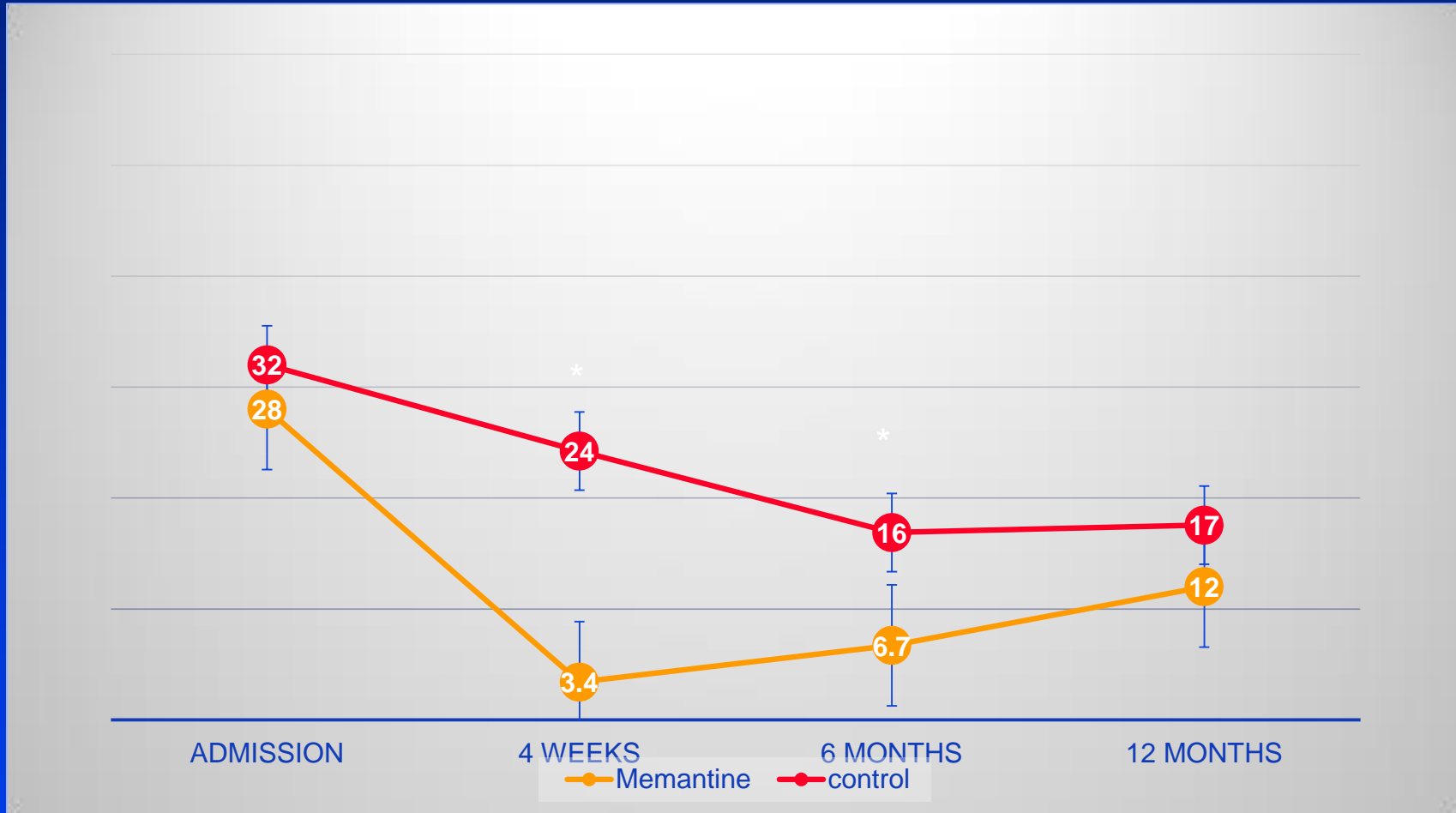


# Perioperatives Schmerzmanagement bei Amputierten mit primären Phantomschmerzen



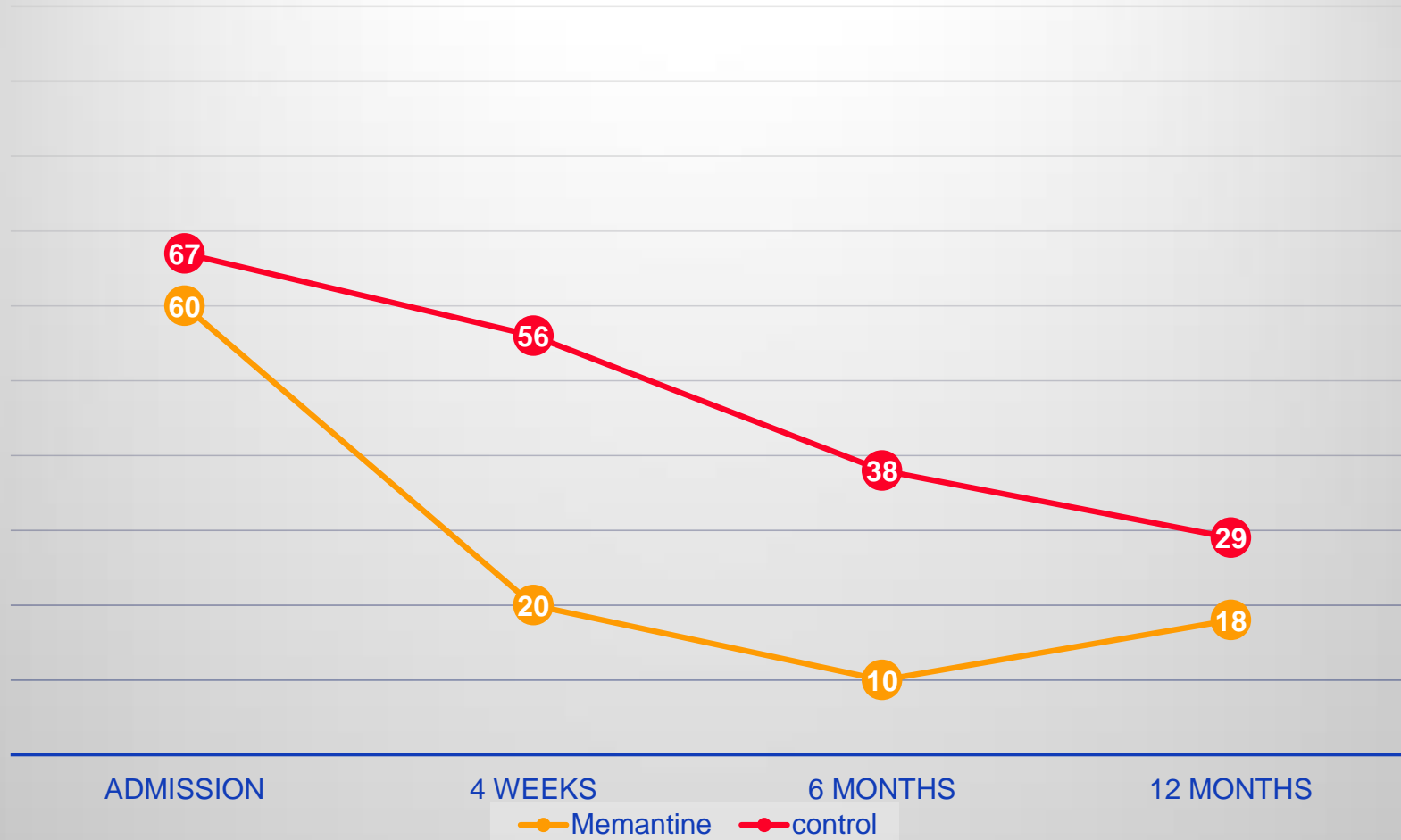
# Zeitverlauf der Schmerzintensität des Phantomschmerzes

Phantom pain Intensity [VAS]



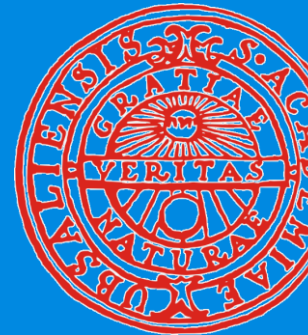
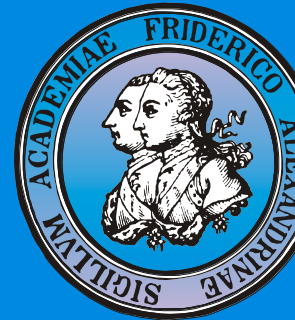
# Prävalenz des Phantomschmerzes

Auftreten von Phantomschmerz [%]





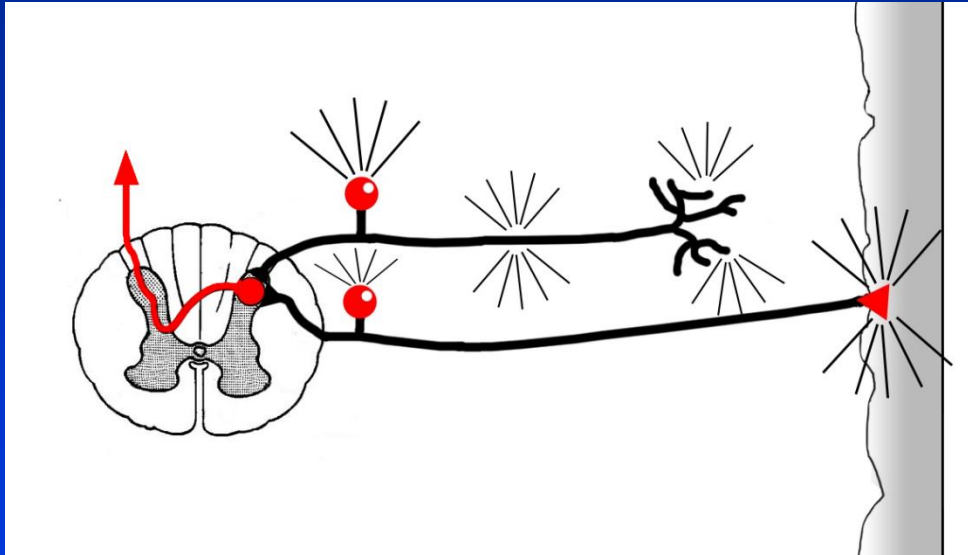
# Neuropathie: wer „Pech“ hat, bekommt auch noch Schmerzen?





# Neuropathischer Schmerz

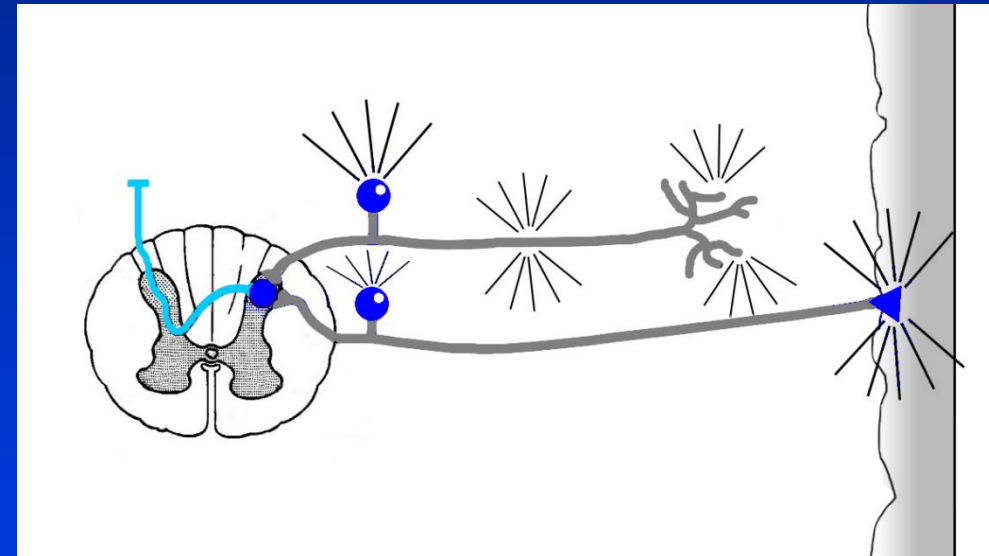
Sensibilisierung  
Spontanaktivität



- Spontanschmerz
- Periphere Sensibilisierung
- Zentrale Sensibilisierung

# Schmerzlose Neuropathie

Degeneration  
Desensibilisierung



- Hyp- Anästhesie
- Hyp- Analgesie
- Taubheitsgefühl

# Neuropathie: mit und ohne Schmerz

## Neuropathie



schmerzlose  
Neuropathie

Neuropathischer  
Schmerz

(intraepi. Faserdichte)



schmerzlose  
Neuropathie

Neuropathischer  
Schmerz

Funktionelle  
(z.B. QST,  
evozierte Potentiale, Sudometrie,  
Axonreflex, RR Variabilität)

# Überblick

Quantitative sensorische Testung  
und Hautbiopsien

bei schmerzhafter und schmerzloser  
traumatischer Neuropathie:

Was kennzeichnet den neuropathischen  
Schmerzpatienten?

# Überblick

Was kennzeichnet den neuropathischen  
Schmerzpatienten?

Ergebnisse vor 20 Jahren

	HP:5				P
	50th to <97.5th		≥97.5th		
	n	Mean	n	Mean	
NSC severity	379	9.12	390	10.74	<0.001
NSC(W)	379	0.16	390	0.32	0.005
NSC(S)	379	7.01	390	8.41	<0.001
NSC(A)	379	1.94	390	2.01	0.766
NSC(LF)	379	1.64	390	2.22	<0.001
NSC(SF)	379	1.30	390	2.10	<0.001
<b>NSC(P)</b>	379	4.05	390	4.07	<b>0.590</b>

## Patterns of Quantitative Sensation Testing of Hypoesthesia and Hyperalgesia Are Predictive of Diabetic Polyneuropathy

PETER J. DYCK, MD  
P. JAMES B. DYCK, MD  
JORGE A. VELOSA, MD

TIMOTHY S. LARSON, MD  
PETER C. O'BRIEN, PHD  
THE NERVE GROWTH FACTOR STUDY GROUP

DIABETES CARE, VOLUME 23, NUMBER 4, APRIL 2000

Keine Korrelation zwischen  
Stärke des neuropathischem Schmerzes (NSC(P))  
und induziertem Hitzeschmerz  
(über 700 Patienten eines NGF-clinical trials)



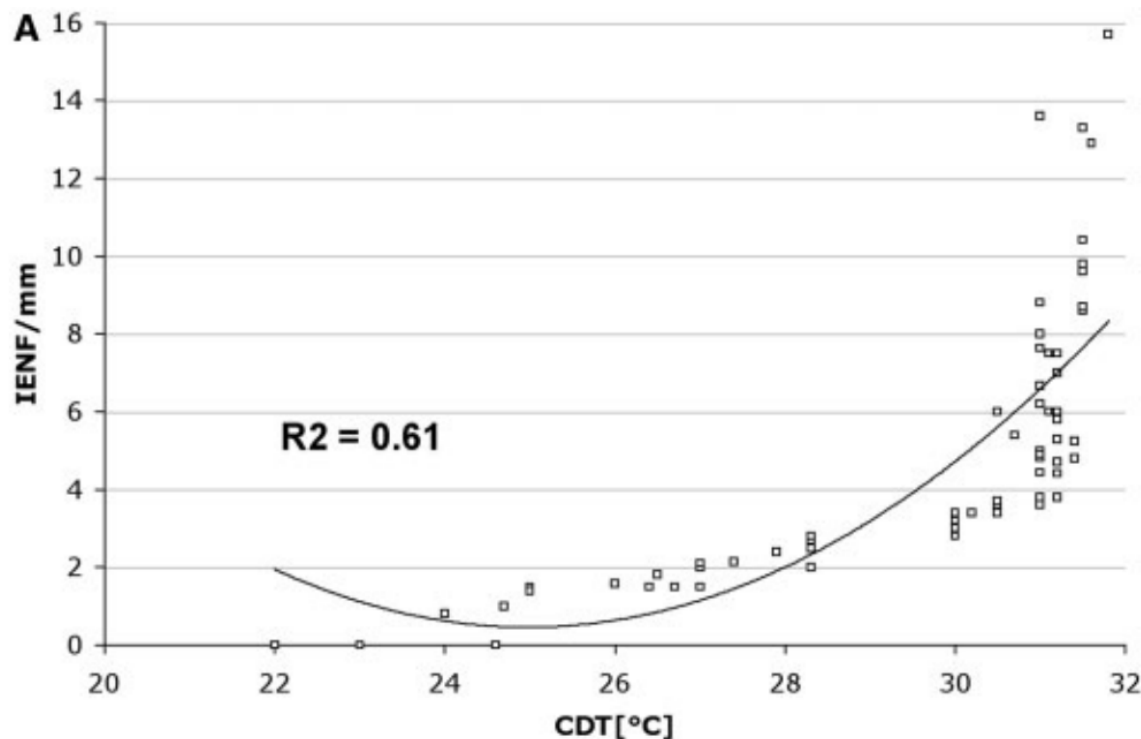
# Überblick

Was kennzeichnet den neuropathischen  
Schmerzpatienten?

Ergebnisse vor 10 Jahren

# The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology

Grazia Devigili,<sup>1</sup> Valeria Tugnoli,<sup>2</sup> Paola Penza,<sup>3</sup> Francesca Camozzi,<sup>3</sup> Raffaella Lombardi,<sup>3</sup> Giorgia Melli,<sup>3</sup> Laura Broglio,<sup>4</sup> Enrico Granieri<sup>1</sup> and Giuseppe Lauria<sup>3</sup>

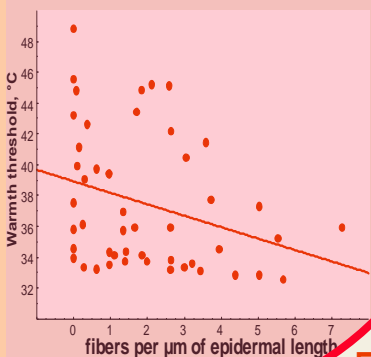


keine Korrelation zwischen Stärke des neuropathischem Schmerzes (VAS) und Nervenfaserdichte

starke Korrelation zwischen thermischen Schwellen und Nervenfaserdichte

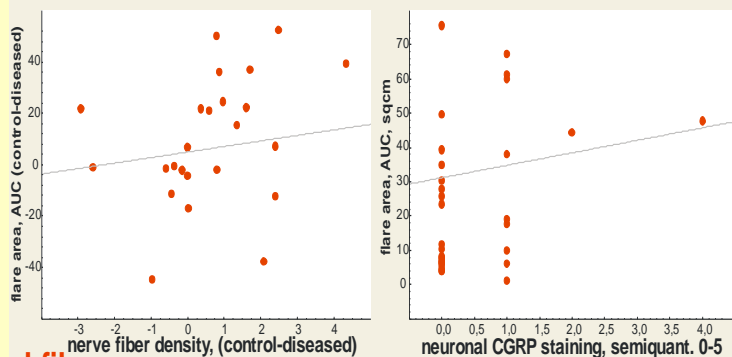
# Innervationsdichte korreliert mit sensorischer Funktion...

## Warmth threshold

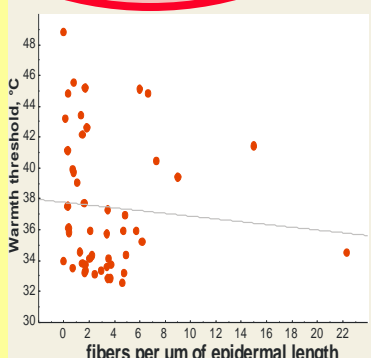
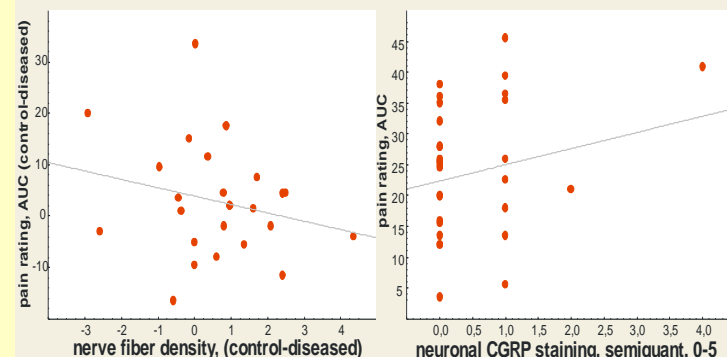


## Epidermal fibers

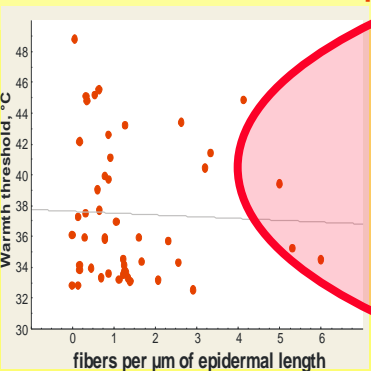
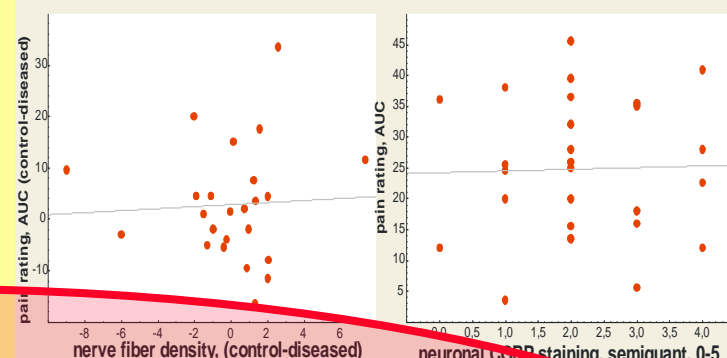
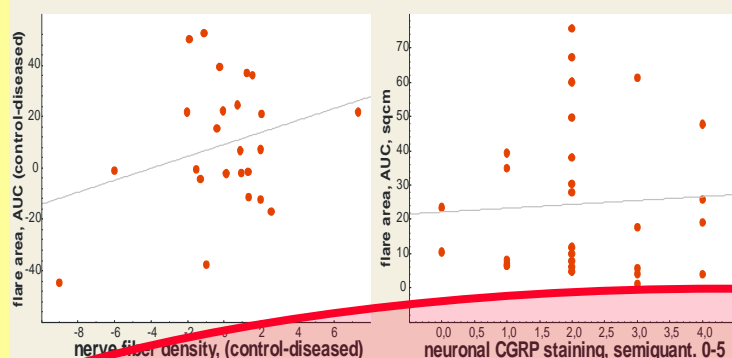
## electrically induced flare



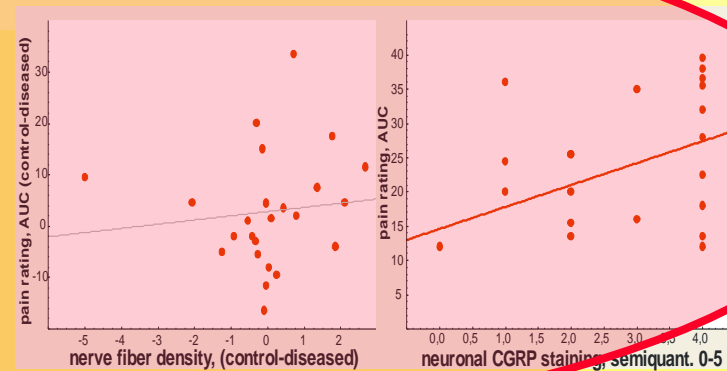
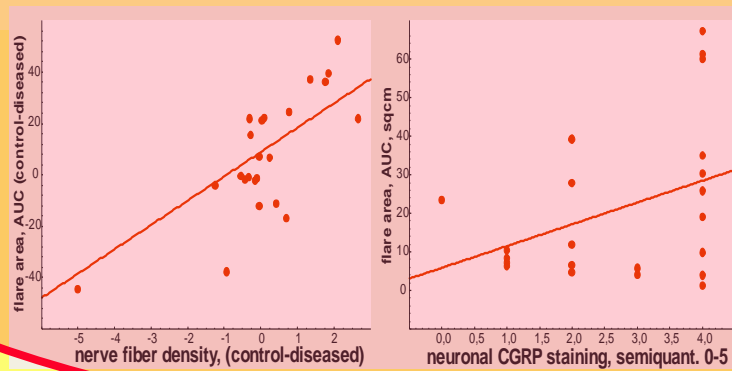
## electrically induced pain



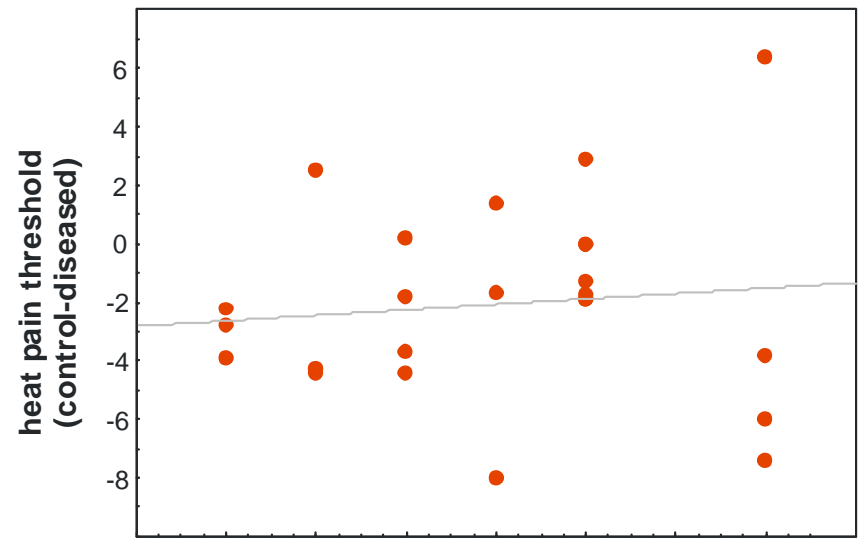
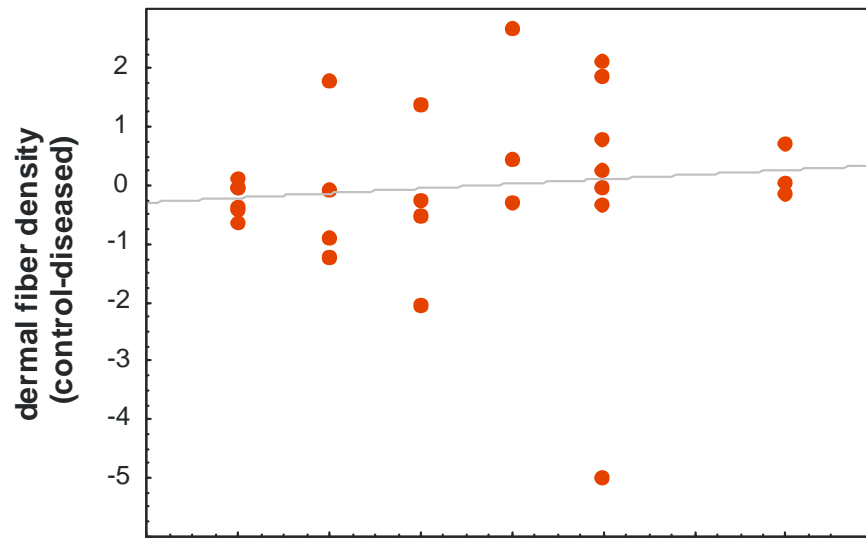
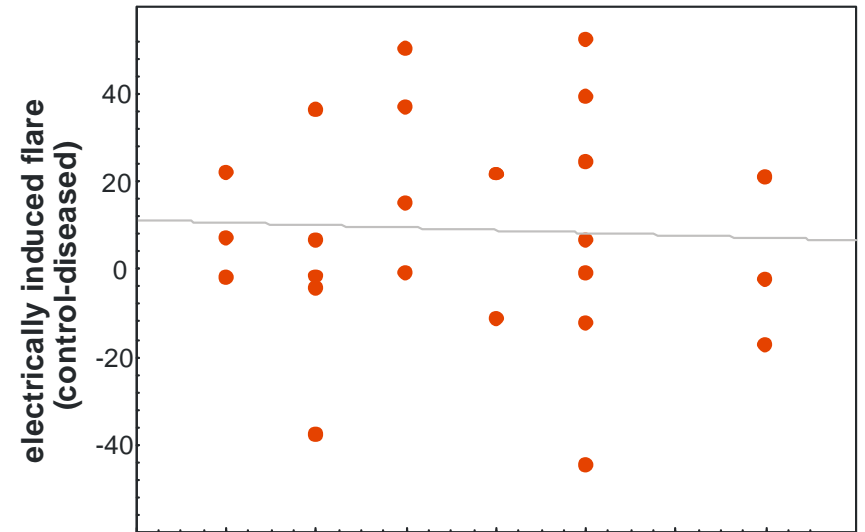
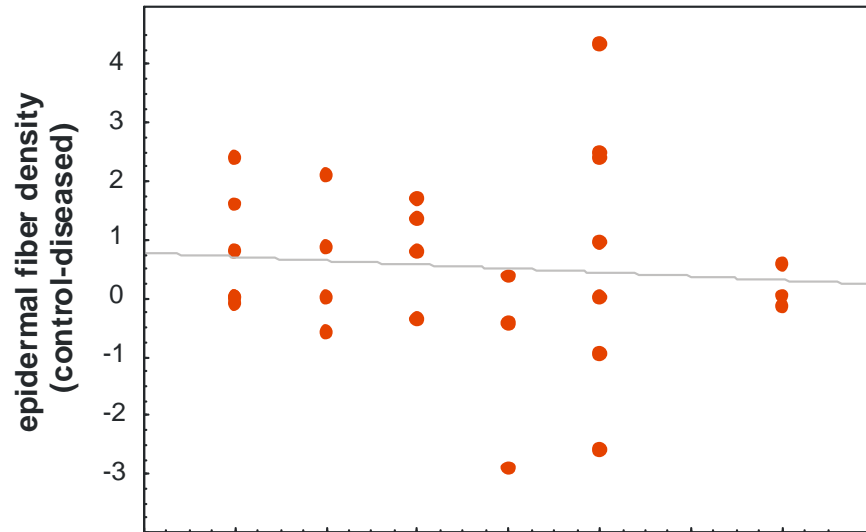
## Upper dermal fibers



## Dermal fibers



# ...aber nicht mit Schmerzstärke!



clinical pain intensity during the last 4 weeks, numerical pain rating (0-10)

# Überblick

Was kennzeichnet den neuropathischen  
Schmerzpatienten?

aktuell

# Wie unterscheiden sich Neuropathie-Patienten mit und ohne Schmerz?

Raputova et al. Pain Dez. 2017

Logistic regression

OR (95% CI)

P

Model 1 (N = 232): Painful DSPN (NRS > 0) (N = 158) vs painless DSPN (N = 74)

mTCNS total score	≥7 (ref. 0-6)	6.184 (2.506; 15.263)	<0.001
PCS total score	≥1 (ref. 0)	16.679 (6.464; 43.031)	<0.001
STAI-T total score	≥37 (ref. 0-36)	4.294 (1.752; 10.522)	0.001
mMRC—Leg total score (R + Muscle strength scale	<60 (ref. 60)	5.212 (1.318; 20.617)	0.019
QST (foot)—WDT	< -1.5 (ref. ≥ -1.5)	3.389 (1.376; 8.345)	0.008

Model 2 (N = 140): Painful DSPN with severe (NRS > 6) pain (N = 66) vs painless DSPN (N = 74)

mTCNS total score Mod. Toronto Neuropath. Skala	≥7 (ref. 0-6)	99.172 (16.079; 611.685)	<0.001
ODSS total score Overall Disability Sum Score	≥1 (ref. 0)	5.343 (1.176; 24.285)	0.028
PCS total score Pain Catastrophizing scale	≥3 (ref. 0-2)	76.099 (11.970; 483.777)	<0.001

	N	AUC (95% CI)	P	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Accuracy of verified multivariate logistic models to predict pain							
Model 1							
Multivariate model	232	0.943 (0.915; 0.971)	<0.001	92.9%	76.1%	89.5%	83.1%
Model 2							
Multivariate model	140	0.977 (0.955; 0.999)	<0.001	87.9%	97.3%	96.7%	90.0%

**Weder ein schmerz-relevanter QST Parameter noch die intra-epidermale Nervenfaserdichte unterscheidet zwischen schmerzhafter vs. nicht schmerzhafter Neuropathie!**



# Wie unterscheiden sich Neuropathie-Patienten mit und ohne Schmerz?

Raputova et al. Pain Dez. 2017

Parameters		starker Schmerz (NRS $\geq$ 4)	Leichter Schmerz (NRS 1-3)	Ohne Schmerz (NRS 0)	P
		N = 106	N = 52	N = 74	
QST - foot					
QST summary*	Normal (no abnormalities)	5(4.7%)	3 (5.8%)	8 (10.8%)	0.265
	Abnormal (at least one abnormality)	101(95.3%)	49 (94.2%)	66 (89.2%)	
QST summary†	Normal (no abnormalities)	20 (18.9%) <sup>a</sup>	12 (23.1%) <sup>a</sup>	28 (37.8%) <sup>b</sup>	0.015
	Abnormal (at least one abnormality)	86 (81.1%)	40 (76.9%)	46 (62.2%)	
Sensory profiles	<b>Irritable nociceptor profile</b>	<b>13 (12.3%)<sup>a</sup></b>	<b>10 (19.2%)<sup>b</sup></b>	<b>8 (10.8%)<sup>c</sup></b>	< 0.001
	Deafferentation profile	61 (57.5%)	24 (46.2%)	20 (27.0%)	
	Other	32 (30.2%)	18 (32.6%)	46 (62.2%)	

# Wie unterscheiden sich Neuropathie-Patienten mit und ohne Schmerz?

**PAIN**

OPEN

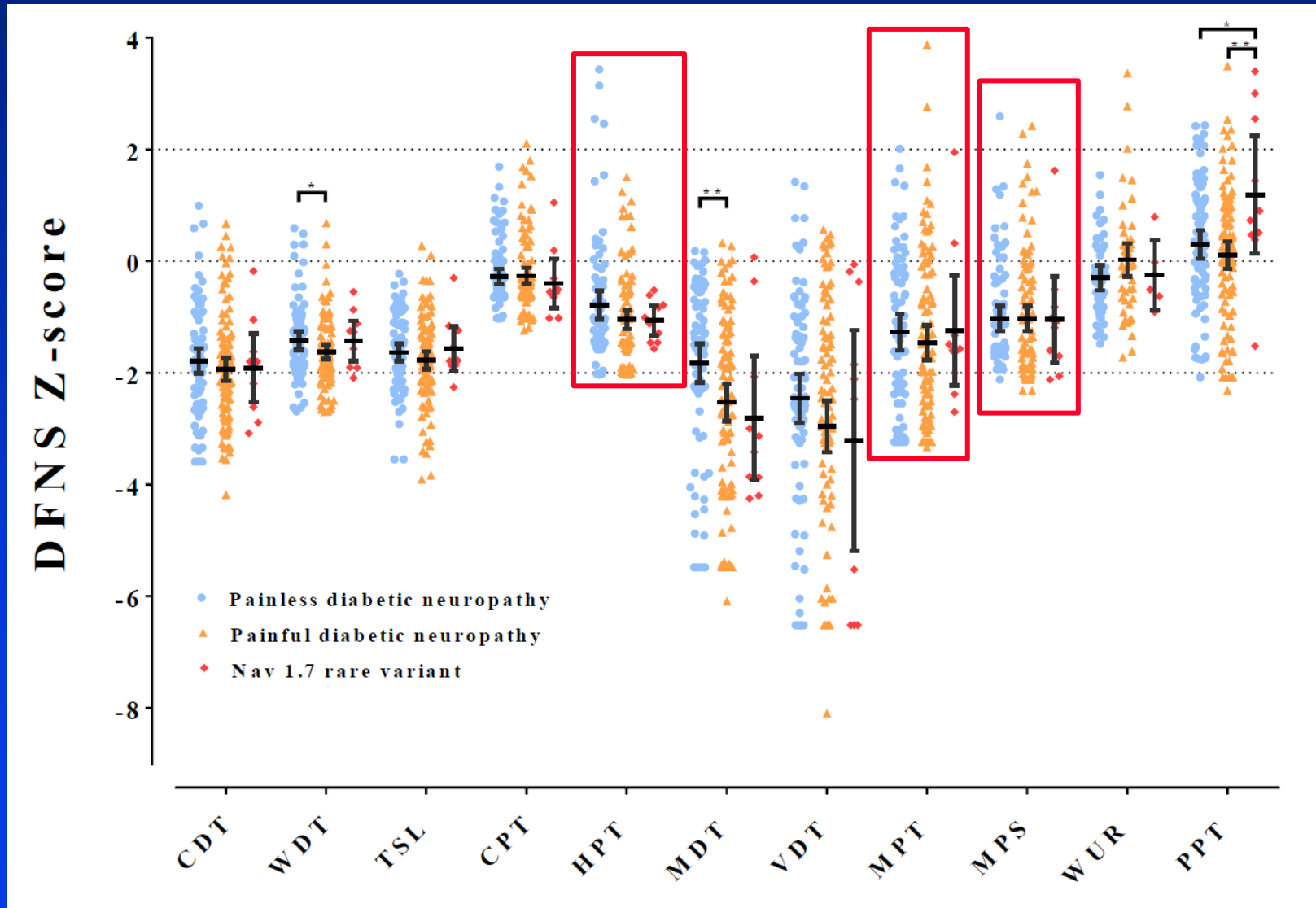
## Rare Nav1.7 variants associated with painful diabetic peripheral neuropathy

Iulia Blesneac<sup>a</sup>, Andreas C. Themistocleous<sup>a,b</sup>, Carl Fratter<sup>c</sup>, Linus J. Conrad<sup>d</sup>, Juan D. Ramirez<sup>a</sup>, James J. Cox<sup>e</sup>, Solomon Tesfaye<sup>f</sup>, Pallai R. Shillo<sup>f</sup>, Andrew S.C. Rice<sup>g</sup>, Stephen J. Tucker<sup>d,h</sup>, David L.H. Bennett<sup>a,h,\*</sup>

**QST Profile bei schmerzhafter diabetischer Neuropathie  
– teilweise Patienten mit  
gesicherter sensibilisierender Mutation des  
spannungsgesteuerten Natriumkanals NaV1.7:  
damit gesicherte „irritable Nozizeptoren“**

# Haben Patienten mit gesicherten irritablen Nozizeptoren einen QST Phänotyp: irritable Nozizeptoren?

Blesneac et al. Pain 2018, in press



# Schlußfolgerung

Quantitative sensorische Testung  
und Hautbiopsien

bei schmerzhafter und schmerzloser Neuropathie:

Biomarker für Neuropathie  
Kein Biomarker für Schmerz

QST Profile unterscheiden Neuropathieverläufe,  
aber keine Schmerzmechanismen



# CRPS

Martin Schmelz

University Heidelberg,

Faculty of Clinical Medicine Mannheim

Dept. Anesthesiology

# CRPS: Klinik

Trauma, +/- periphere Nervenläsion  
=>  
5% der Patienten (Prädisposition?)

CRPS

**PNS**

Schmerz

Entzündung

Trophik

Schwitzen

**ZNS**

Hyperalgesie

Motorik

Vasokonstriktion



# CRPS: Was gibt es Neues?

---

- Auto-Antikörper – IgM (exp. CRPS Modell)
- Auto-Antikörper gegen Keratin 16 (Patienten)
- No pain – no gain (Therapie-Ansatz; klin. Studie)

# Injektion von Serum betroffener Mäuse löst bei Kontrollmäusen Schmerzverhalten aus

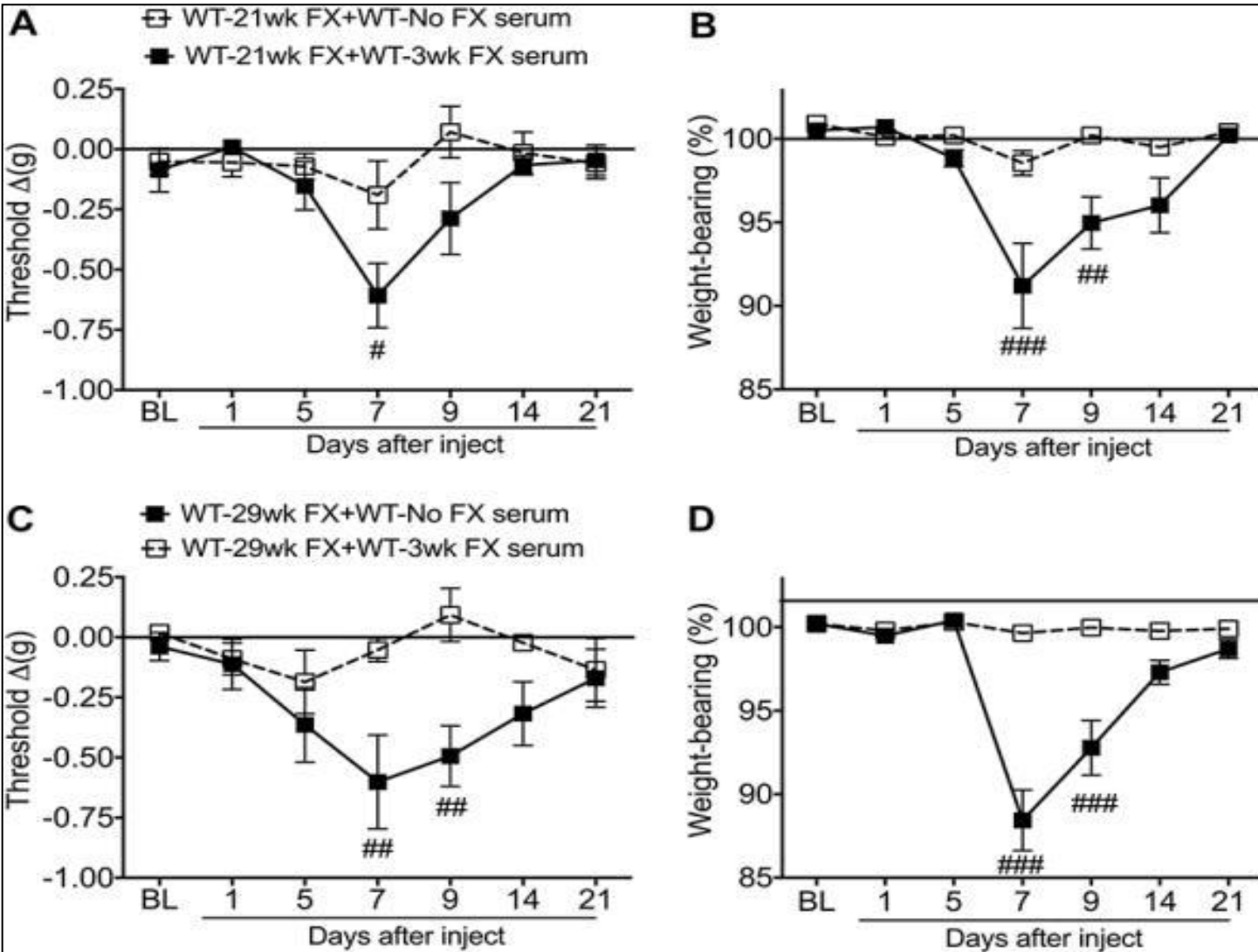
Passive transfer autoimmunity in a mouse model of complex regional pain syndrome.

Guo, Tian-Zhi; Shi, Xiaoyou; Li, Wen-Wu; Wei, Tzuping; Clark, John; Kingery, Wade

Pain. 158(12):2410-2421, December 2017.

DOI: 10.1097/j.pain.0000000000001046

Figure 4. Serum from 3-week postfracture (FX) wild-type (WT) mice was pronociceptive in 21- and 29-week post-FX WT mice that had resolved allodynia and unweighting. Wild-type mice exhibited unilateral hind paw von Frey allodynia and unweighting at 3-week post-FX and these pain behaviors gradually resolved over the ensuing 21 weeks (Fig. 1). Serum from 3-week post-FX WT mice was injected into 21- and 29-week post-FX WT mice to test the hypothesis that pronociceptive autoantigens persist in the FX hind limb and corresponding lumbar cord after the resolution of post-FX pain behaviors. Injection of 3-week post-FX WT serum (500 [mu]L, i.p.) caused a reoccurrence of the fracture limb hind paw allodynia and unweighting in both the 21- (A and B) and 29- (C and D) week post-FX WT mice but had no effect in the contralateral limb or in control nonfractured mice (data not shown). A 2-way repeated-measures analysis of variance was performed followed by a Holm-Sidak test for post hoc contrasts. Data are expressed as mean values +/- SEM. #P < 0.001 for WT-21 wk FX + WT-3 wk FX serum (n = 8/cohort) vs WT-21 wk FX + WT-no FX serum (n = 8/cohort) and WT-29 wk FX + WT-3 wk FX serum (n = 8/cohort) vs WT-29 wk FX + WT-no FX serum (n = 8/cohort). FX, fracture; no FX serum, serum from WT mice that did not undergo FX; 3-wk FX serum, serum from 3-week post-FX WT mice; BL, baseline.



# .. auch die Injektion von aufgereinigtem IgM aus Serum betroffener Mäuse

Passive transfer autoimmunity in a mouse model of complex regional pain syndrome.

Guo, Tian-Zhi; Shi, Xiaoyou; Li, Wen-Wu; Wei, Tzuping; Clark, John; Kingery, Wade

Pain. 158(12):2410-2421, December 2017.

DOI: 10.1097/j.pain.0000000000001046

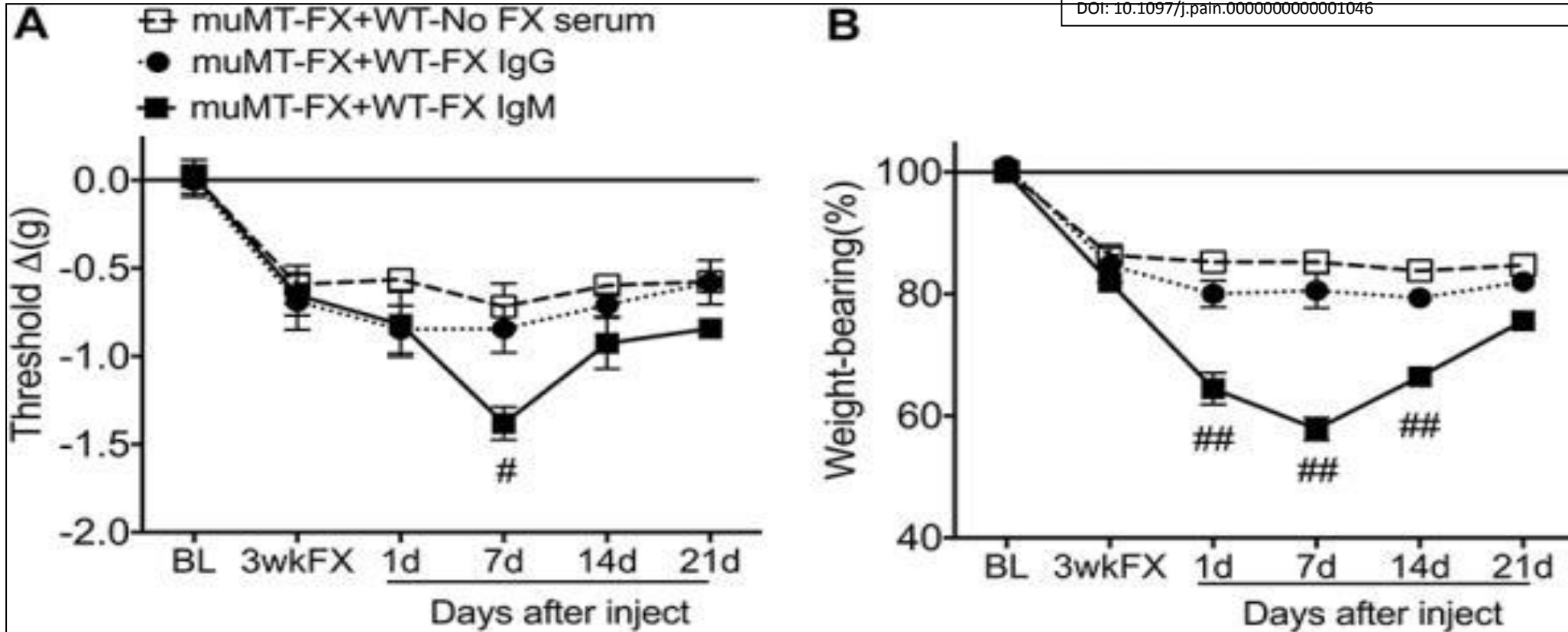
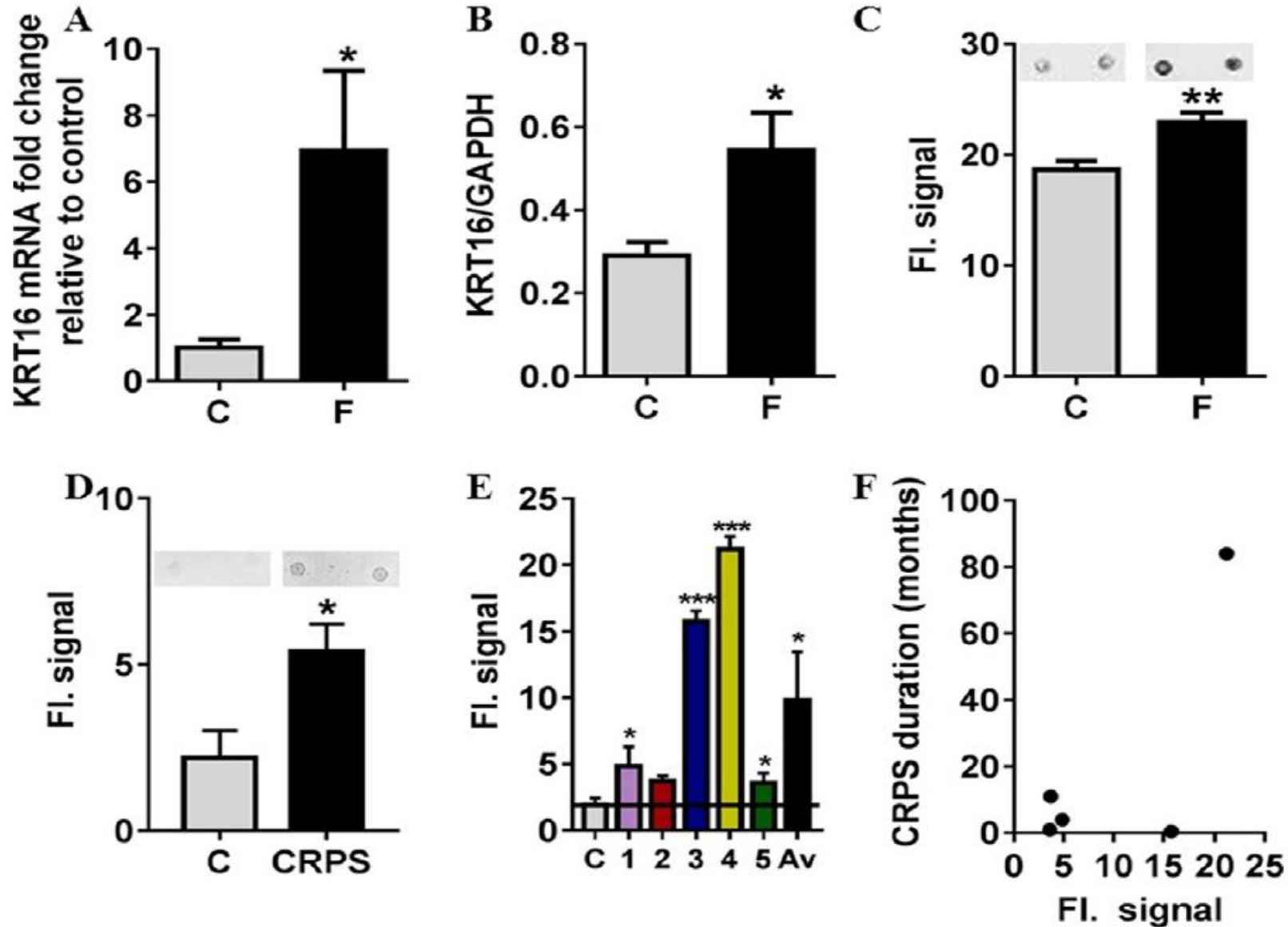


Figure 5. Immunoglobulin M (IgM) pronociceptive effects in postfracture (FX) muMT mice lacking B cells. Injection of purified IgM (0.5 mg, i.p.) from wild-type (WT) 3-week post-FX mice gradually increased fracture limb hind paw von Frey allodynia (A) and unweighting (B) in 3-week post-FX muMT mice, with significant effects at 7 days after injection. IgM injection had no effect on nociceptive testing in the contralateral hind paw (data not shown). IgG (5.0 mg, i.p.) injection had no effect. A 2-way repeated-measures analysis of variance was performed followed by a Holm-Sidak test for post hoc contrasts. Data are expressed as mean values  $\pm$  SEM. <sup>#</sup>  $P < 0.01$  for muMT-FX + WT-FX IgM (n = 9-11) vs muMT-FX + no FX-WT serum (n = 9-11) or muMT-FX + WT-FX IgG (n = 9-11). muMT, mice lacking B cells; FX, fracture; BL, baseline; 3-wk FX, 3-week post-FX.

# Auto-Antikörper (IgM) gegen Keratin 16 bei CRPS Patienten

M. Tajerian et al. / *Experimental Neurology* 287 (2017) 14–20



# CRPS: Klinik

Trauma, +/- periphere Nervenläsion  
=>  
5% der Patienten (Prädisposition?)

CRPS

**PNS**

Schmerz

Entzündung

Trophik

Schwitzen

**ZNS**

Hyperalgesie

Motorik

Vasokonstriktion

# Kälteallodynie

Bei Patienten mit peripherem Nervtrauma der Hand:

- QST diagnostizierte Kälteallodynie korreliert nicht mit neuropathischem Schmerz
- Klinische Untersuchung mit dem Metallroller ist spezifischer als langsames Abkühlen
- Unspezifische Kälteüberempfindlichkeit bei traumatischem neuropathischem Schmerz der Hand





# Kälte reduziert Schmerz

- **Langsamere Natriumkanäle:  
schlechtere Weiterleitung (z.B. Kühlspray)**



- **Weniger aktive Na/K Pumpe: leichte  
Depolarisation (z.B. Erythromelalgie)**



# Kälte reduziert Schmerz

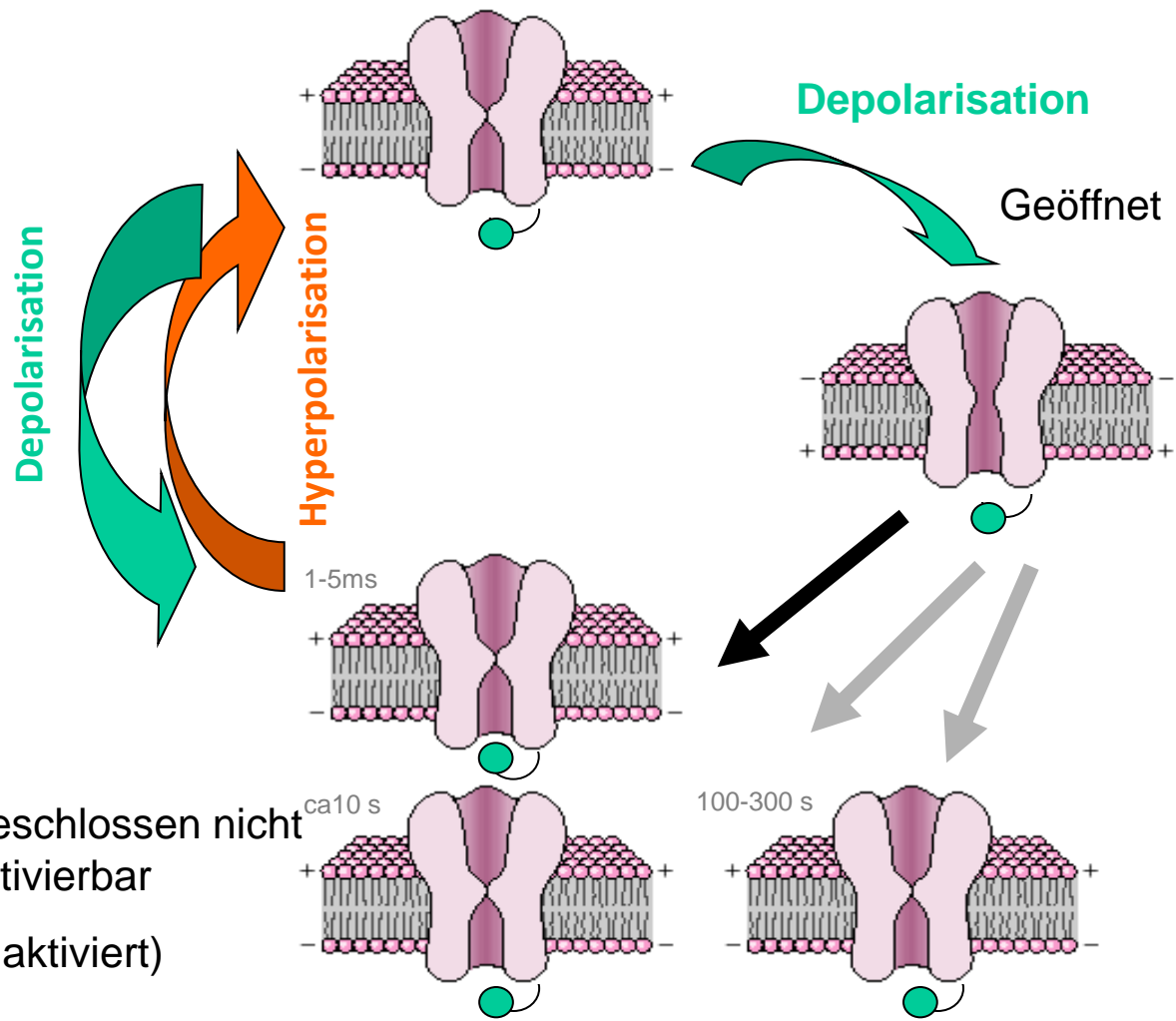
- **Weniger aktive Na/K Pumpe: leichte Depolarisation (z.B. Erythromelalgie): Natriumkanal-Inaktivierung**





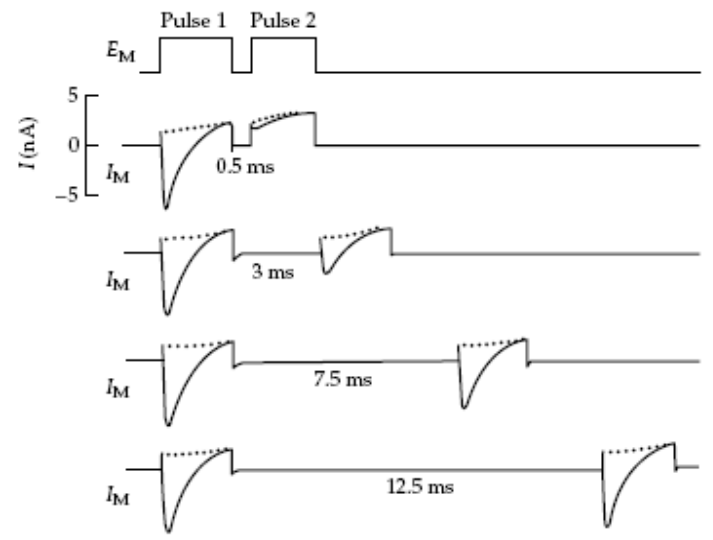
# Spannungsabhängige Zustände von Natriumkanälen

Geschlossen  
aktivierbar

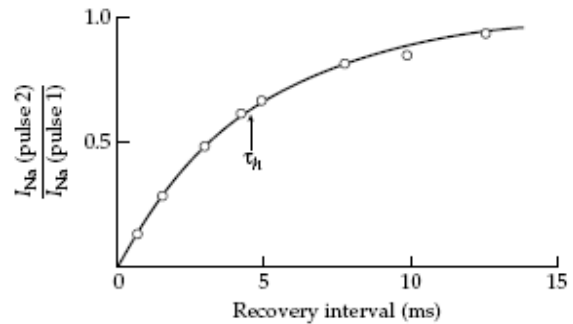


## Beobachtung

(A) TWO-PULSE EXPERIMENT



(B) RECOVERY CURVE





# Kälte erzeugt „Schmerz“

- **Kaltüberempfindlichkeit während der Oxaliplatinbehandlung**
- **Kalt wird stärker, unangenehm und länger empfunden (Berühren kalter Objekte, Schlucken von kalten Flüssigkeiten)**
- **Muskelkrämpfe**
- **Parästhesien**



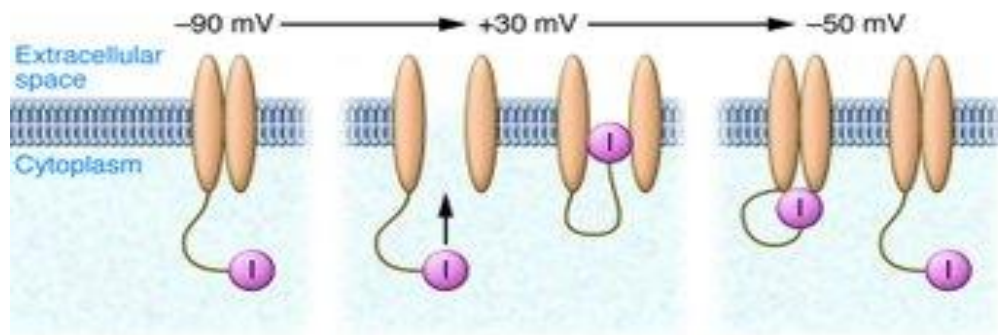
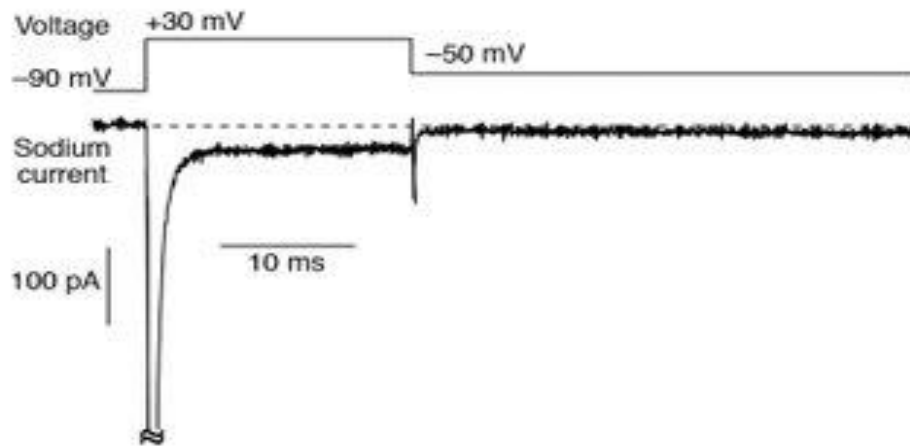
# Kälte erzeugt „Schmerz“

- **Akute Neuropathie?**
- **Akute Medikamentenwirkung auf dick und dünn myelinisierte Nervenfasern!**
- **„resurgent currents“ von Natriumkanälen myelinisierter Fasern (NaV1.6)**
- **„Fuß in der Tür“ – Prinzip**

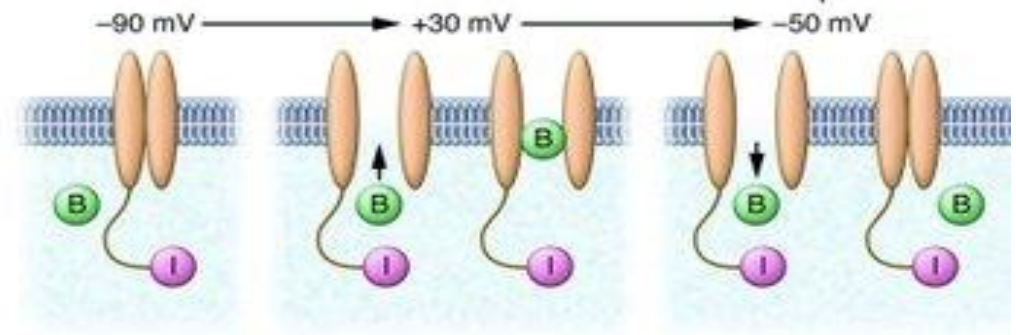
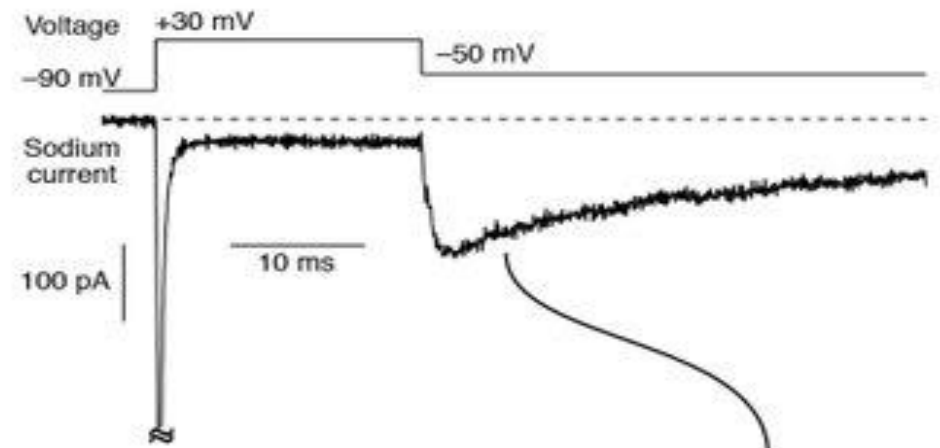


# „Fuß in der Tür des Natriumkanals NaV1.6“: resurgent currents

**A** Classic sodium current (hippocampal pyramidal neuron)



**B** Resurgent sodium current (cerebellar Purkinje neuron)

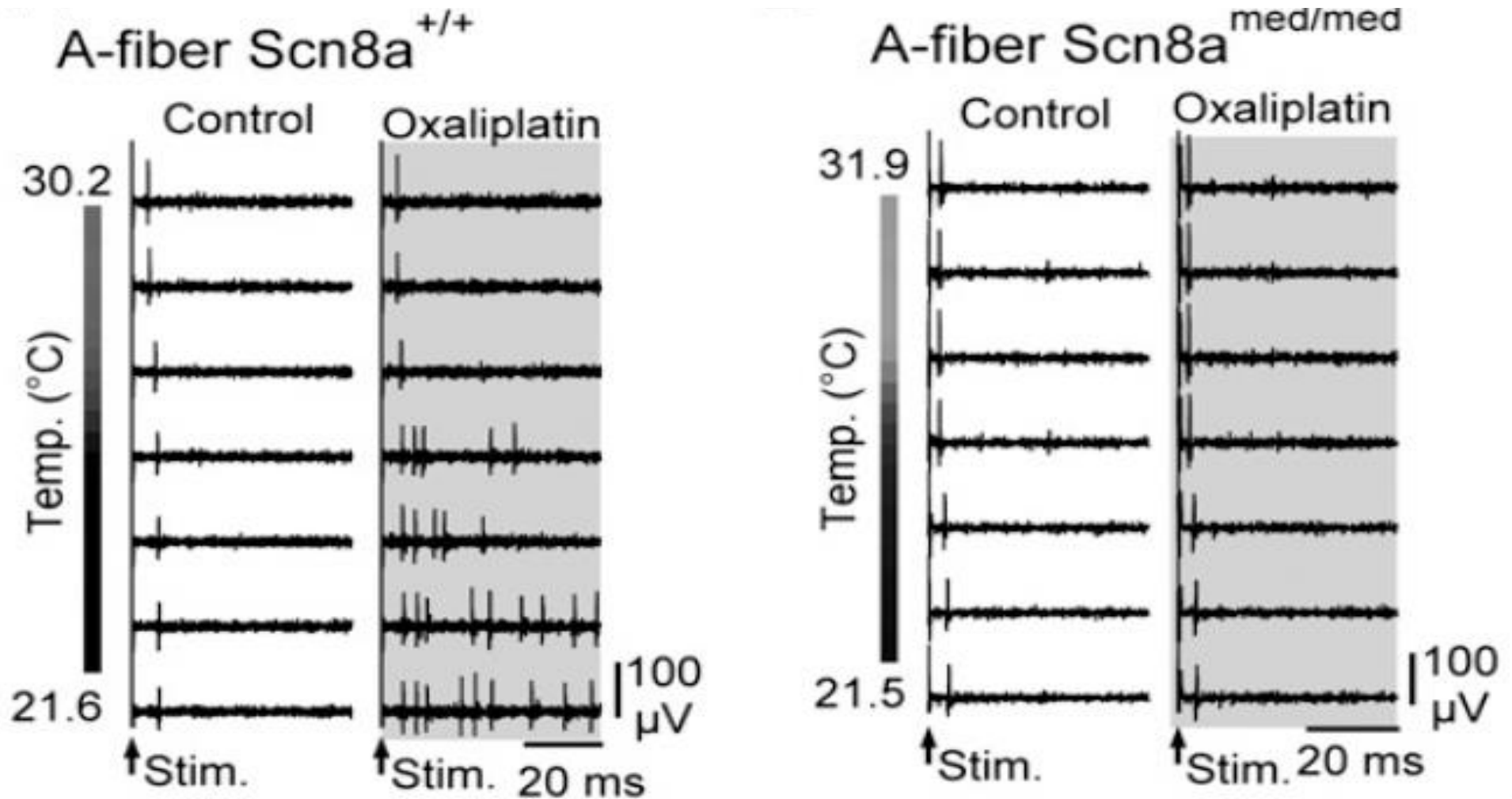






# „Fuß in der Tür des Natriumkanals NaV1.6“: resurgent currents

## Aktionspotentiale einzelne Nervenfasern







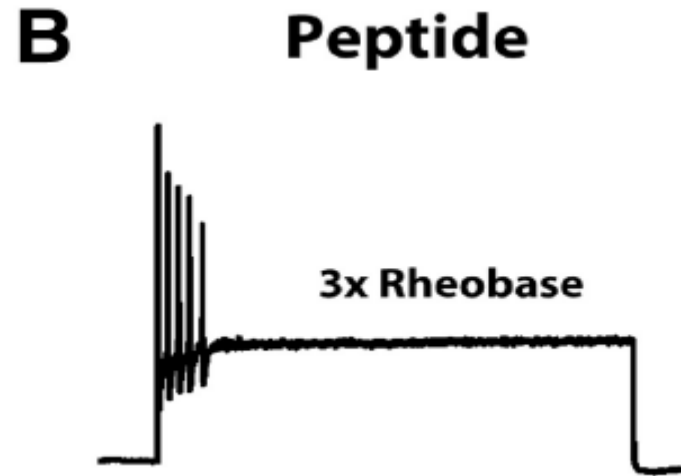
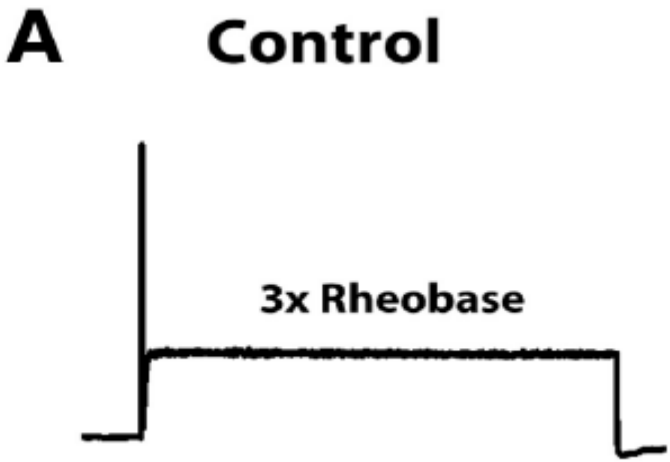
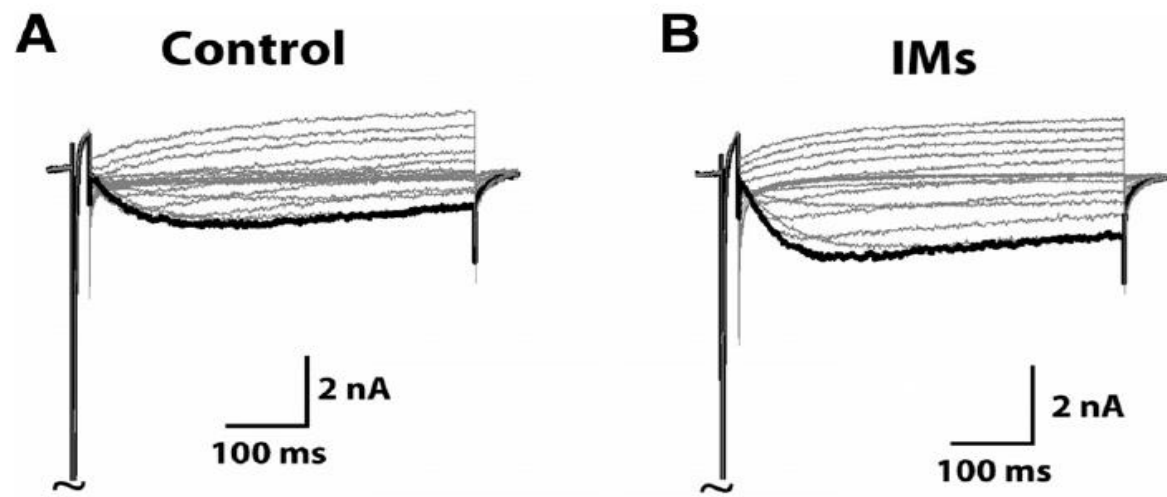
# Kälte erzeugt Schmerz

- **Späterer Verlauf: echte Kaltallodynie**
- **„resurgent currents“ von Natriumkanälen unmyelinisierter Fasern (NaV1.8)?**
- **„Fuß in der Tür“ – Prinzip – allerdings bei Nozizeptoren**



# „Fuß in der Tür des Natriumkanals NaV1.8“: resurgent currents

**TTXr Ströme  
in Spinalganglienzellen,  
verstärkt  
durch Entzündungs-  
mediatoren (IM)**



**Nachentladungen  
durch  
„Fuß in der Tür“ –  
Peptid  
(NaV  $\beta$ 4)**

Tan et al. 2014, J Neurosci



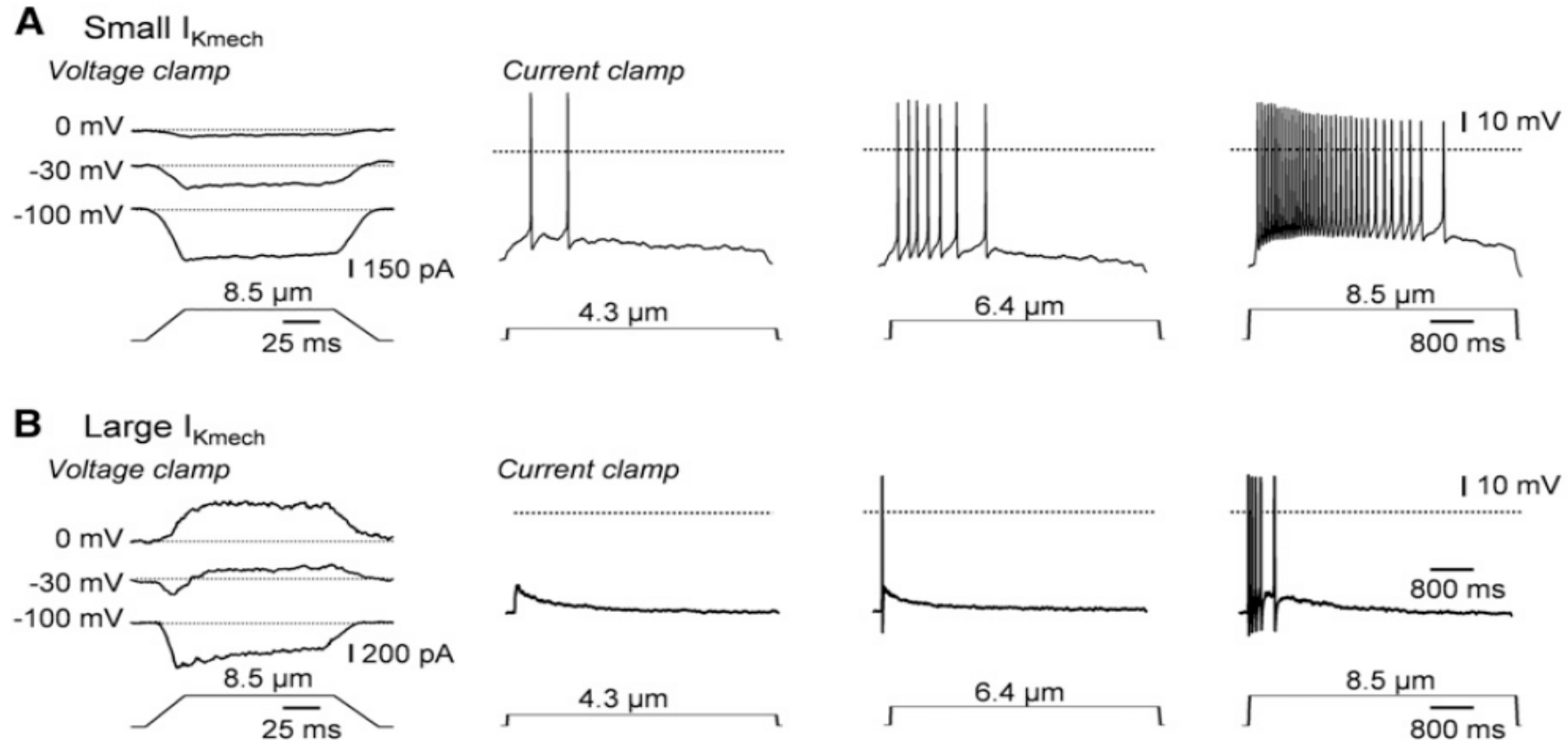
# Kälte erzeugt Schmerz

- **Kaltallodynie**
- **Schließen von „bremsenden“ Kaliumkanälen (Kv1.7)**
- **Leichte Depolarisation**
- **Größere Empfindlichkeit gegenüber anhaltenden Membranströmen**



# „fehlende Bremse“: Kaliumkanal Kv1.1 / 1.2

## Mehr Entladung von Spinalganglienzellen mit wenig Kv 1.1

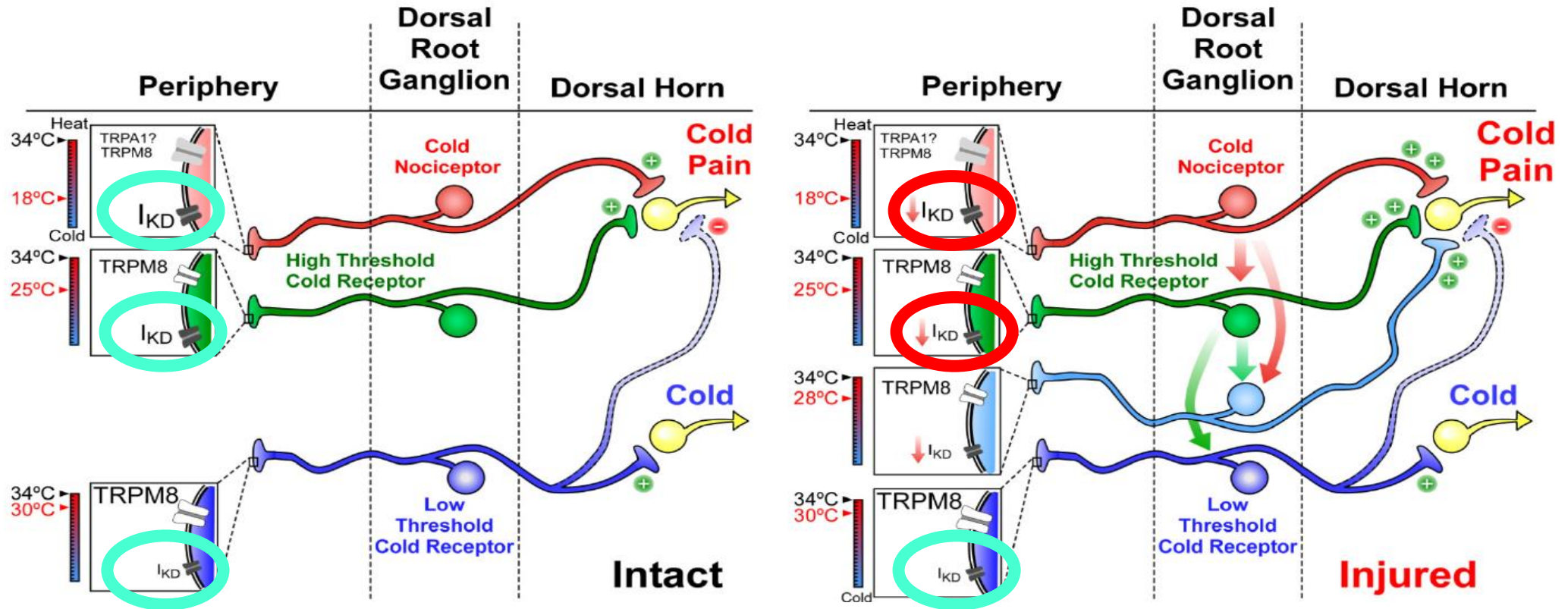


Hao et al. 2013, Neuron



# „fehlende Bremse“: Kaliumkanal Kv1.1 / 1.2

Höhere Kaltempfindlichkeit von Nozizeptoren bei fehlender Bremse



Gonzalez et al. 2017, J Neurosci



# Klinische Beispiele: was heißt das jetzt für den Patienten?

- **Kälteallodynie bei  
„non-freezing cold injury“**

**Niedrige Kaltschmerzschwelle,  
aber nur geringer Schmerzanstieg  
bei weiterer Abkühlung**

(Ellen Jorum, Clin. Neurophysiol. Oslo, personal communication)



# **Klinische Beispiele: was heißt das jetzt für den Patienten?**

- **Kälteallodynie nach Nervenverletzung**

**Klinische Zeichen von  
fehlender Bremse oder „resurgent currents“?**



# Kälteallodynie

Bei Patienten mit peripherem Nervtrauma der Hand:

- Unspezifische Kälteüberempfindlichkeit auch bei Patienten ohne Schmerzproblem!
- Klinische Untersuchung mit dem Metallroller trennt besser zwischen Patienten mit und ohne Schmerz
- klinische Befunde:  
Kein klarer Hinweis auf Mechanismus





# Klinische Implikationen von Kälte-induziertem Schmerz

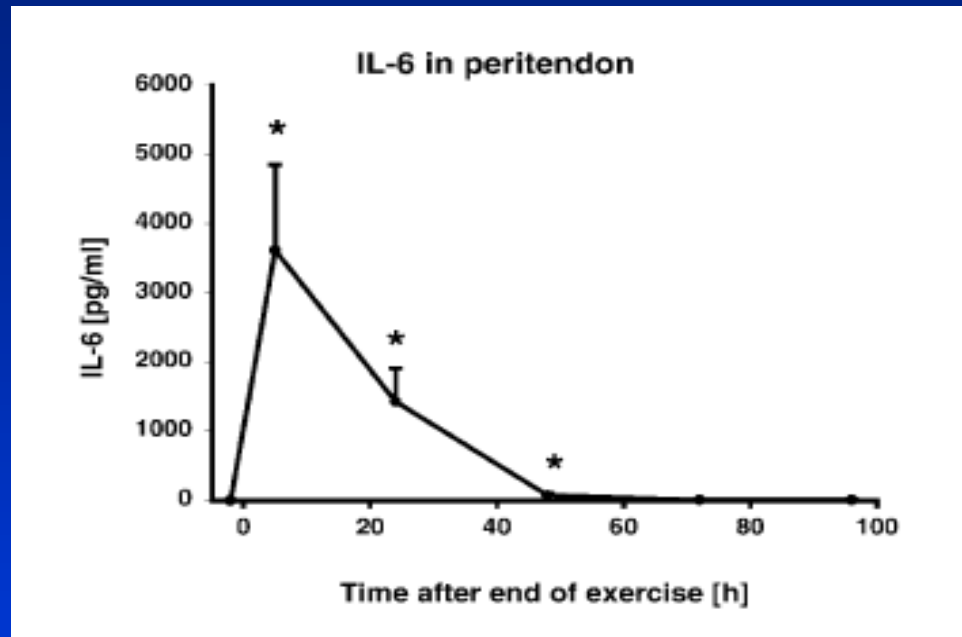
- **Ort der Überempfindlichkeit =  
Quelle der schmerzhaften Nervenaktivität?**
- **Lokale Behandlungsmöglichkeit (Capsaicin,  
Lidokain)**



# Klinische Implikationen von Kälte-induziertem Schmerz

- **Statische oder dynamische Überempfindlichkeit**
- **„Nachentladung“ = „resurgent currents“?**
- **Dauerkaltschmerz = „fehlende Bremse“ ?**

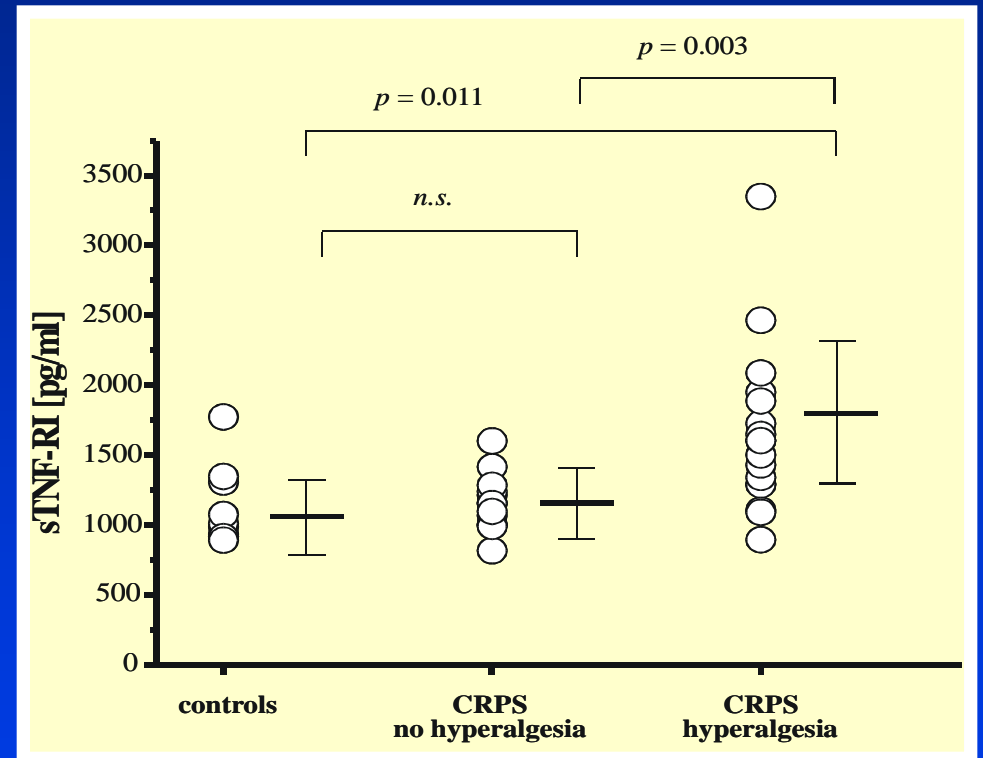
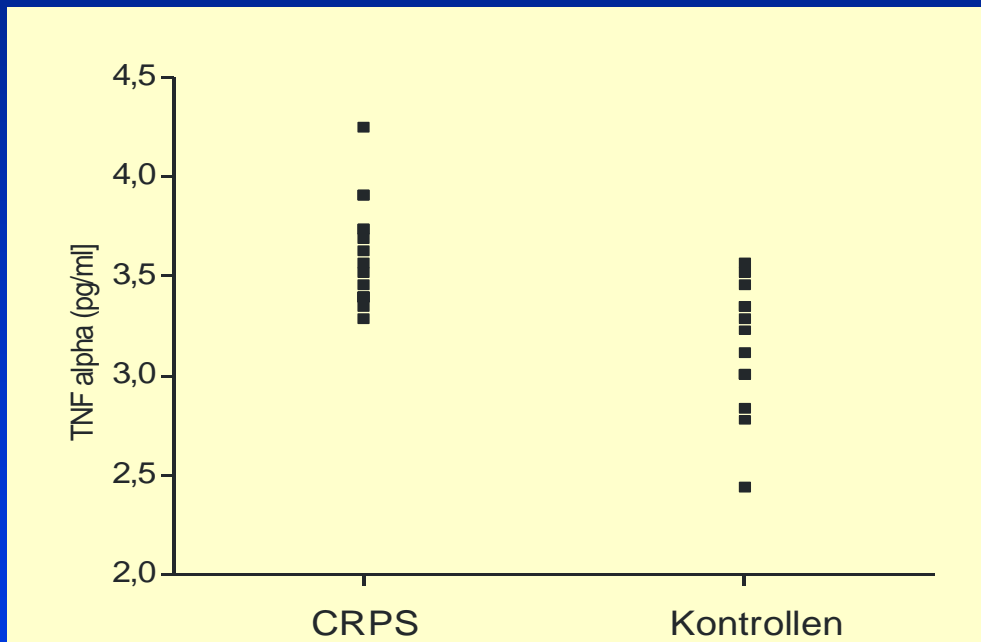
## Zytokine sind nach jedem Trauma rasch erhöht!



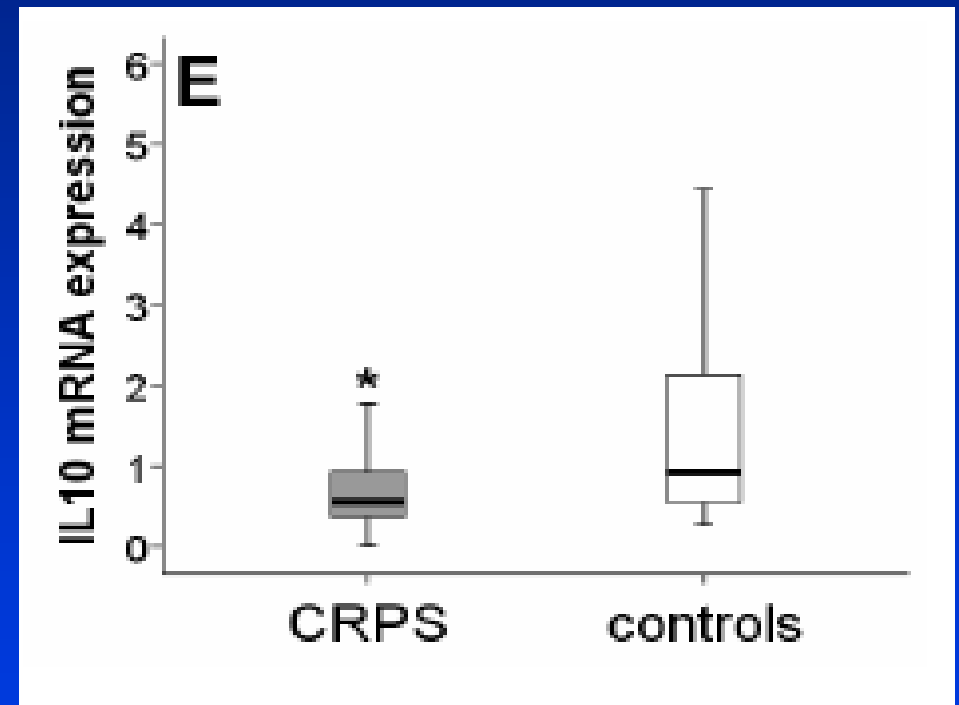
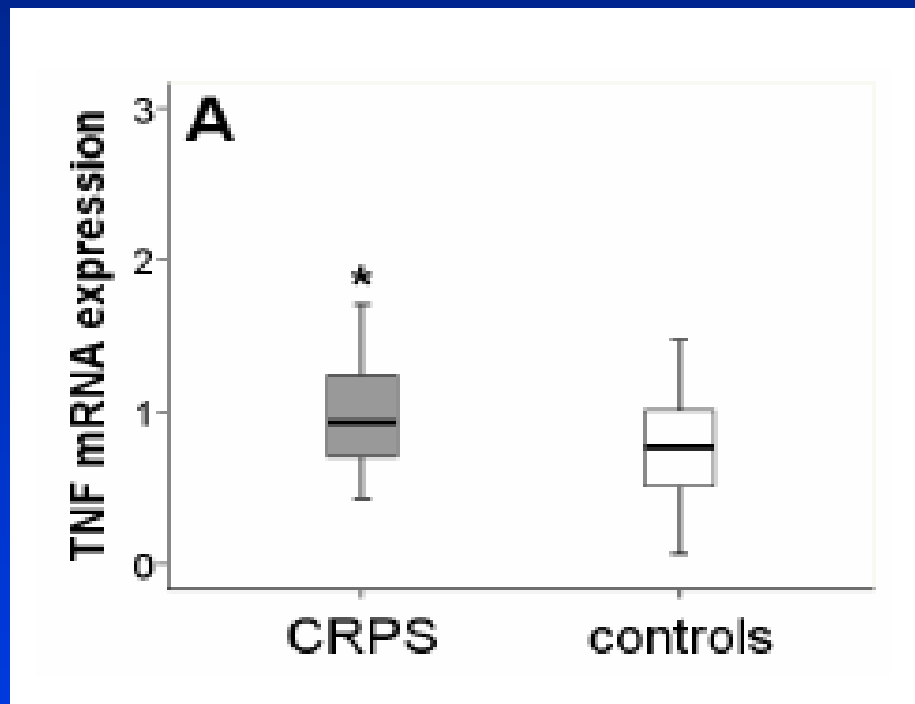
Langberg et al, J Physiol. 2002

- Gleichzeitige Regulation anti-inflammatorischer Stoffe
- Allmähliche Rückbildung der Entzündungsreaktion
- Rückbildung der Schmerzen

# TNF alpha / -R1 im Serum

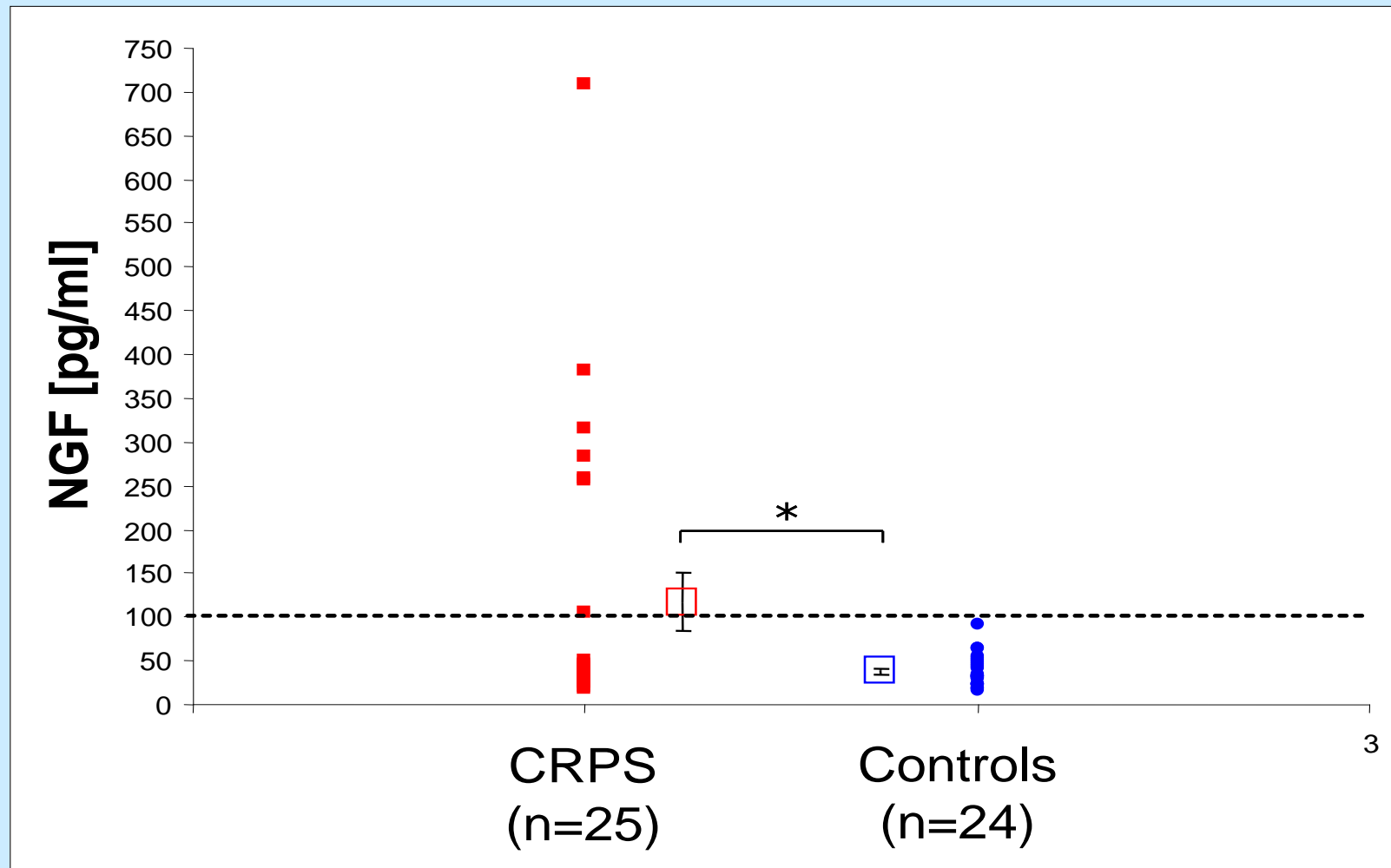


# CRPS Patienten haben ein proinflammatorisches Profil



Uceyler et al., Pain, in press

Nicht nur Zytokine, sondern auch NGF kann erhöht sein



## Weiterer Hinweis: TNF alpha Blockade erfolgreich

---

### Successful treatment of CRPS 1 with anti-TNF.

*Huygen FJ, Niehof S, Zijlstra FJ, van Hagen PM, van Daele PL.*  
J Pain Symptom Manage. 2004 Feb;27(2):101-3.

A Multicenter, Open-Label, 12-Week Study with Extension to  
Evaluate the Safety and Efficacy of Lenalidomide (CC-5013)  
in the Treatment of Complex Regional Pain Syndrome Type-1.

*G. Irving; R. Schwartzman; M. Wallace; R. Rauck; S. Dogra; S. Raja;*

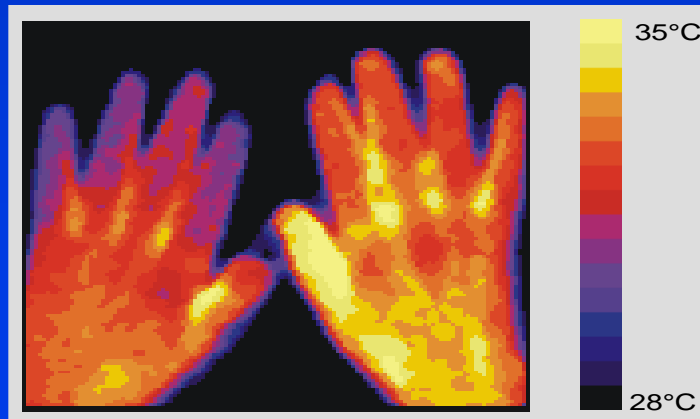
*A. Cooper; H. Faleck; J. Zeldis; D. Manning*

Abstract World Congress on Pain, Sydney 2005

# Die Entzündung bei CRPS

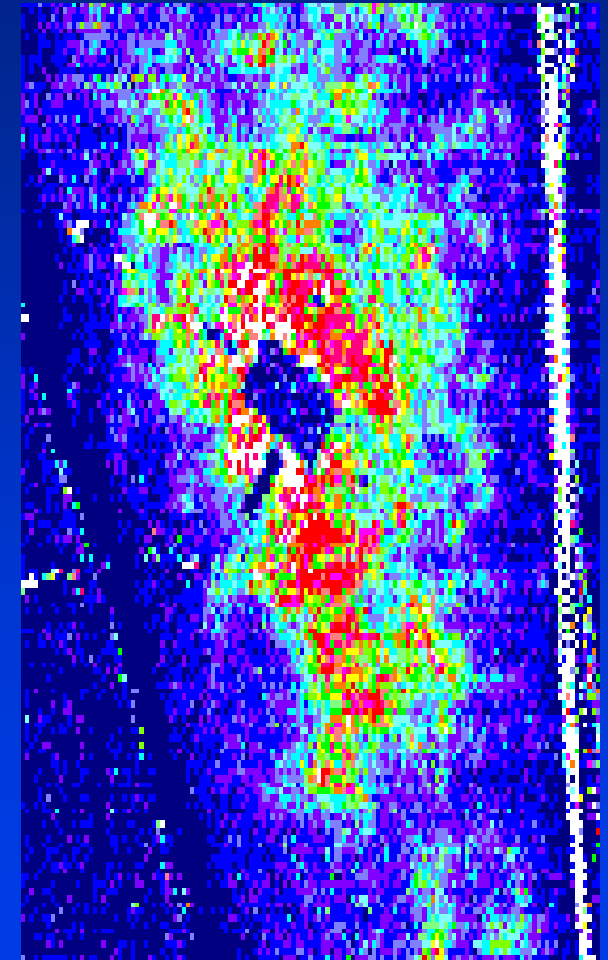
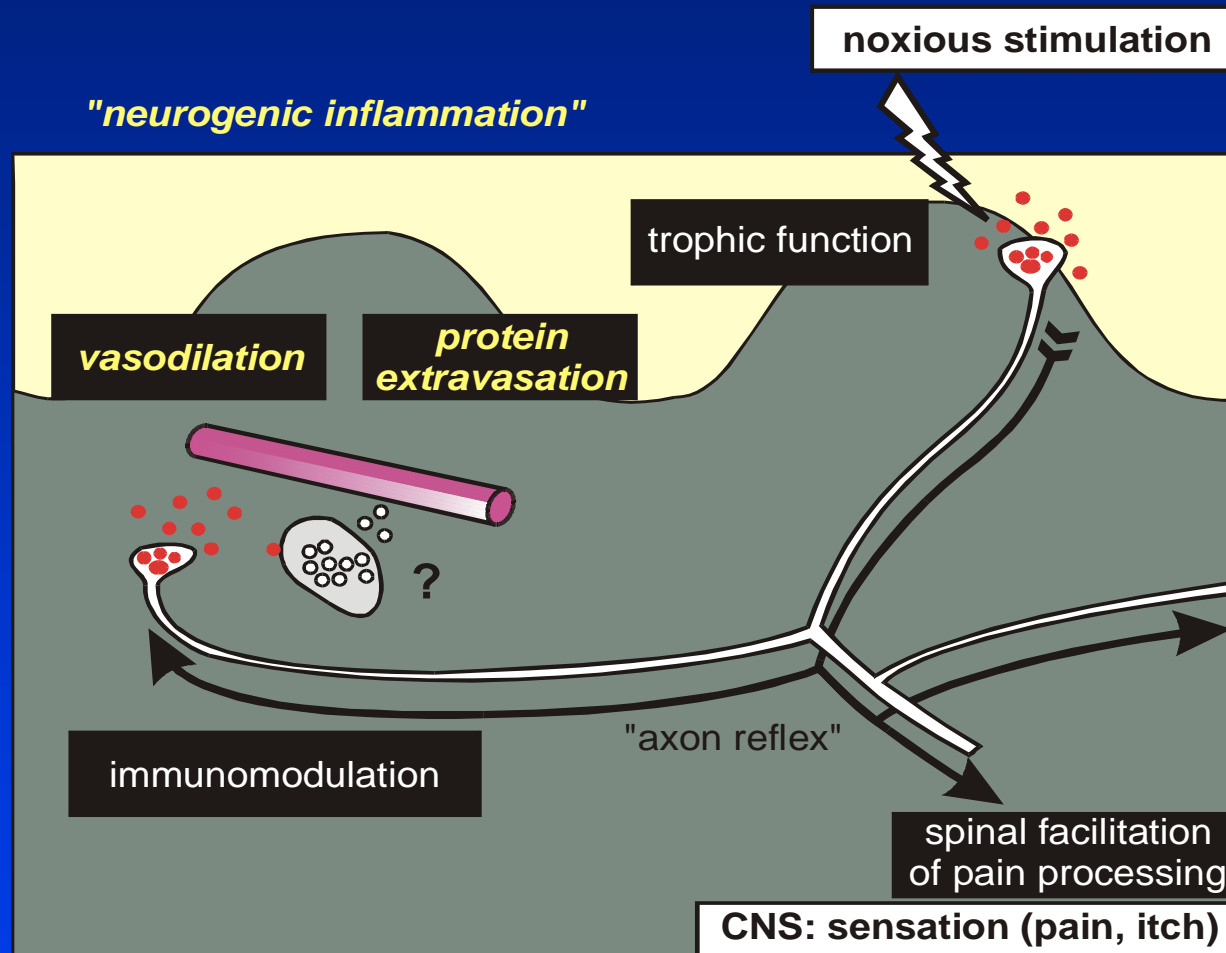
Ödem (SP)

Überwärmung (CGRP)



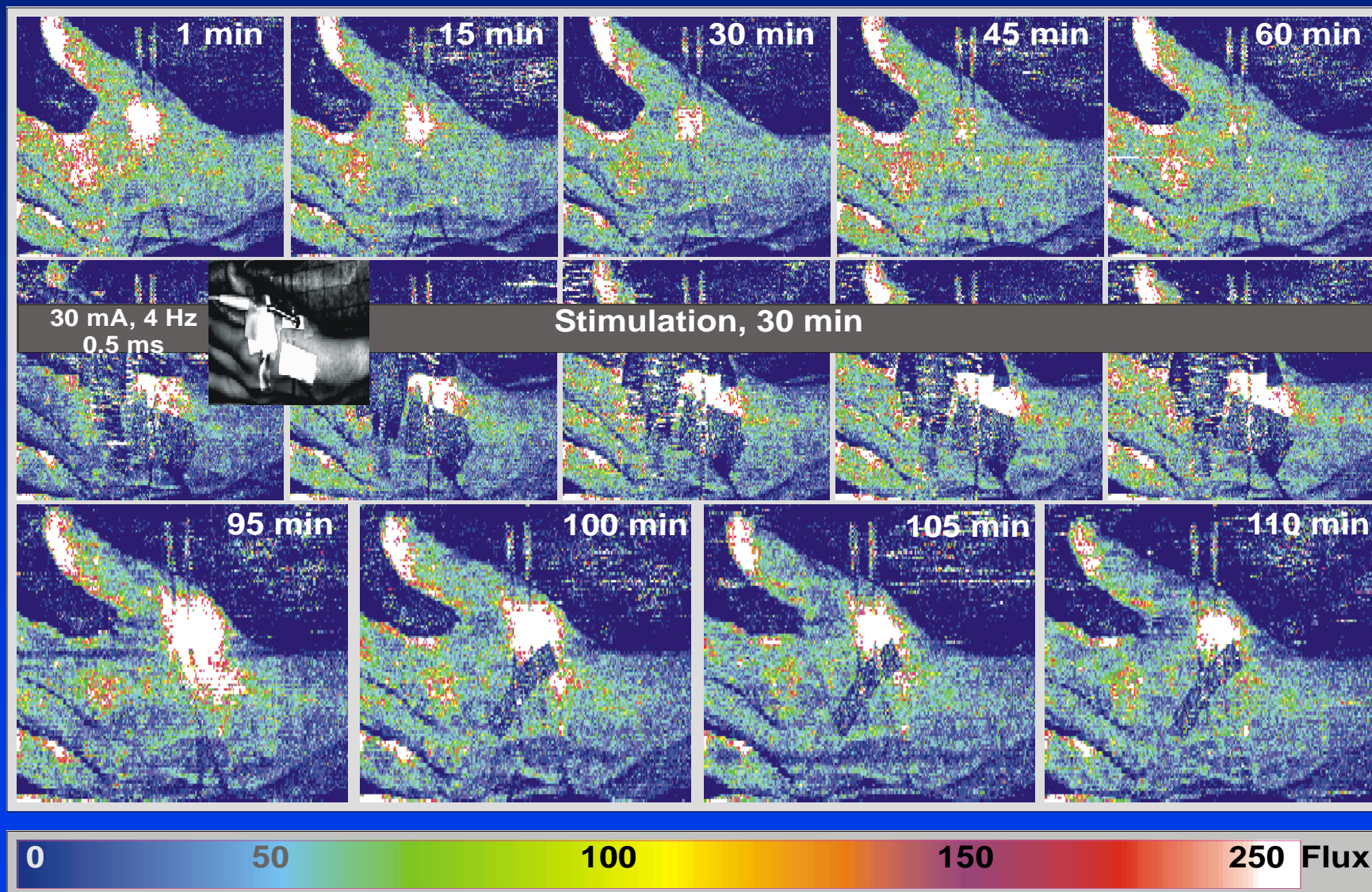


# Konzept der "Neurogenen Entzündung"

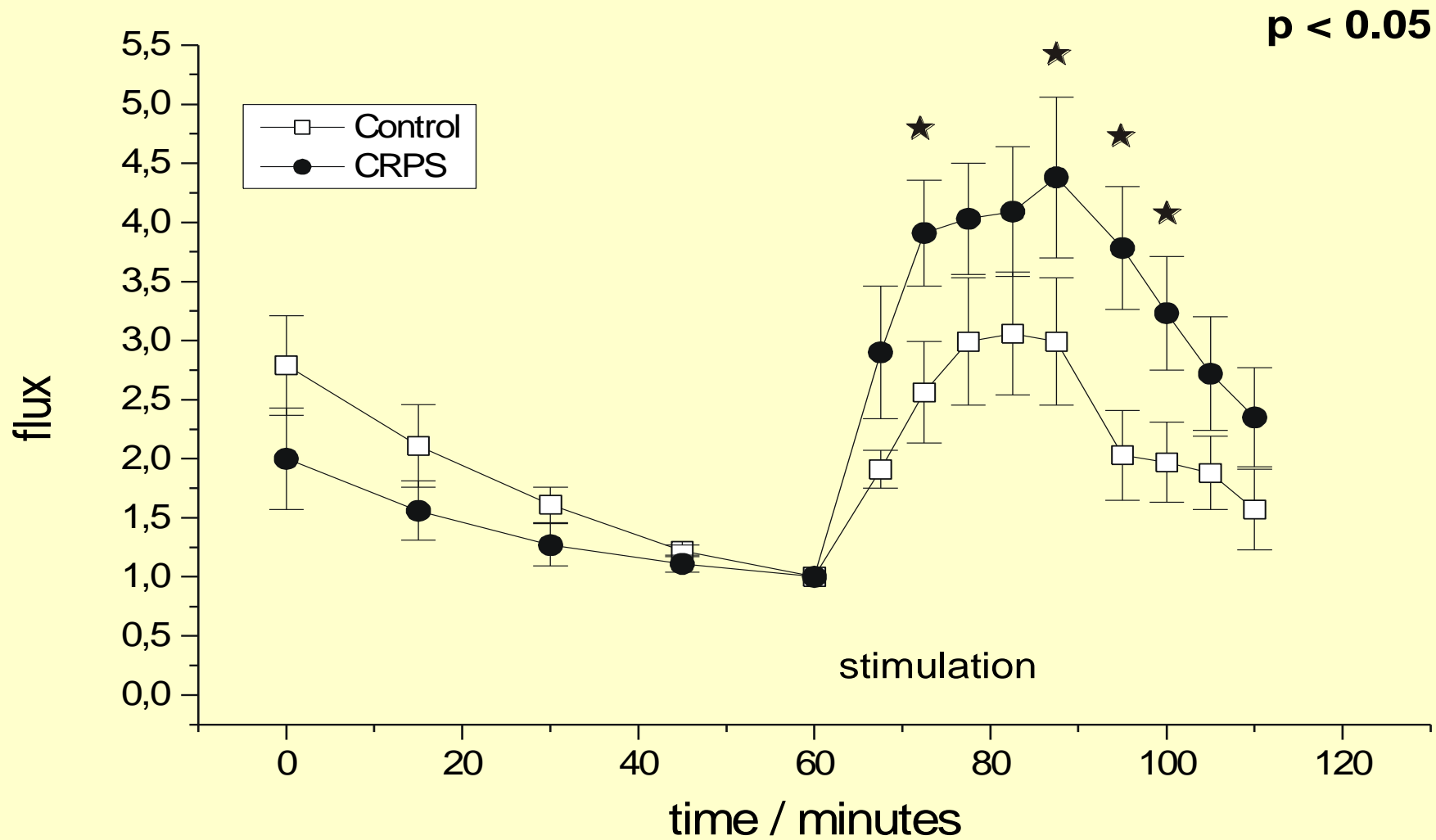




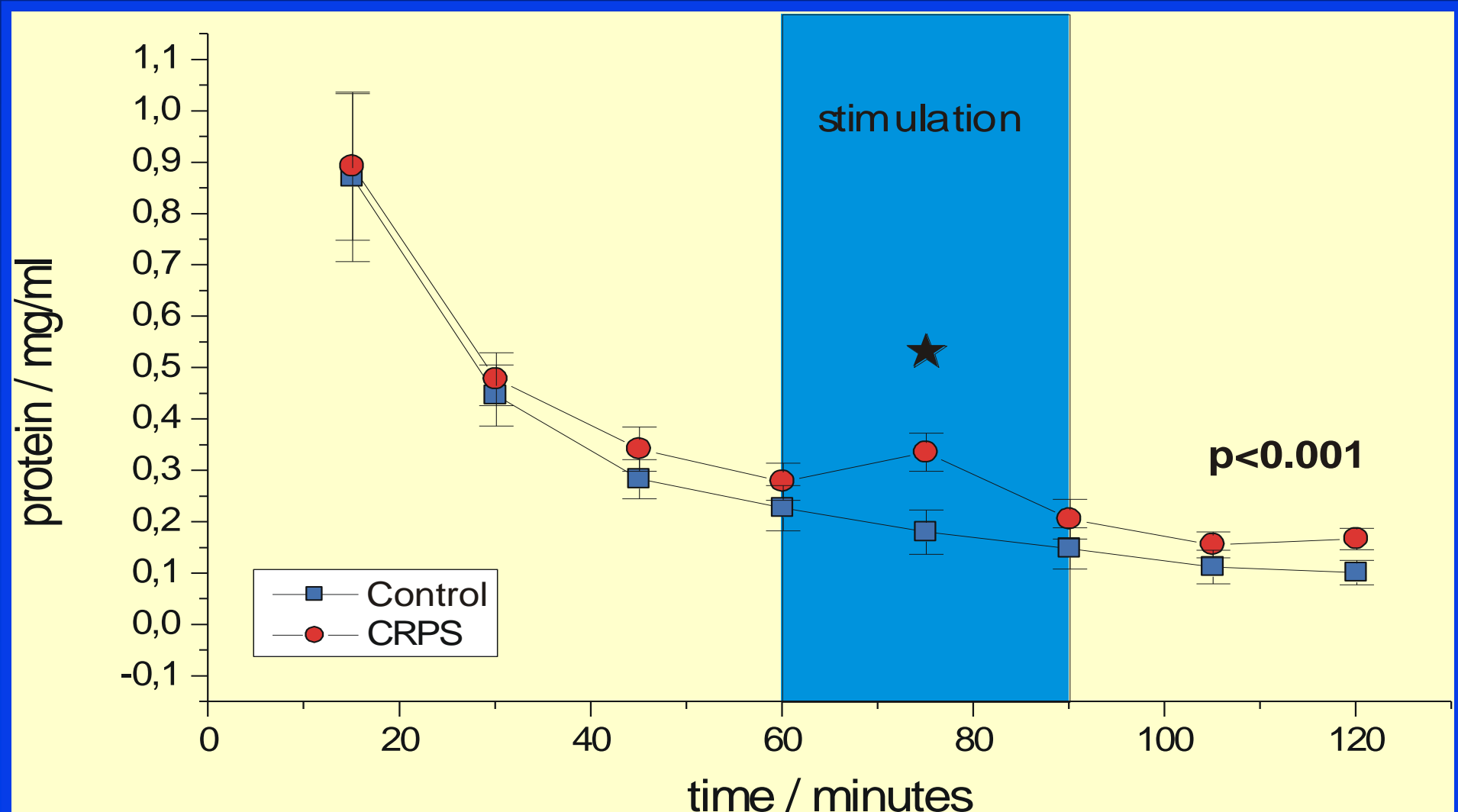
# Flare durch CGRP



# Flare (Rötung) ist verstärkt!

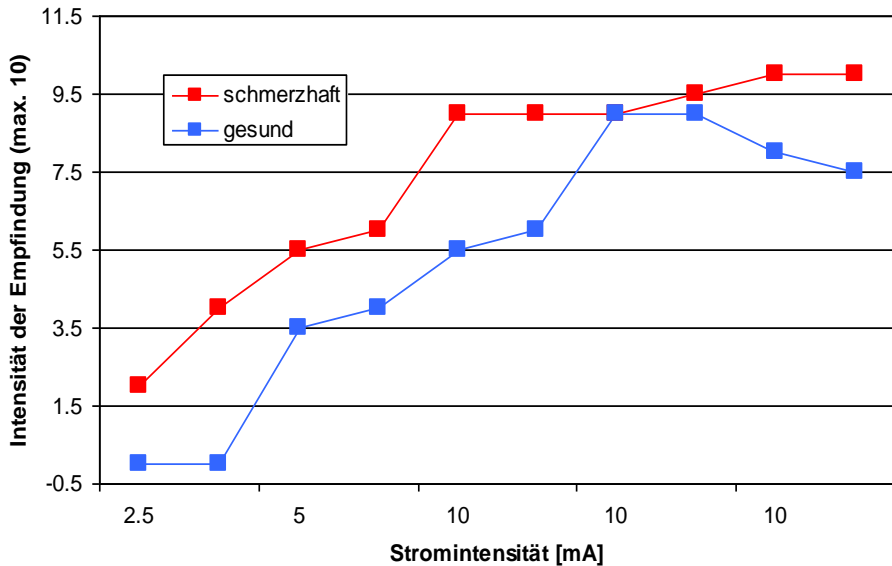


# Plasmaextravasation (Ödem) tritt auf

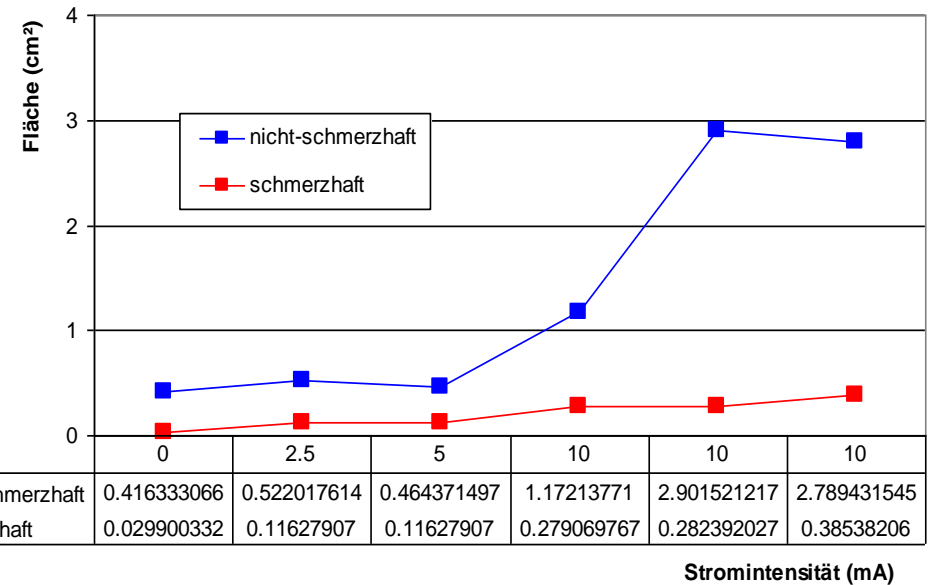


# CRPS - Perspektiven...

Schmerzempfindung während elektrischer Nervenstimulation



Fläche der Hautdurchblutung während transkutaner elektrischer Reizung



Increased warm threshold – cold and heat pain thresholds normal

Epidermal fibers normal – dermal fibers at about 75% no deep dermal fibers



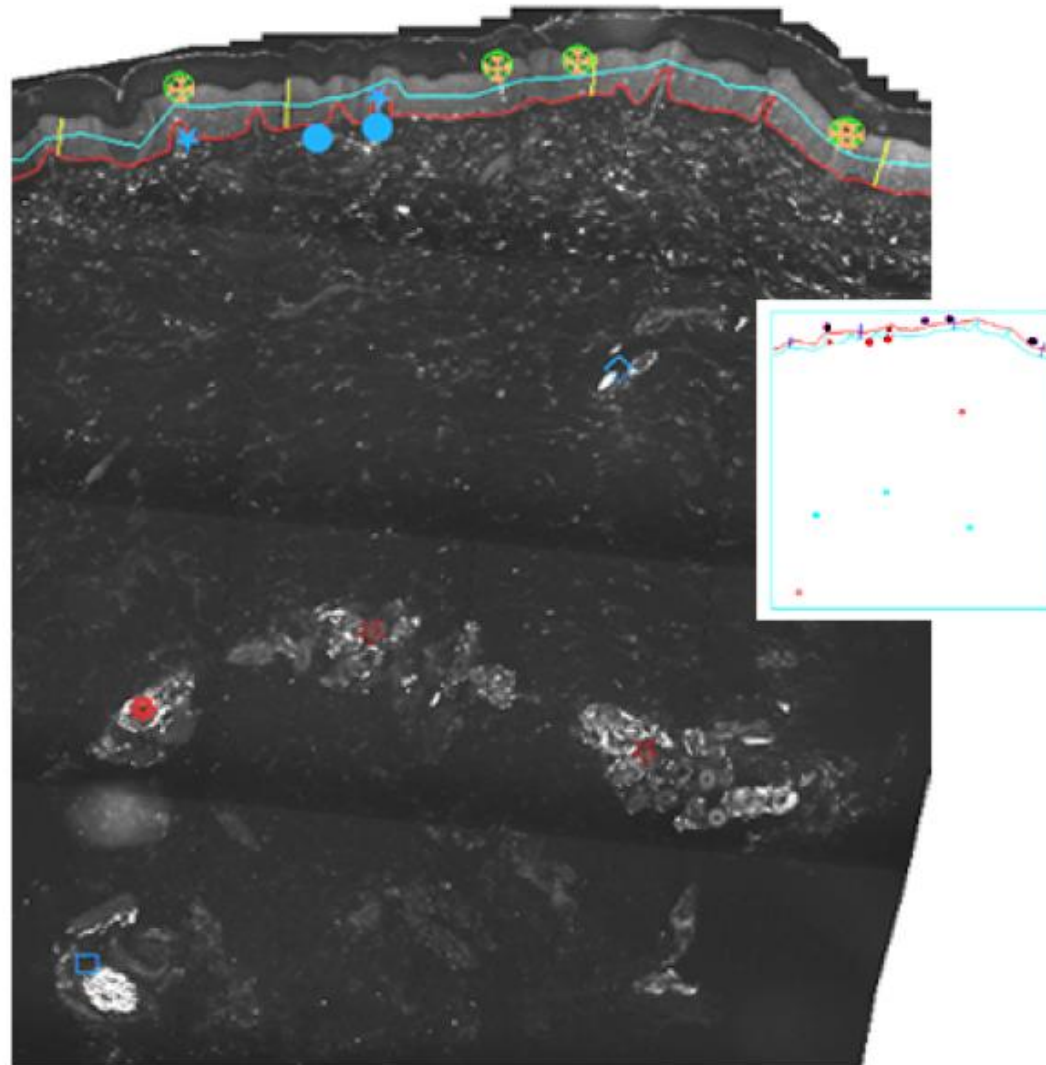
# CRPS - Hautbiopsie

## Marker

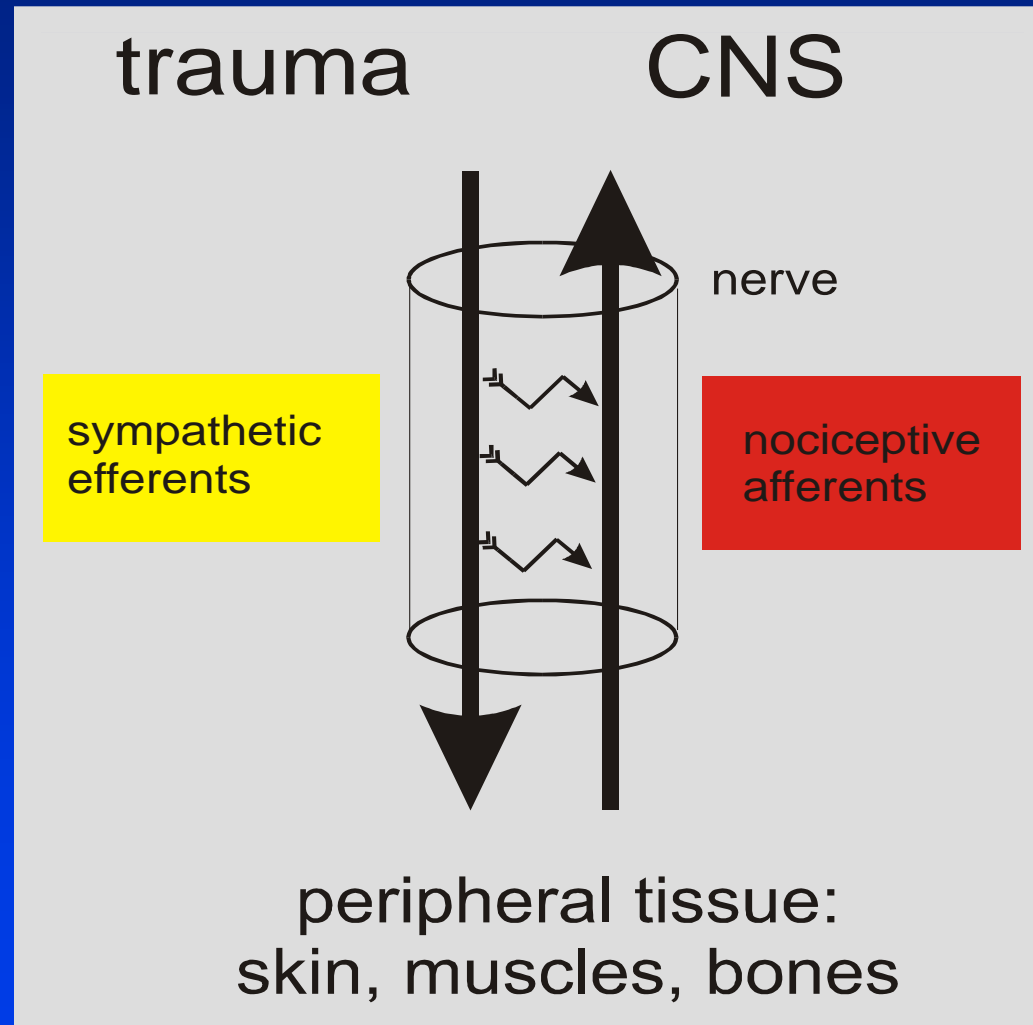
⊠	PGP epi ending
○	straight, unbranched
×	multi-branched
+	oblique
△	through derm pap
▽	between derm pap
★	sub-epi nerve
●	upper derm nerve
◇	dermal nerve
□	deep derm nerve
■	A beta Merkel
◆	A beta Meissner
⊗	HFolli associated
⊕	between HFolli
▲	Hair Follicle
☆	sweat gland
*	pap derm arterial
* (with asterisk)	retic derm artery

## Contour

▬ (blue)	epi length
▬ (red)	derm/epi border
▬ (yellow)	epi thickness



# CRPS und sympathische Störungen: SMP

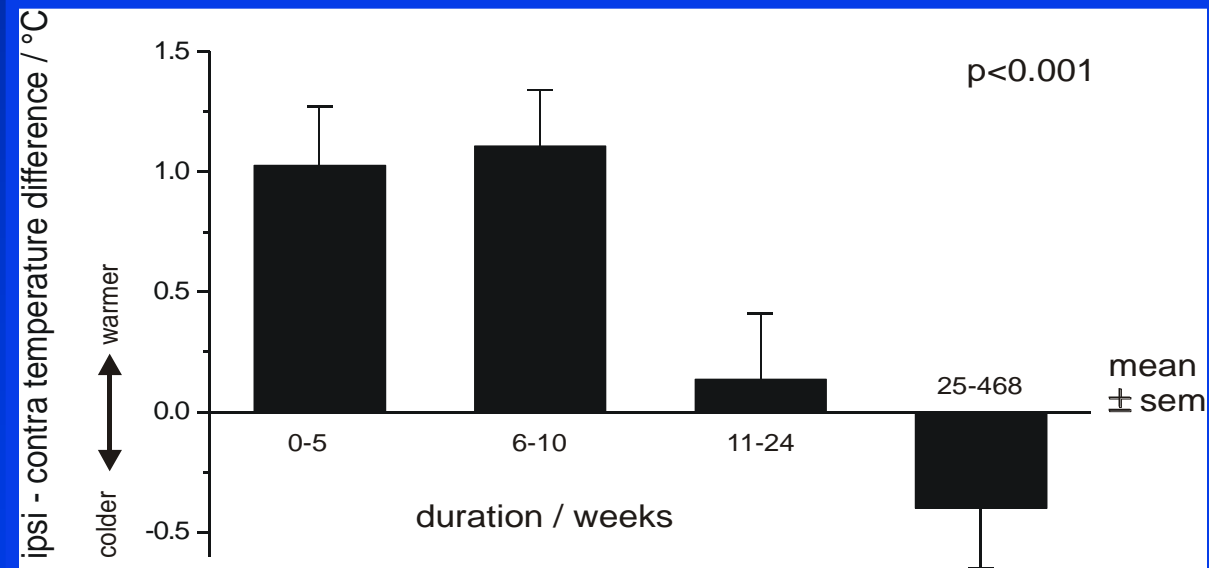
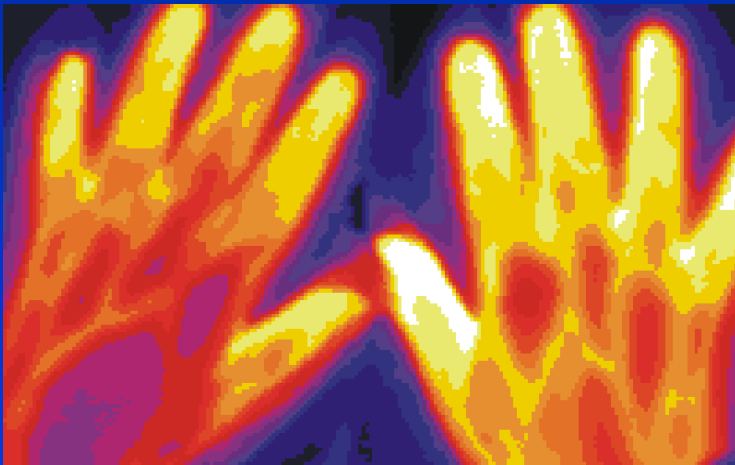




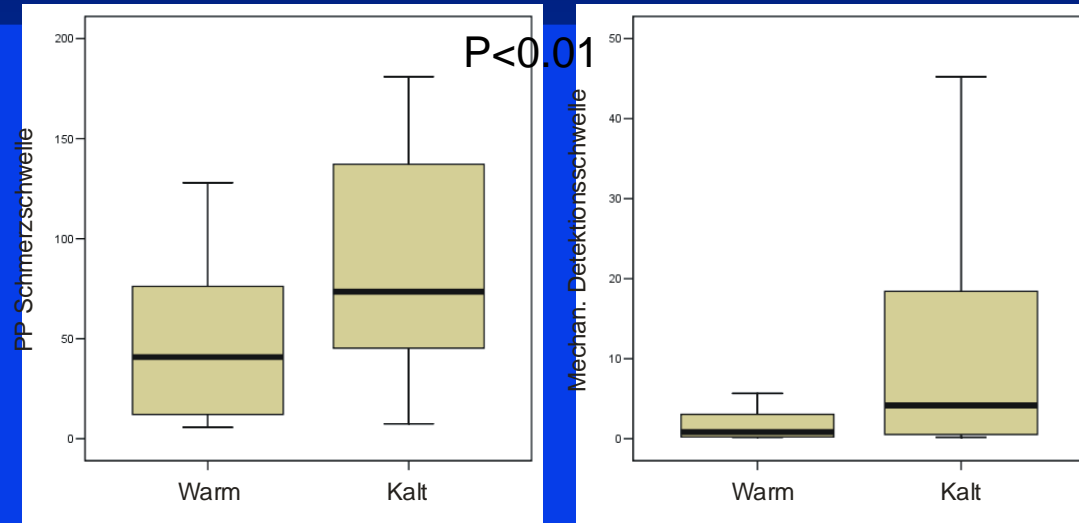
# Hauttemperatur: Primär und im Verlauf kalt!

primär kalt

stadienabhängig kalt



# Unterschiede primär kaltes vs. warmes CRPS

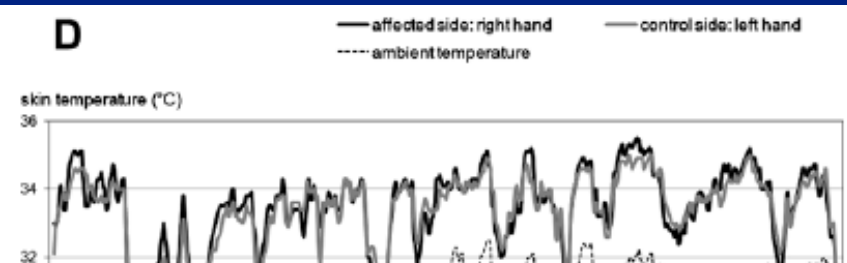
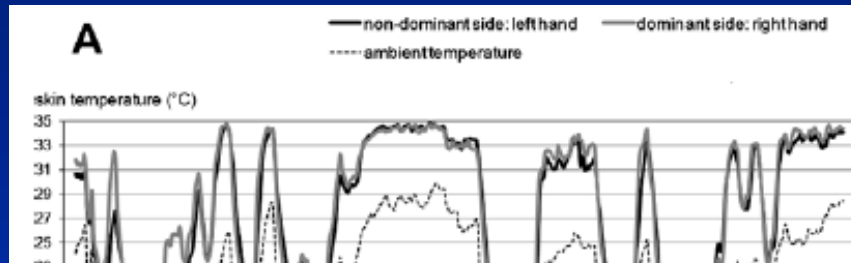


TNF-alpha:  
Entzündung + Hyperalgesie



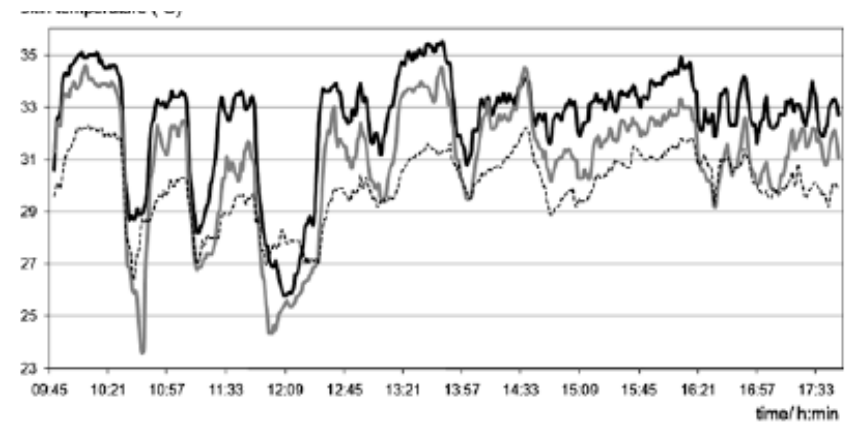
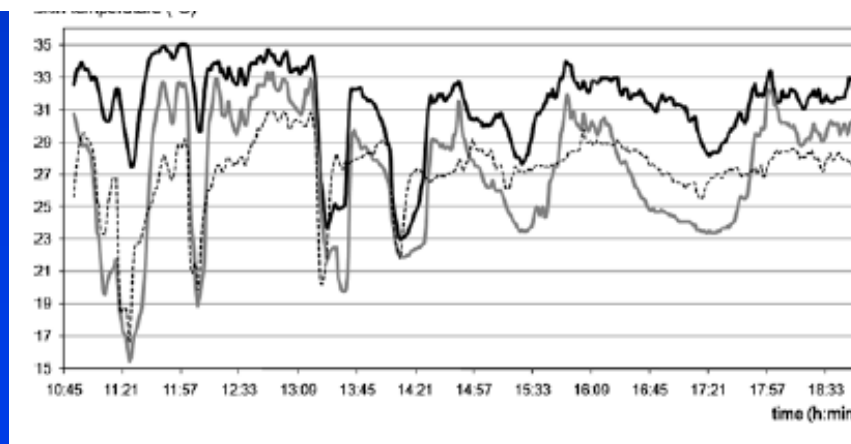
	Kein Neglekt	Neglekt	
<b>warm</b>	29	31	60
<b>kalt</b>	6	18	24
	35	49	$P < 0.05$

# Langzeittemperaturmessung bei CRPS

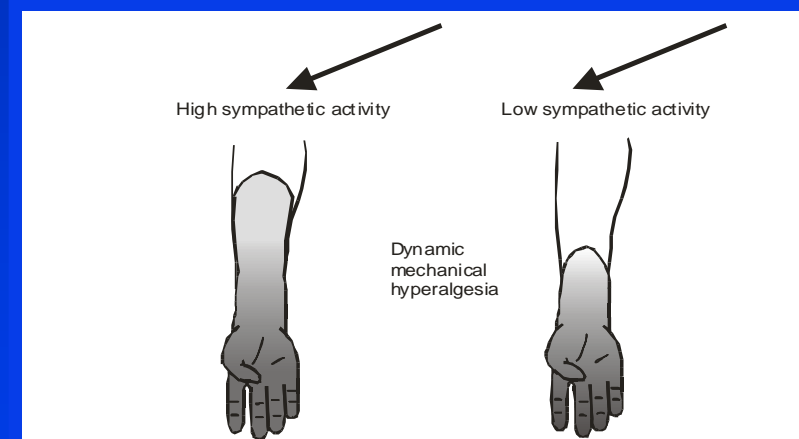
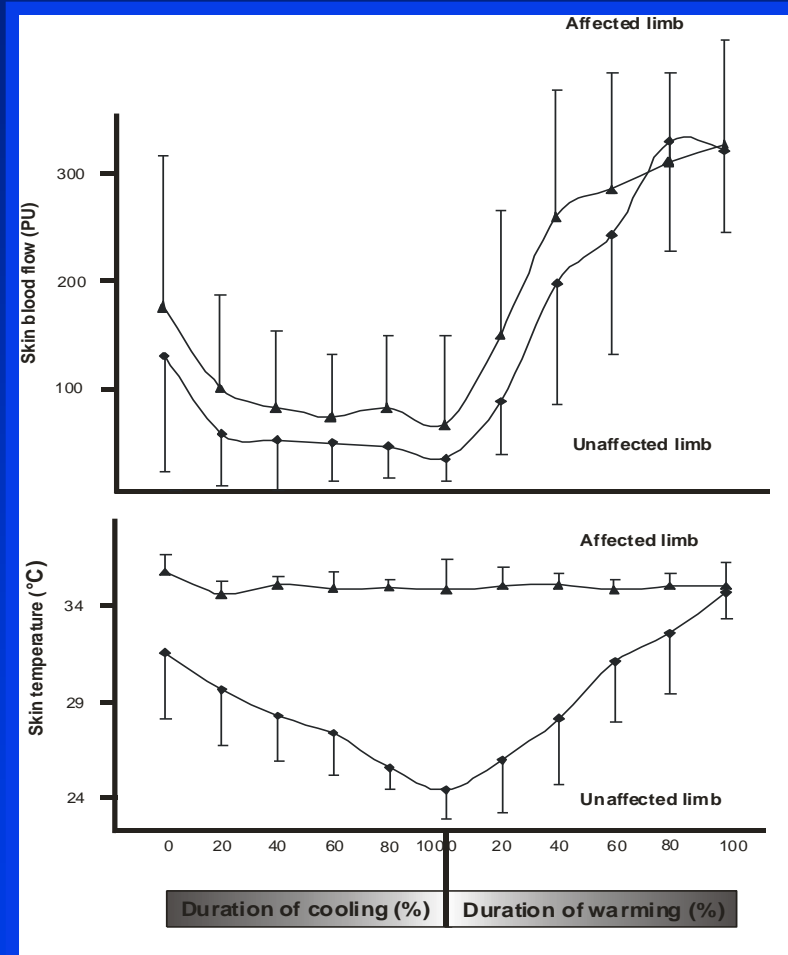


Long-term skin temperature measurements – A practical diagnostic tool in complex regional pain syndrome

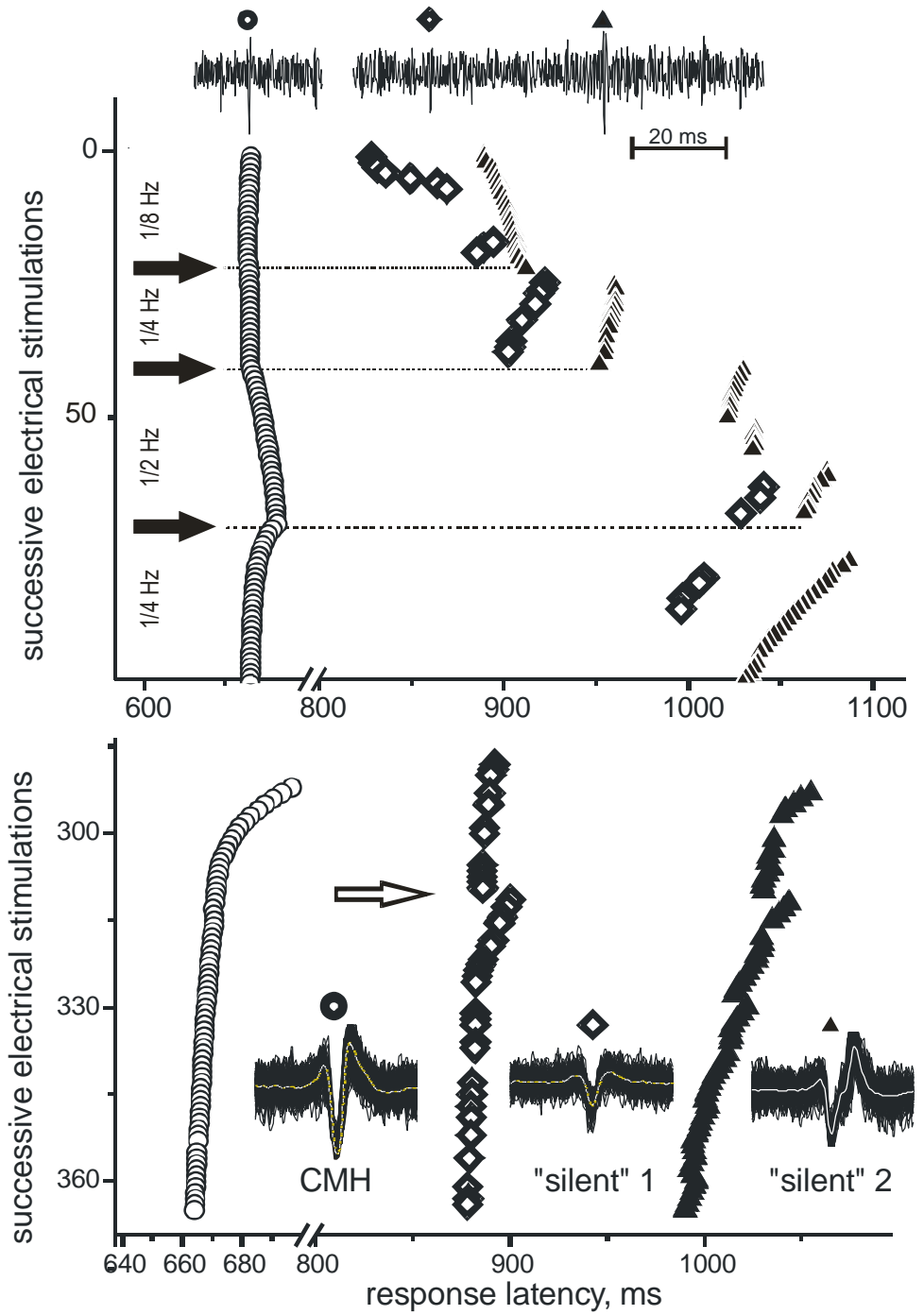
Elena K. Krumova<sup>a,1</sup>, Jule Frettlöh<sup>a</sup>, Sabrina Klauenberg<sup>a</sup>, Helmut Richter<sup>a</sup>,  
Gunnar Wasner<sup>b</sup>, Christoph Maier<sup>a,\*</sup>



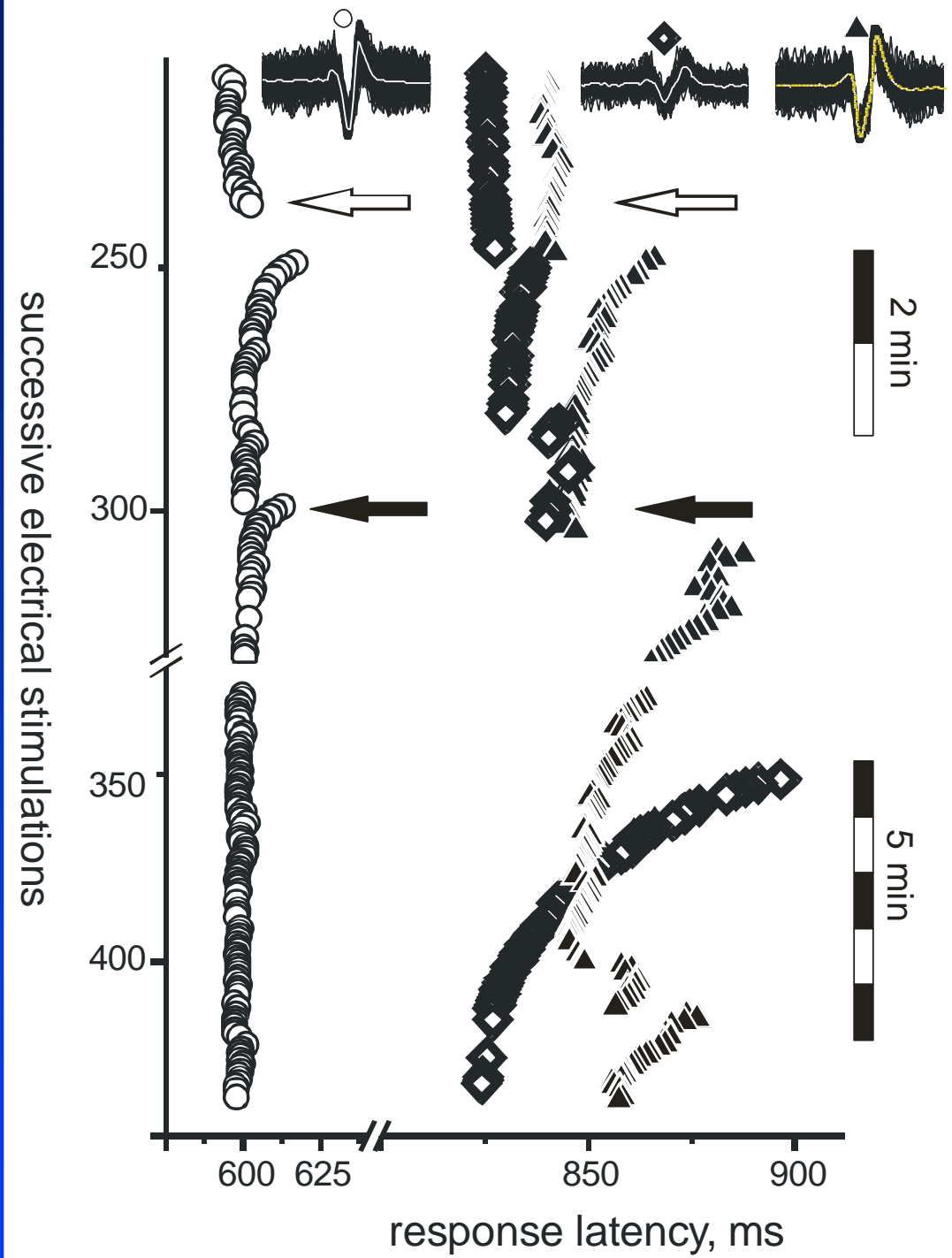
# Sympathikusaktivierung verstärkt Schmerz (SMP)



# Sympathikusaktivierung verstärkt Schmerz (SMP) Nozizeptoraktivierung durch sympathische Reize



Sympathikusaktivierung  
verstärkt Schmerz (SMP)  
Nozizeptoraktivierung  
durch Katecholamine

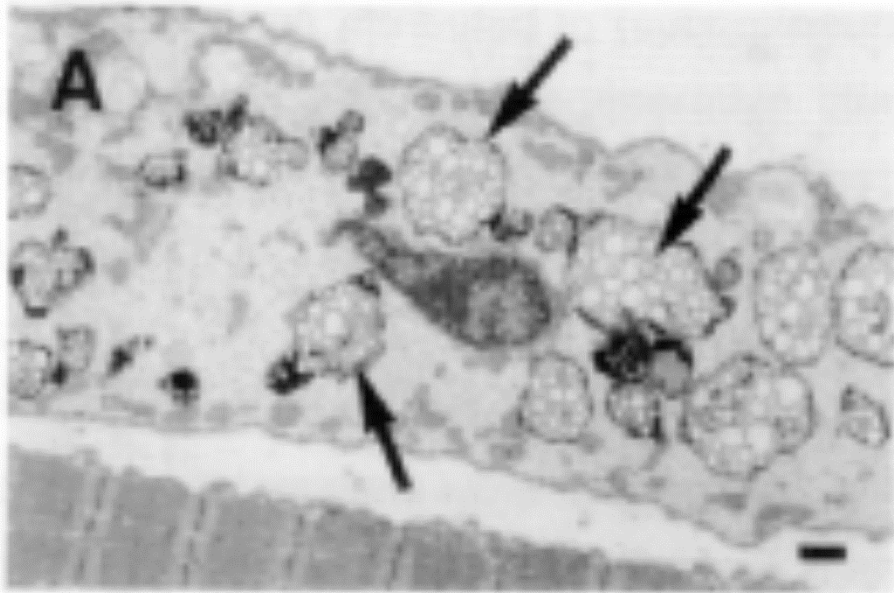


# Therapie SMP des CRPS

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- Sympathikusblockaden

# Chronische Folgen: Hypoxie im Gewebe

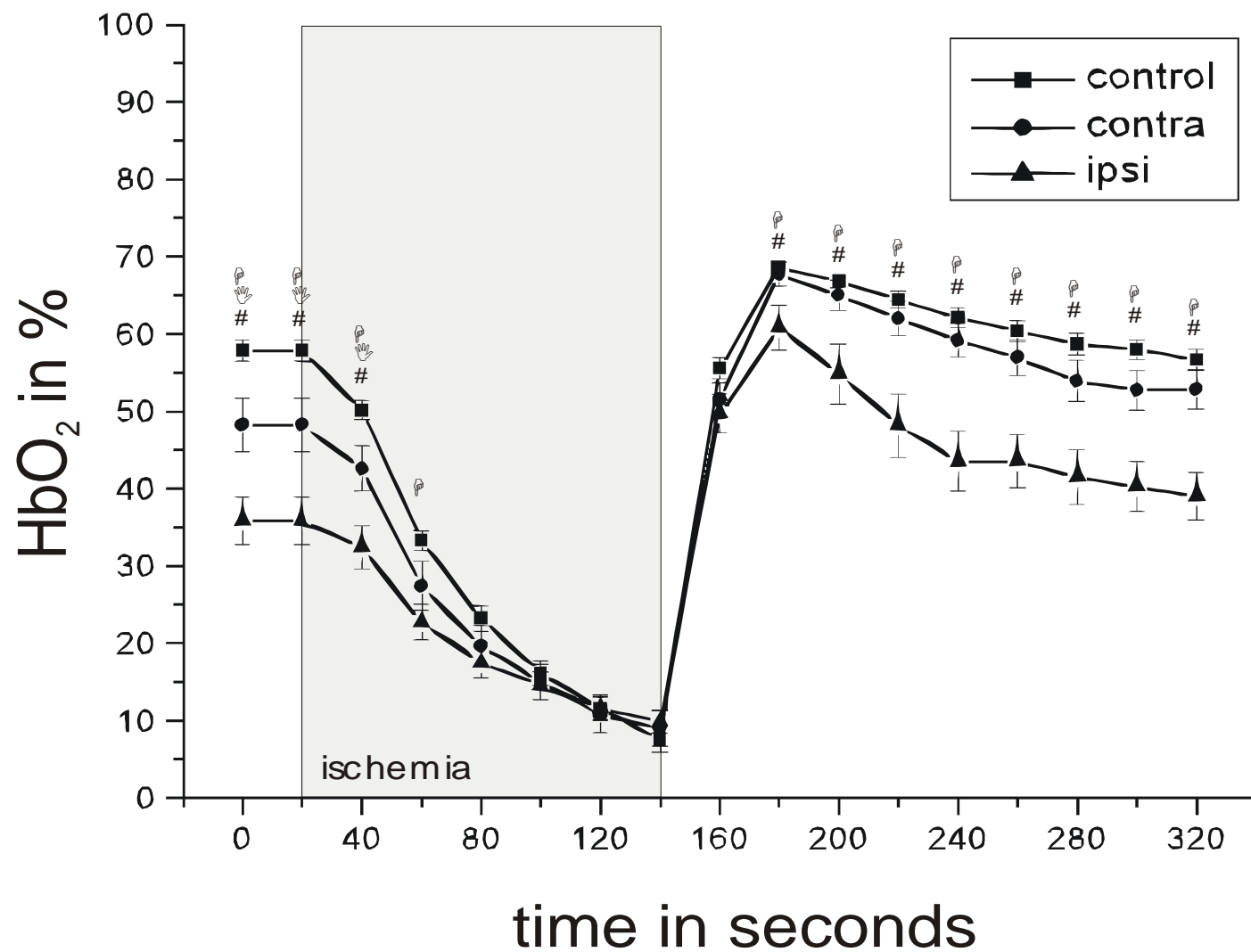


Levan der Loon et al.

2007



# Hypoxie

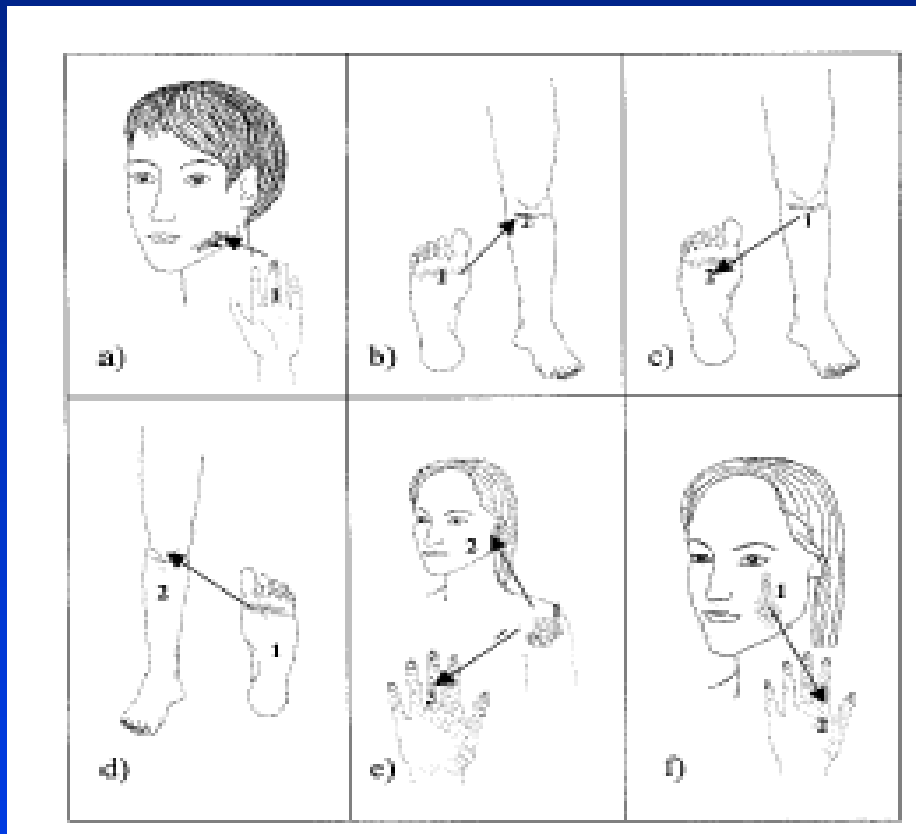


# Therapie der Hypoxie / freier Sauerstoffradikale

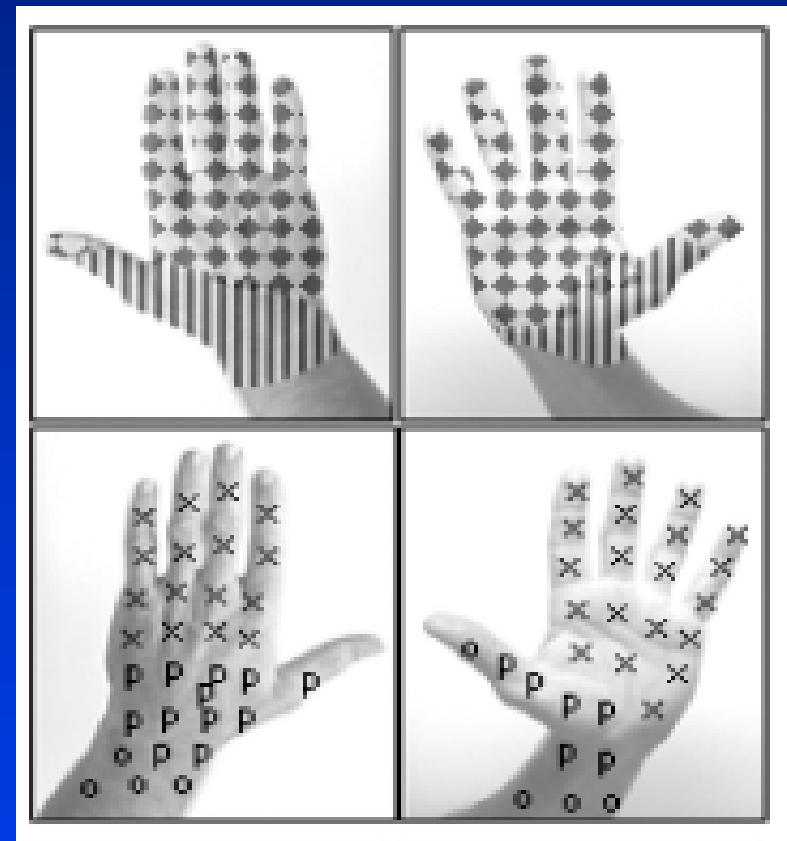
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- DMSO 50%
- Verbesserung der Mikrozirkulation

# Periphere Veränderungen triggern ZNS Symptome: Taktile Mißlokalisierung

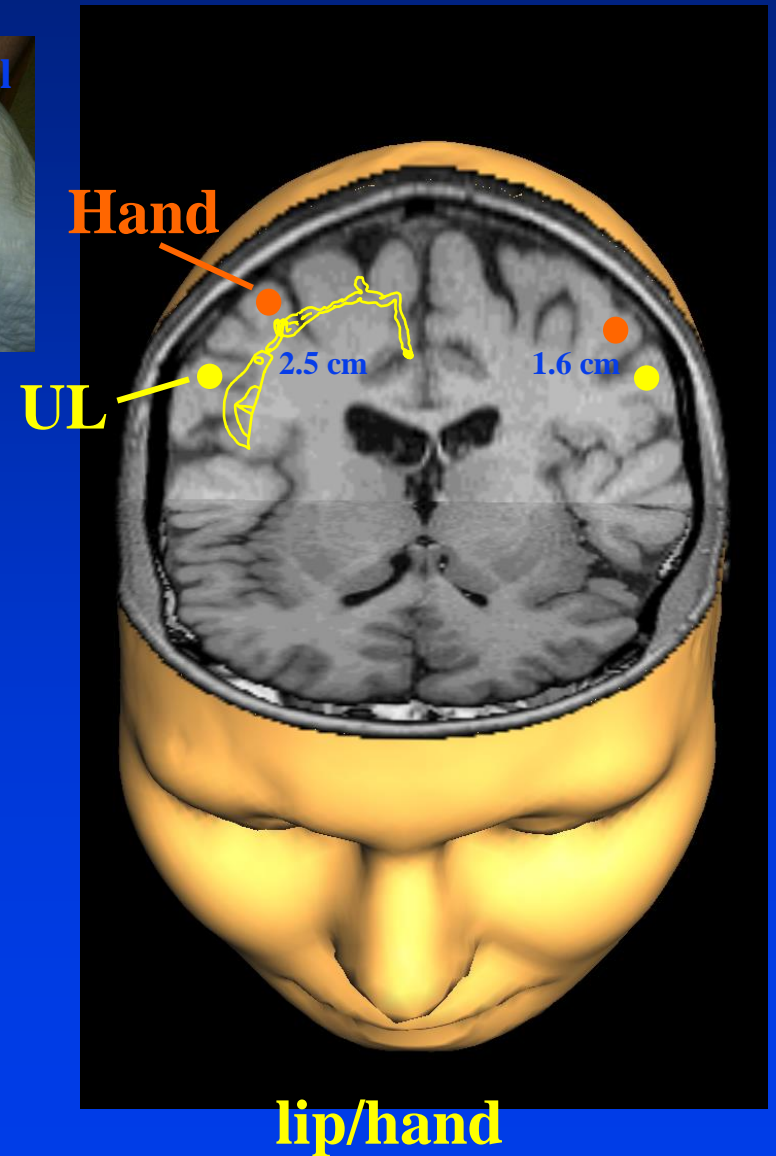
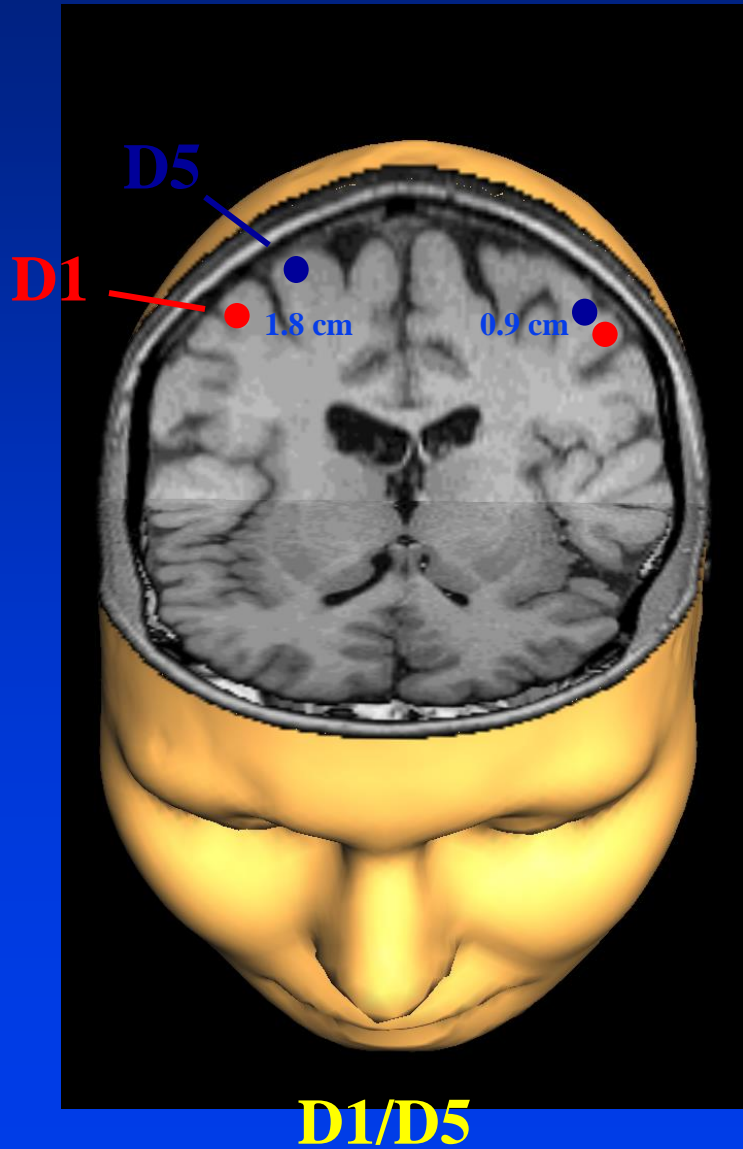


McCabe et al. 2003

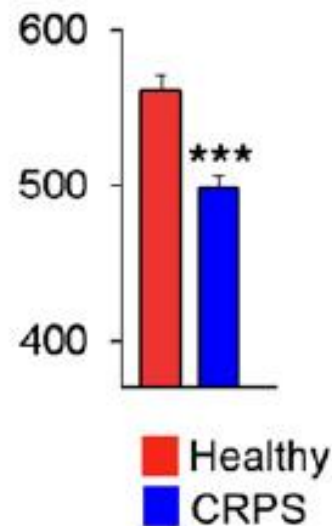
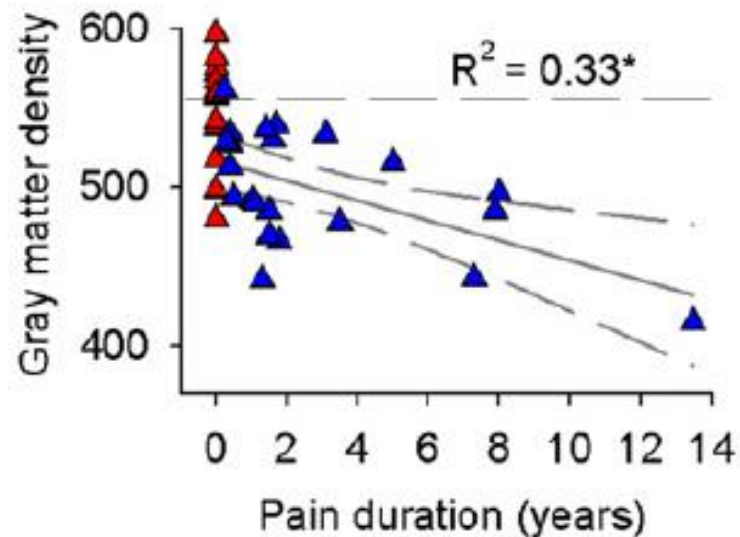
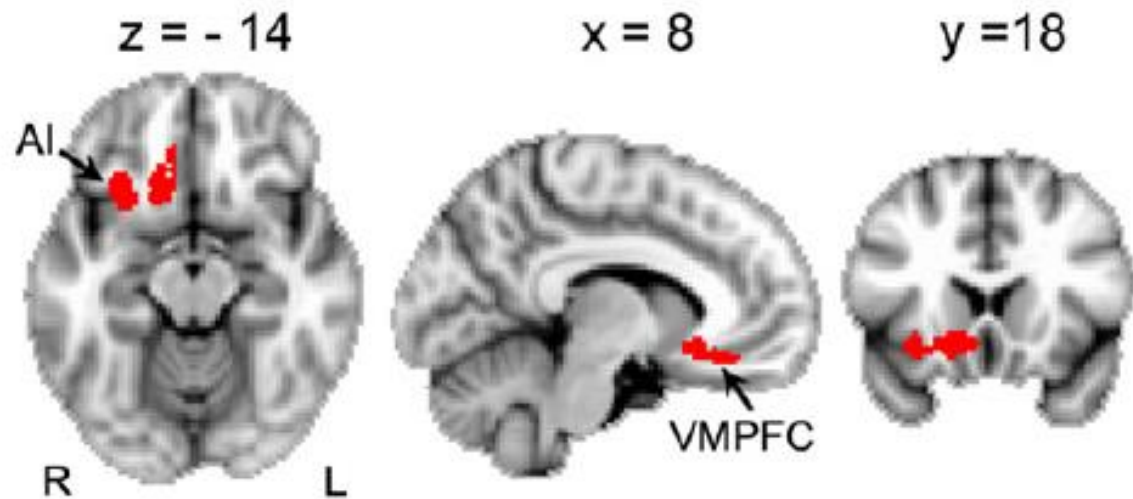


Moseley et al. 2005

# Schmerz führt zur kortikalen Reorganisation



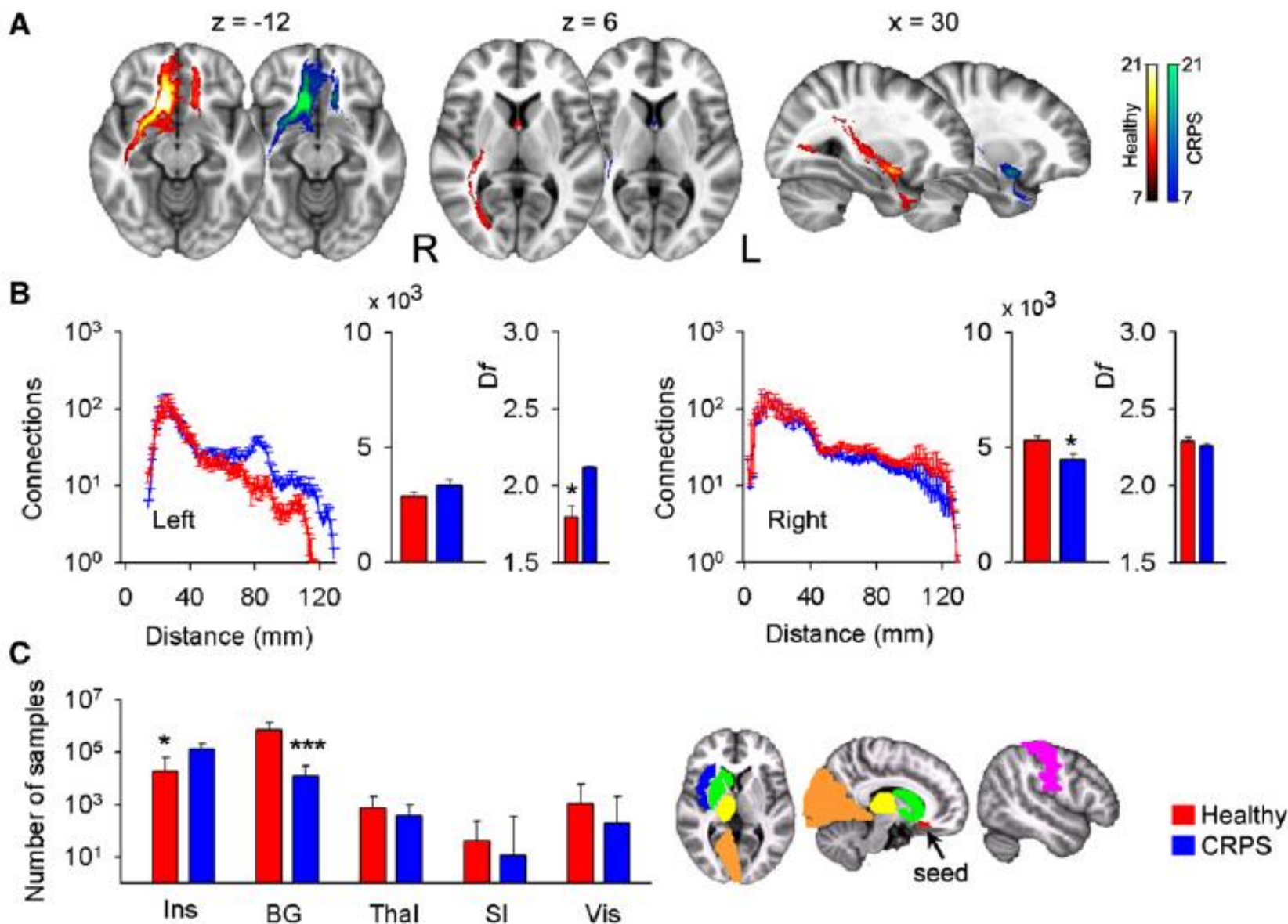
# Schmerz führt zur kortikalen Reorganisation Reduktion grauer Substanz ventromedialer Präfrontalkortex



The Brain in Chronic CRPS Pain:  
Abnormal Gray-White Matter Interactions  
in Emotional and Autonomic Regions

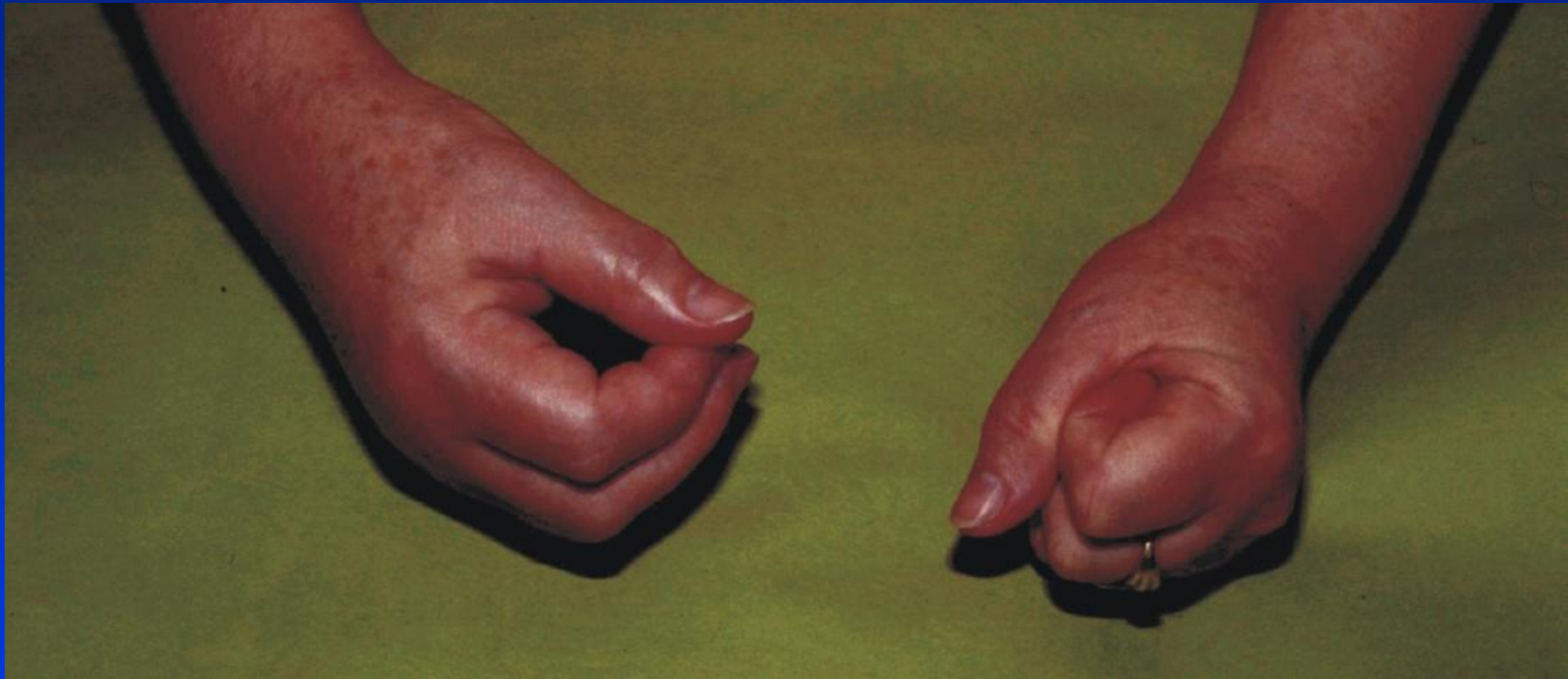
# Schmerz führt zur kortikalen Reorganisation – Konnektivitätsanalyse

## Reduzierte Konnektivität zu Basalganglien, erhöht zur Insula



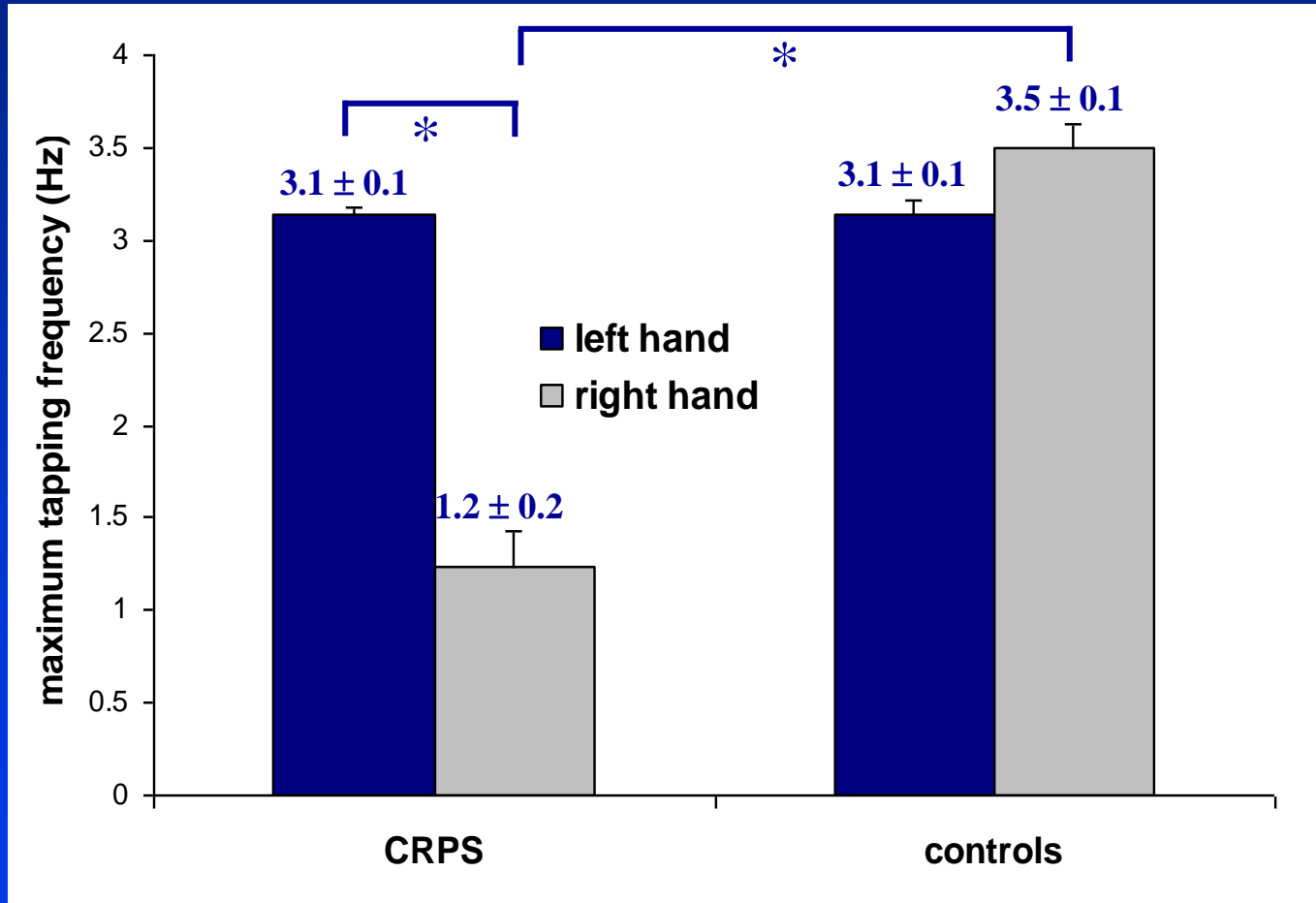


# Motorik und CRPS



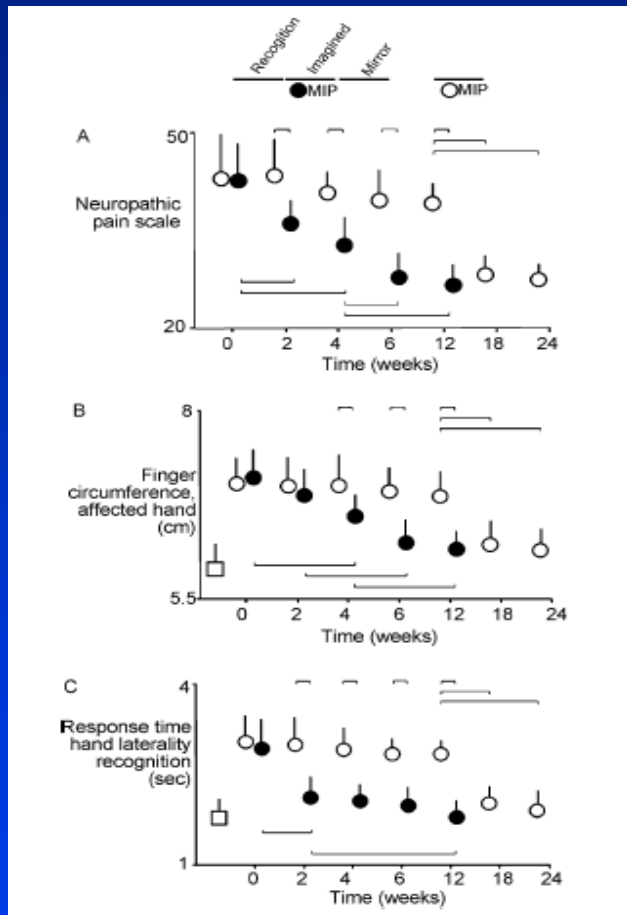
12. Woche nach distaler Radiusfraktur re.  
Ödem, Glanzhautbildung  
Beweglichkeit↓ bei Faustschluß

# Test: Finger Tapping





# Verhaltenstherapie: Motor imagery



	OR Pain < 3	OR Function > 5	OR Both criteria
<b>Outcome</b>	13 (3 – 56)	30 (5.5 – 160)	9 (2 – 36)
	Pain decreased by $\geq 50\%$		Function increased by $\geq 3$
	OR	NNT	OR
<b>Response to treatment</b>	9 (2 – 40)	3 (2 – 6)	11 (3 – 43)
		NNT	2 (1 – 4)
			OR
			NNT
			16 (2 – 138)
			3 (2 – 8)

Moseley, 2006

Moseley 2004

# Integraler Bestandteil des motor imagery: Spiegeltherapie



McCabe et al. 2003

Mein Dank gilt:

Frank Birklein in Mainz

Ellen Jorum in Oslo

Christian Maihöfner

Margarete Weber

Stefan Leis

Andreas Bickel

Claudia Sommer

Bernd Rautenstrauss

## Expose or protect? A randomized controlled trial of exposure in vivo vs pain-contingent treatment as usual in patients with complex regional pain syndrome type 1

Marlies den Hollander<sup>a,b,f,\*</sup>, Mariëlle Goossens<sup>a,c</sup>, Jeroen de Jong<sup>a,c,f</sup>, Joop Ruijgrok<sup>c</sup>, Jan Oosterhof<sup>d</sup>, Patrick Onghena<sup>e</sup>, Rob Smeets<sup>b,c,h</sup>, Johan W. S. Vlaeyen<sup>a,g</sup>

	<u>Pretreatment</u>	<u>Posttreatment</u>	<u>Follow-up</u>
	<u>Mean (SD)</u>	<u>Mean (SD)</u>	<u>Mean (SD)</u>
Primary outcome: disability			
Disability upper extremity (RASQ, 0-5*)			
EXP	"No pain, no gain" 3.14 (0.89)	1.86 (0.91)	1.87 (0.62)
TAU	"With pain no gain" 3.49 (0.96)	3.02 (1.19)	3.08 (1.23)
Disability lower extremity (WAQ, 0-10*)			
EXP	"No pain, no gain" 6.97 (2.48)	1.44 (2.15)	1.56 (2.23)
TAU	"With pain no gain" 6.99 (1.76)	4.57 (2.90)	5.35 (3.10)





## Autoimmunity Reviews

Volume 16, Issue 1, January 2017, Pages 22-33



Review

### The clinical relevance of complex regional pain syndrome type I: The Emperor's New Clothes

Andrea T. Borchers, M. Eric Gershwin  

- The use of diagnosis CRPS I has become a catch all phrase with serious questions on whether it exist at all; this has led to an extraordinary number of poorly defined diagnostic criteria.
- The overdiagnosis of CRPS has led to overzealous use of pain medications, including narcotics.
- The diagnostic criteria for CRPS I, and therefore the diagnosis itself, is unreliable
- The underlying pathophysiology of the signs and symptoms of CPRS I are not biologically plausible