Emotional learning and neuroplasticity in chronic pain: implications for treatment

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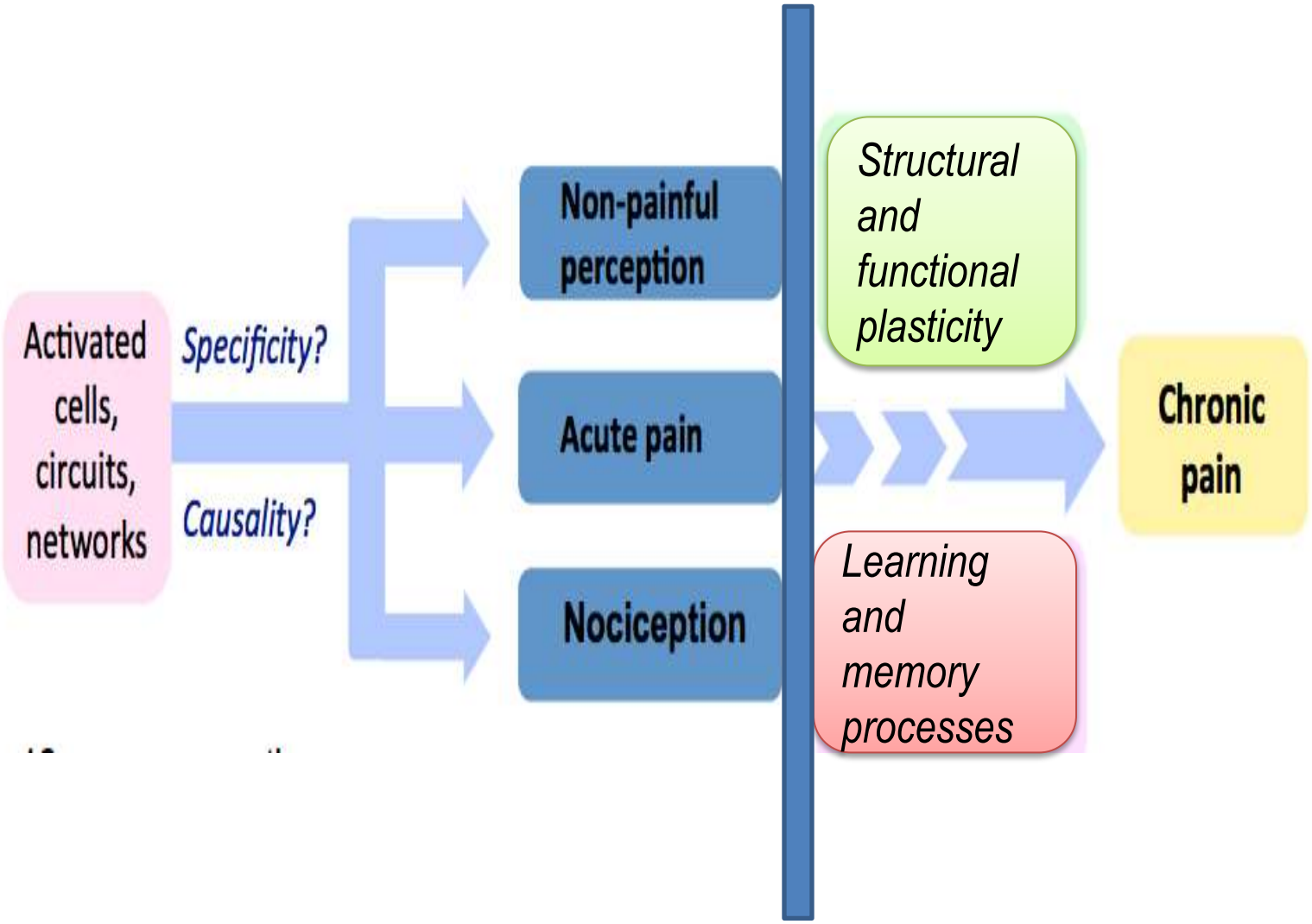
The chronicity process



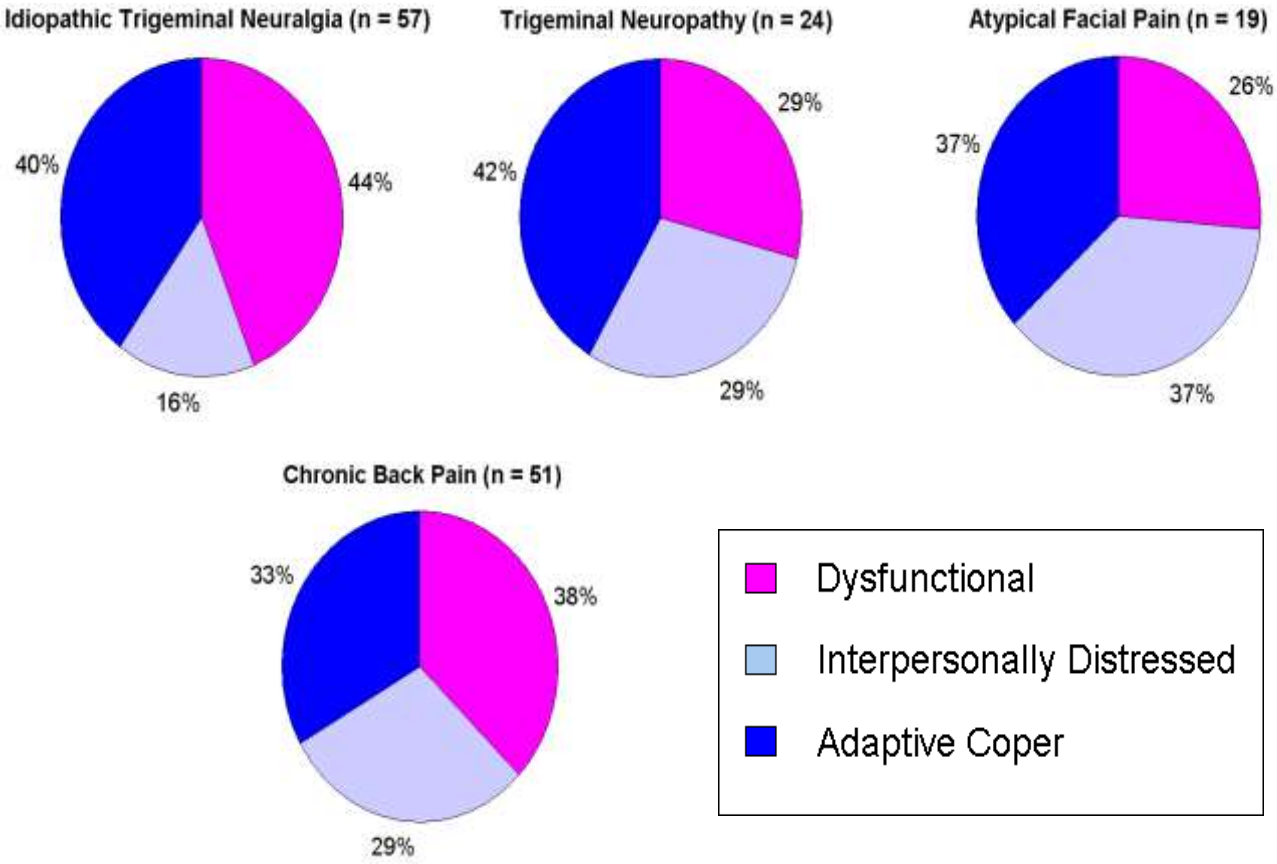
Predictors of chronicity

- Stress and distress from epidemiological studies
- Operant conditioning of pain behaviors
- Acquired fear of pain/movement
- Hypervigilance/catastrophizing/inadequate coping
- Abnormal structural and functional connectivity of limbic and cortical sites
- Comorbidity of depression and anxiety
- Yellow flags
- Quantitative sensory testing: hypo/hypersensitivity
- Deficient descending inhibition/Conditioned pain modulation
- Genes/epigenetic factors

Goals

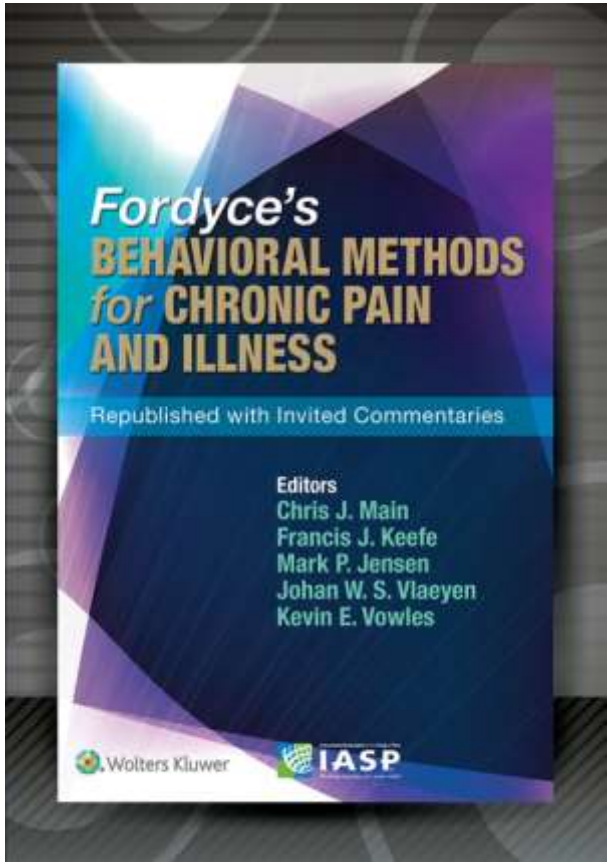
- Identification of common and distinct learning, memory and brain plasticity mechanisms across pain disorders
- Development of mechanism-based assessment and classification
- Development and testing of tailored mechanism-based behavioral, pharmacological and combined treatments

Psychosocial Subgroups (MPI)



Flor et al., in prep.

Chronic pain can develop by reward learning



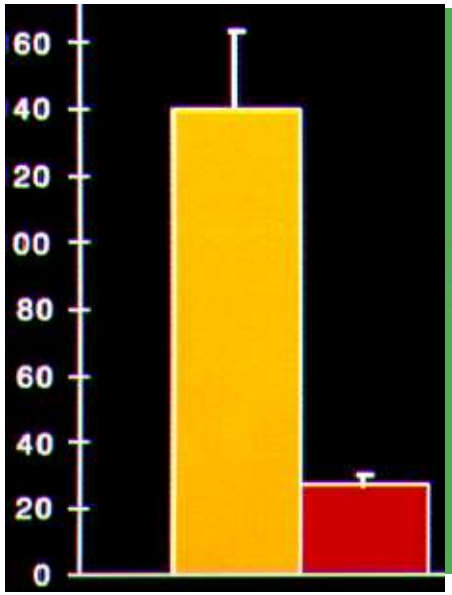
- Positive reinforcement (e.g. attention for pain)
- Negative reinforcement (e.g. pain stops because of rest or medication)
- Lack of reinforcement for healthy behaviors

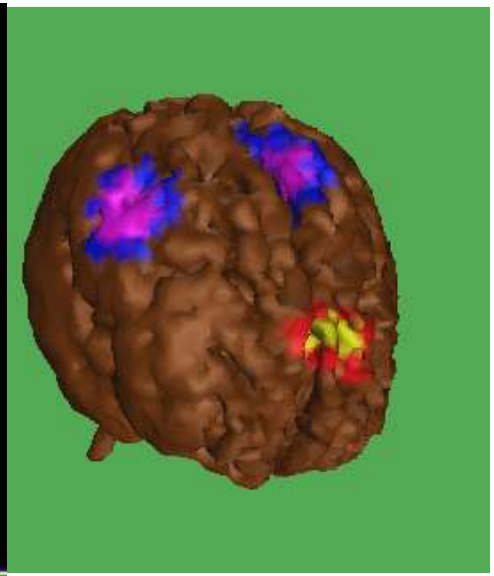
W.E. Fordyce, 1976
Main et al., 2015
See also Linton, Keefe,
And for extensions Fields, Porreca

Social reward determines the brain response to pain

solicitous

non solicitous





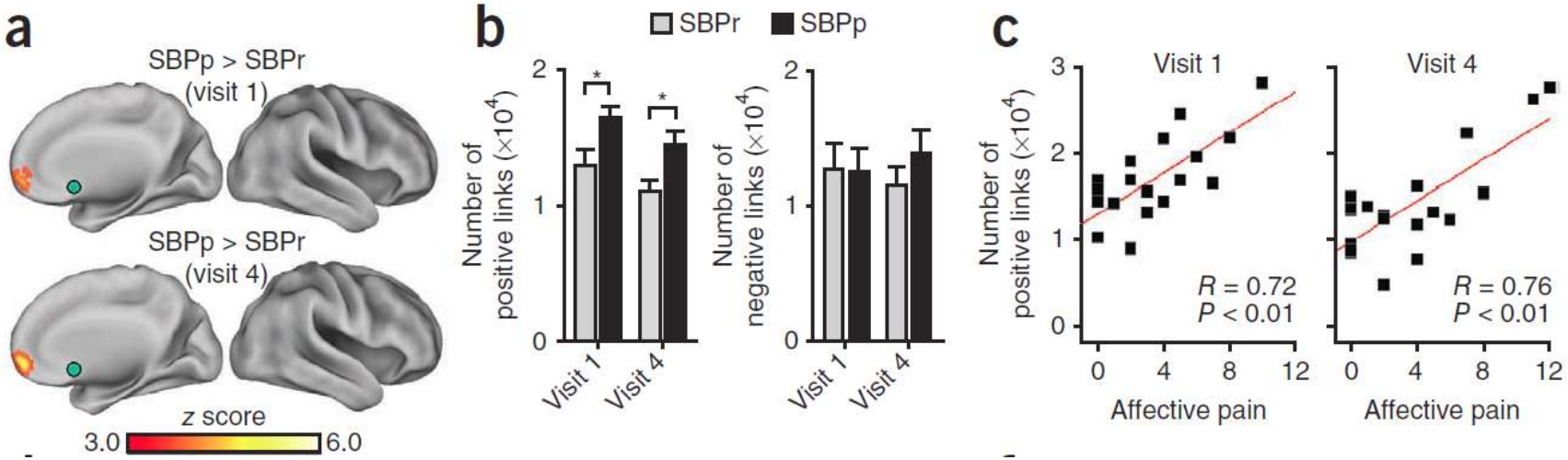
pain rating

inside outside

brain activity

Flor et al., Am Psychol, 2014

Connectivity of reward-related brain areas - vulnerability marker for chronicity?



Baliki et al., Nat NS, 2012

Mechanism-based analysis of mental disorder: IMAGEN

N=2400 children

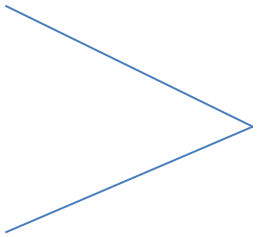
Reward sensitivity Inhibitory Control Emotional reactivity

Brain imaging

Behavior

Neuropsychology

Genes



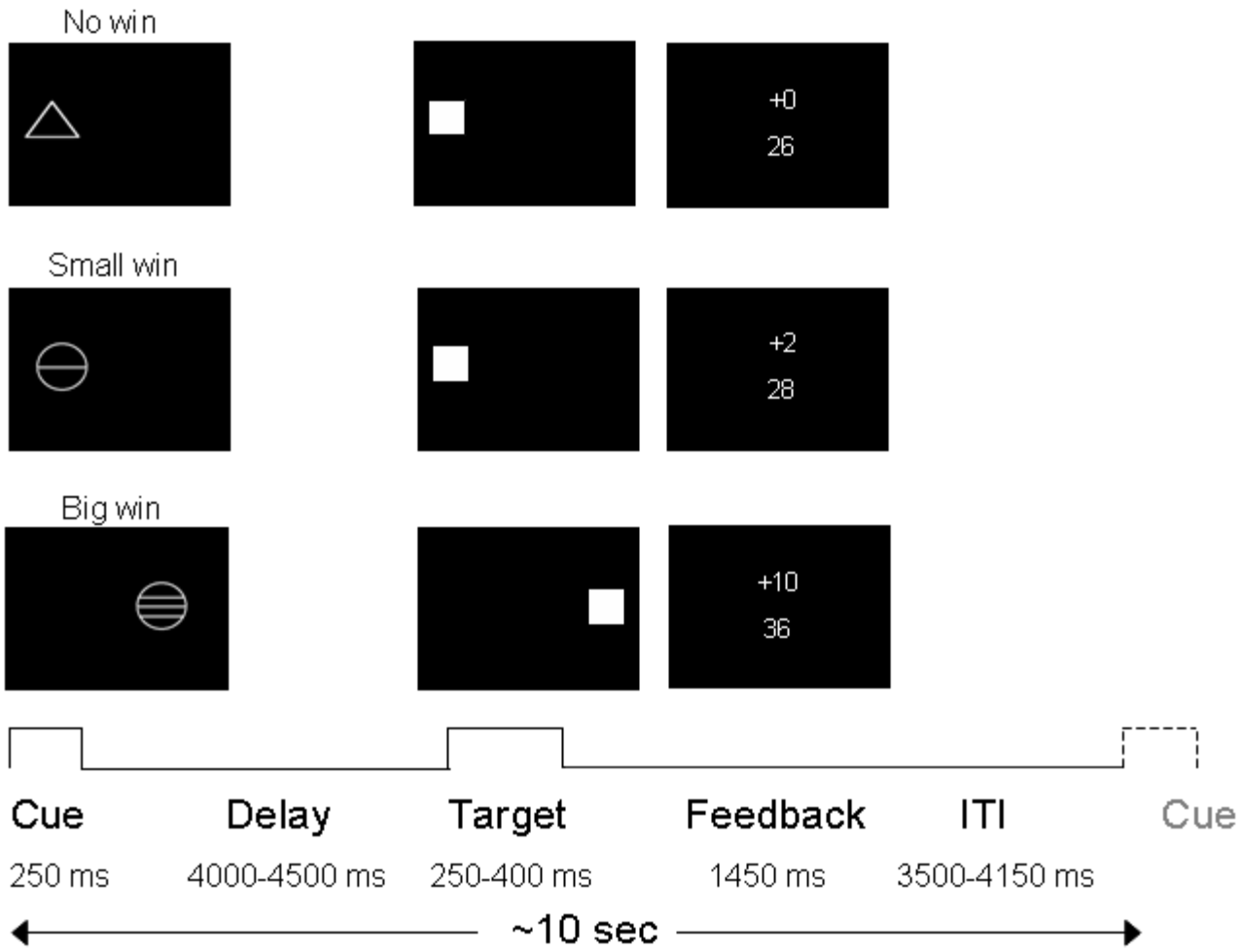
Integrate stepwise

Multiple disorders: symptom level

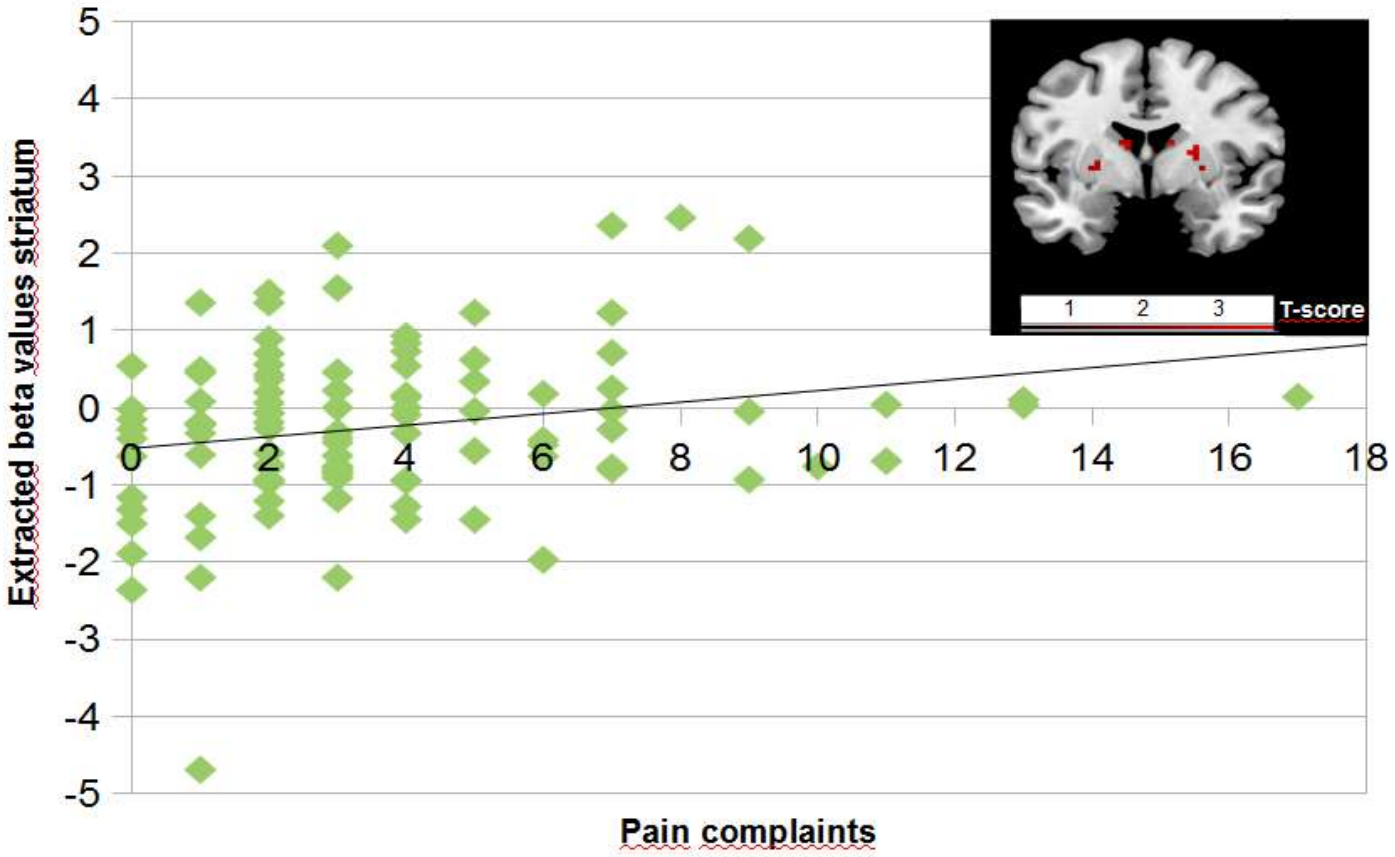
Mechanism-based treatment, prevention

Schumann et al., Mol Pstr., 2010

Monetary incentive delay task



Reward feedback related brain activation predicts pain complaints two years later

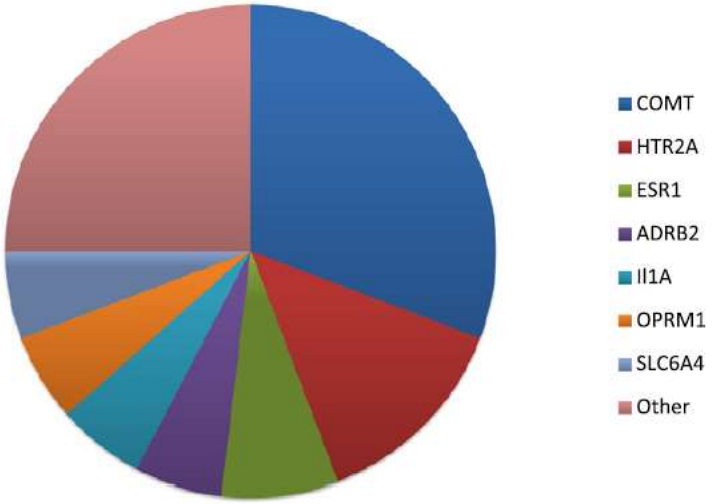


Significant prediction of the development of pain complaints in adolescents at age 16-17 by the activation in the dorsal striatum during reward feedback at age 14

Nees et al., Pain, 2017

Genetic loci associated with musculoskeletal pain disorders

Gene	# of citations
COMT	16
HTR2A	7
ESR1	4
ADRB2	3
IL1A	3
OPRM1	3
SLC6A4	3
Other	13

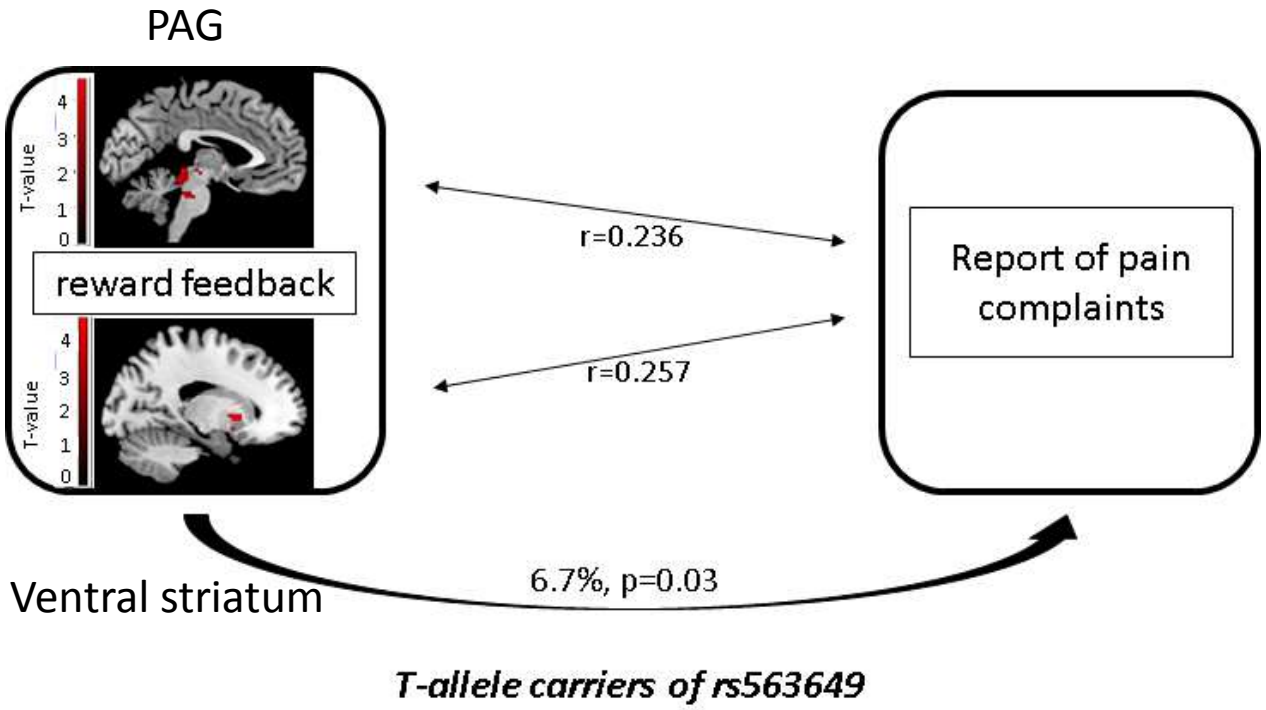


e.g., Zorina-Lichtenwalter, Meloto, Khoury & Diatchenko, Neuroscience, 2016; Diatchenko, Fillingim, Smith, & Maixner, Nat Rev Rheumatol, 2013

Pain complaints, reward processing and OPRM1

Role of the μ-opioid receptor:
Significant prediction of pain complaints by activation in the periaqueductal grey, dorsal and ventral striatum during reward feedback related to specific variants (T allele of rs563649)

Significant mediation by the level of **early life stress**

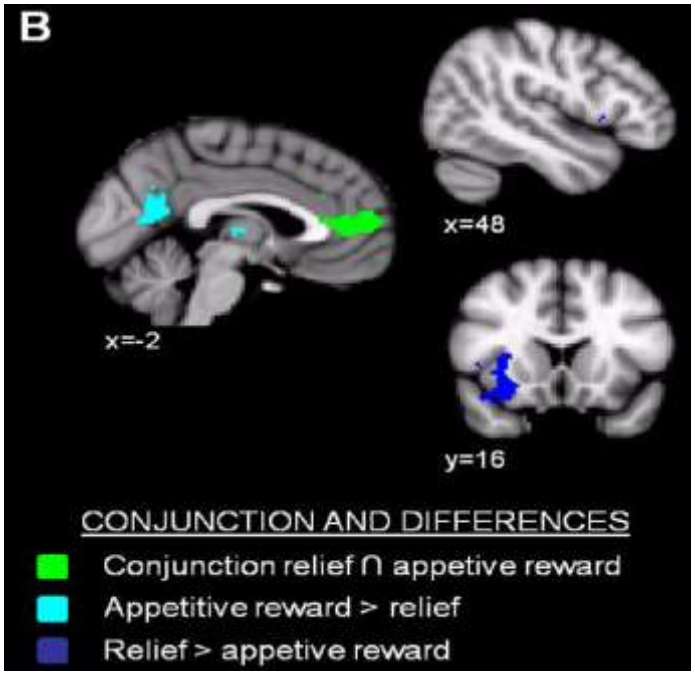


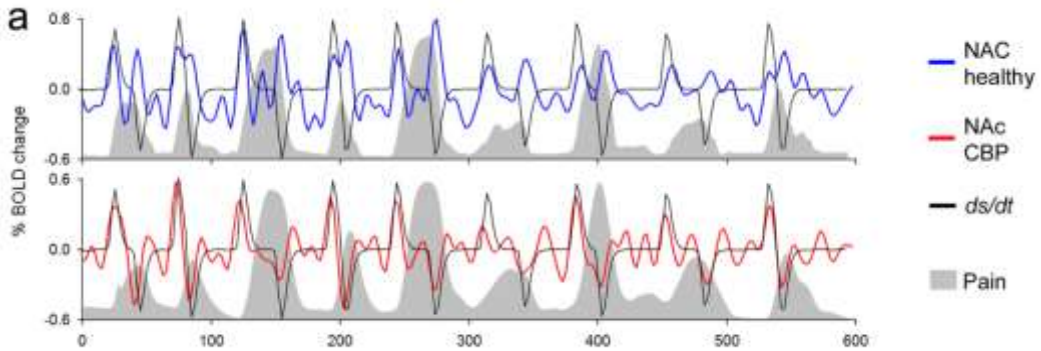
No sig. effect for rs179971

(Nees et al., Pain, 2017)

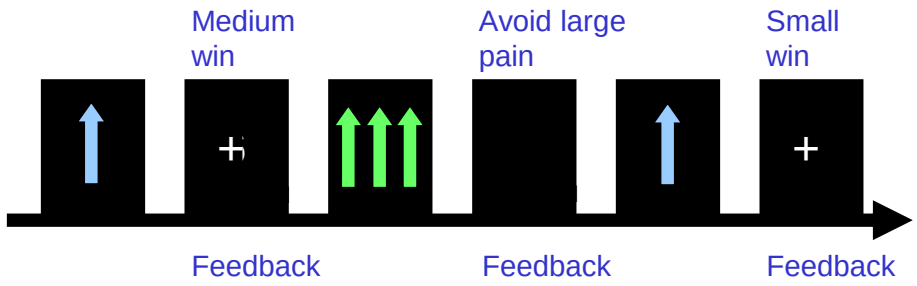
Ongoing research

Longitudinal Study on reward versus pain relief: neural difference (Leknes et al., 2011), alterations in transition to chronic pain (e.g., Baliki et al. 2010), relationship to yellow flags, depression, QST

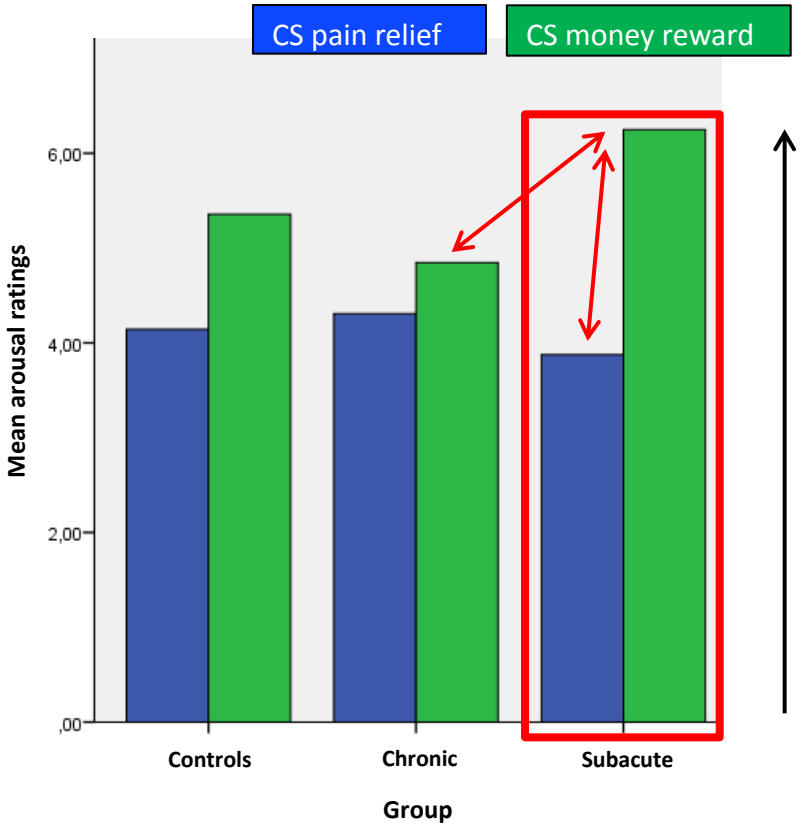




Instrumental conditioning during fMRI: pain relief / monetary reward as USs



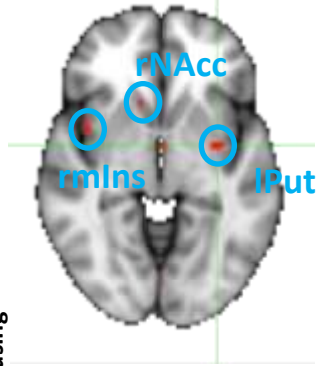
Self-reported correlates of monetary reward versus pain relief learning: subacute back pain versus chronic back pain versus healthy controls



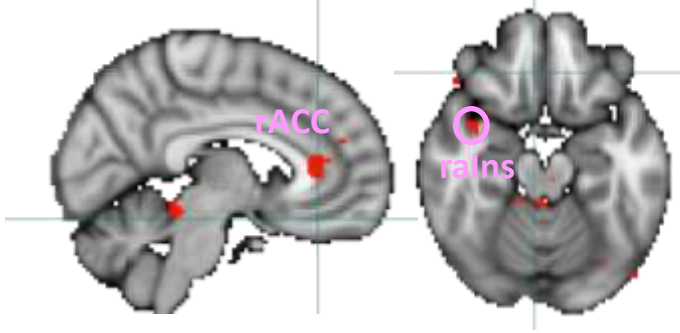
Higher arousing

Pain relief CS

Chronic < controls

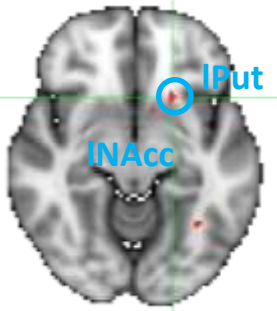


Chronic > controls

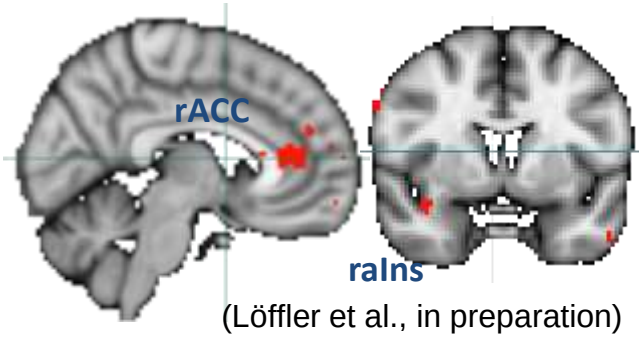


Monetary reward CS

Chronic < controls

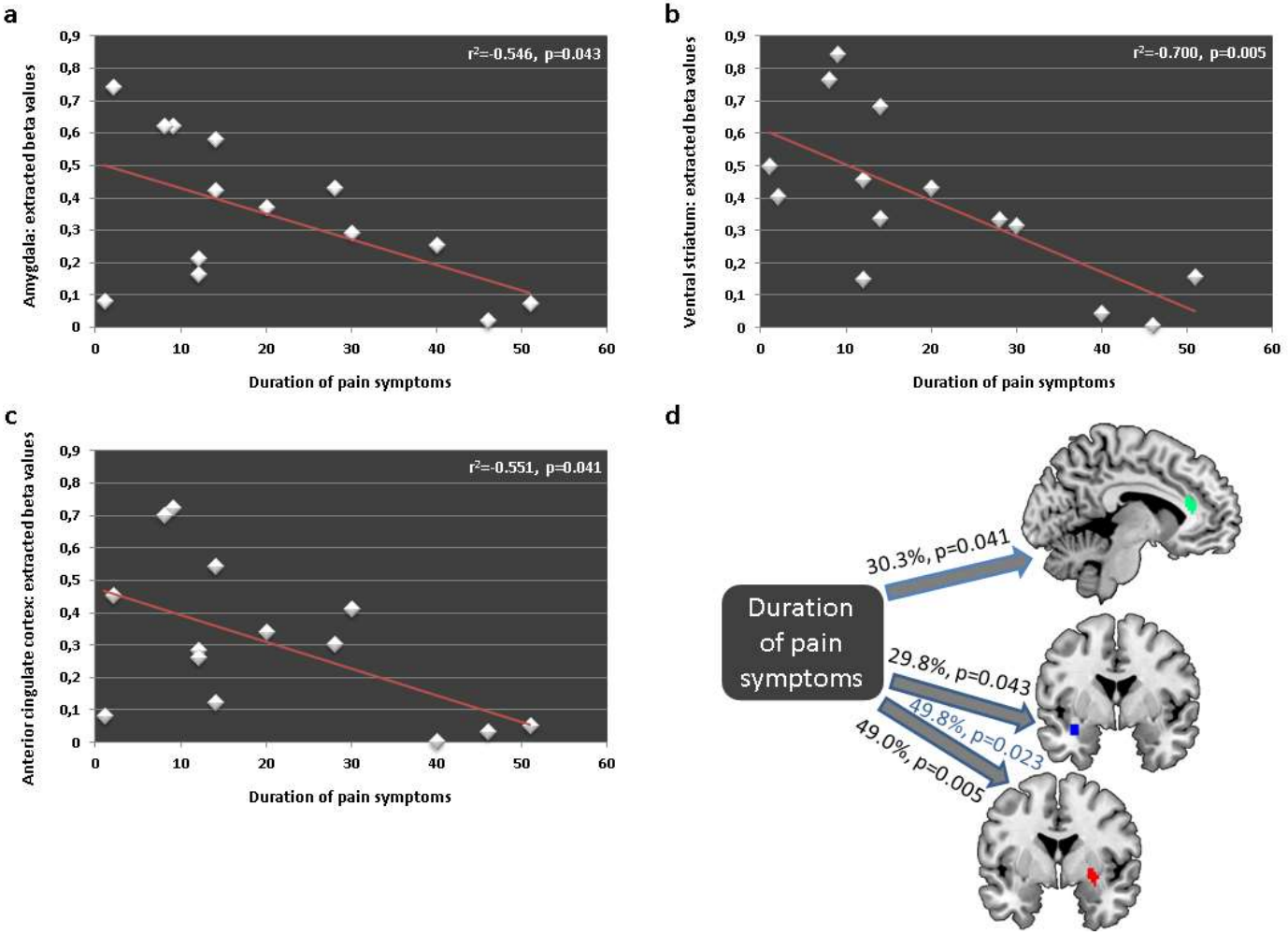


Chronic > controls



(Löffler et al., in preparation)

Association between brain responses during reward learning and pain symptom duration



(Nees et al., under review)

Emotional Learning -Pavlovian Conditioning

US
(injury-pain)

→

UR
(sympathetic activation,
fear, tension)

CS
(neutral stimuli)

→

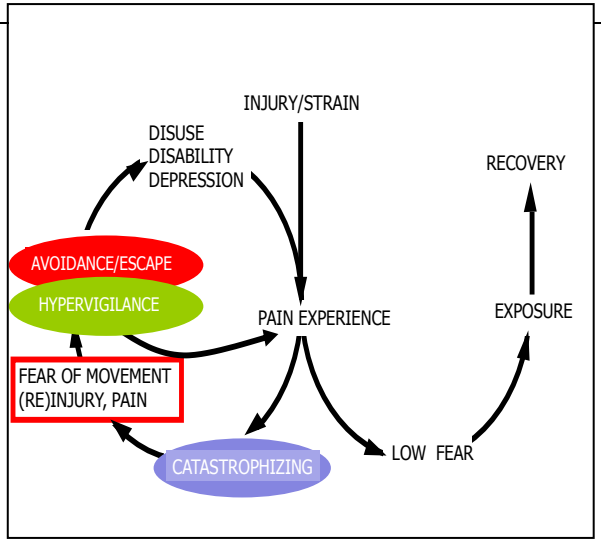
CR
(sympathetic activation,
fear, tension, worry)

CS+
Danger

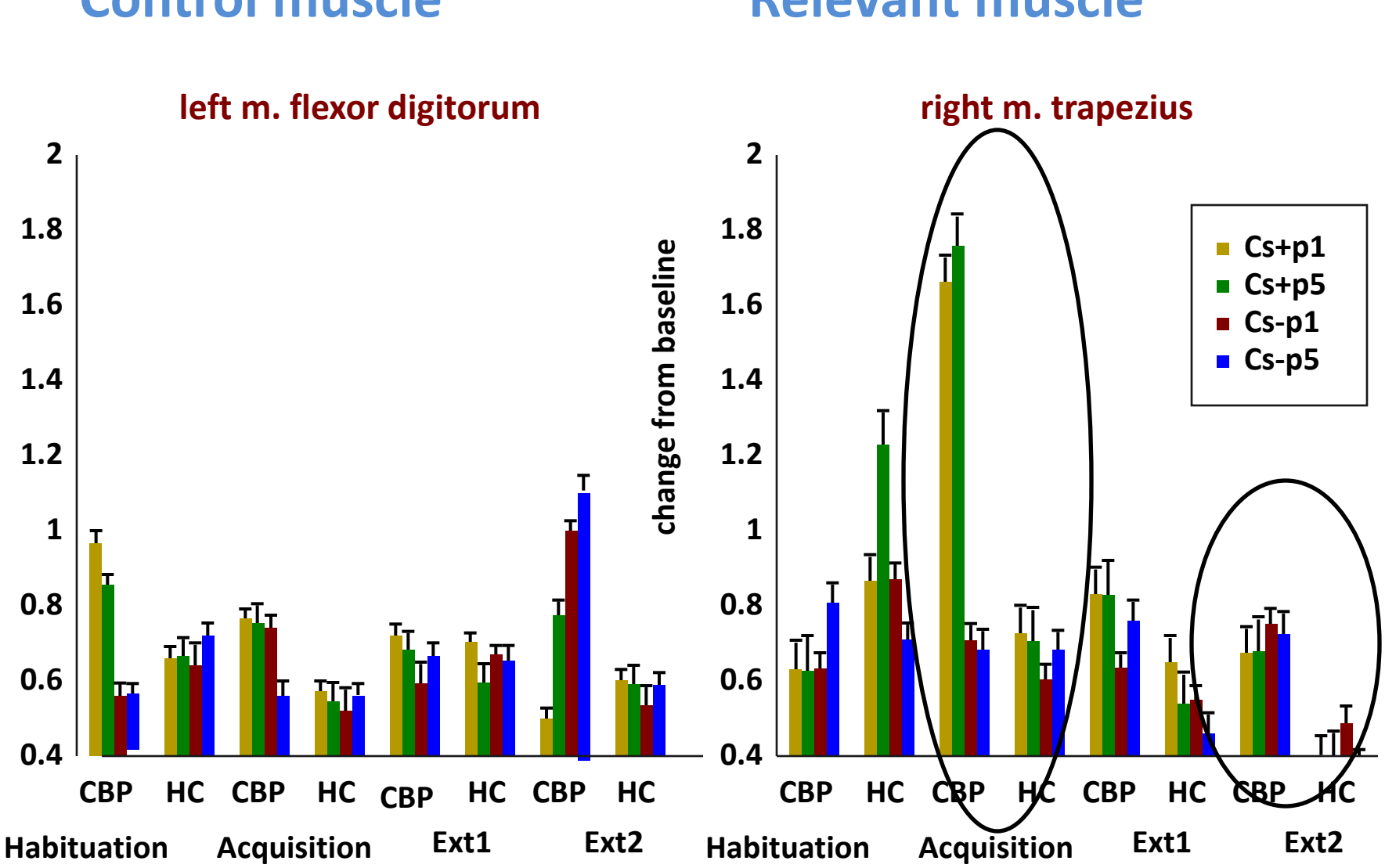
CS-
Safety

↓

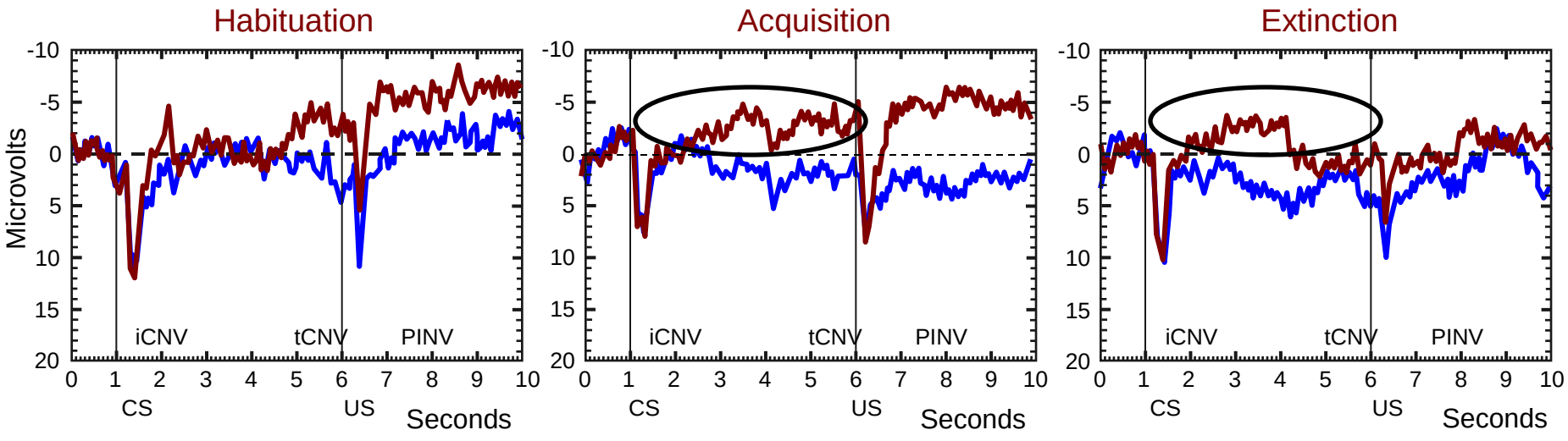
Pain



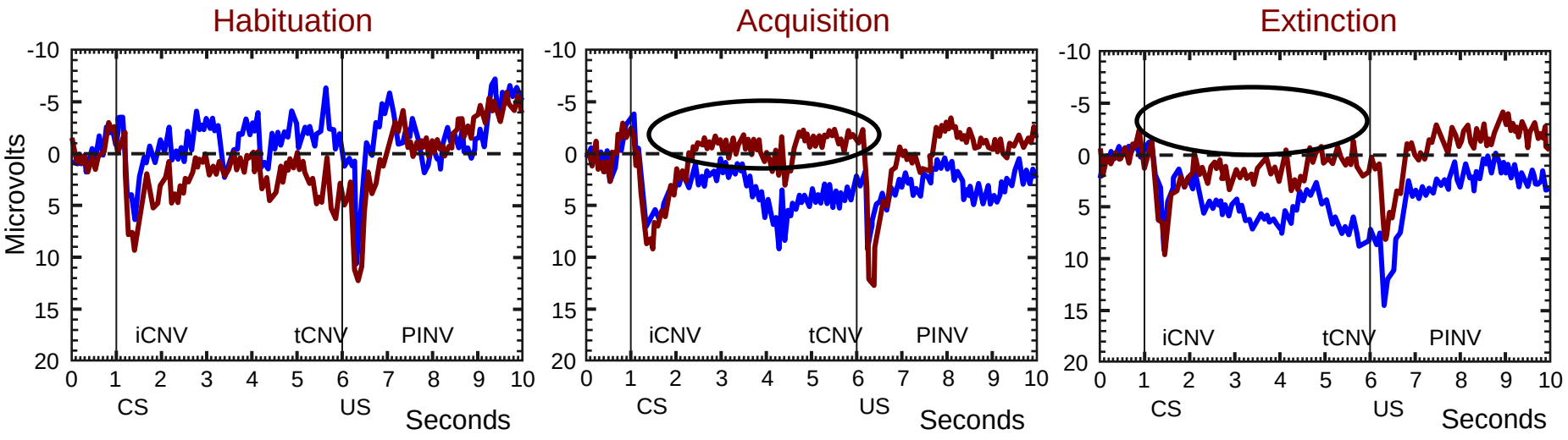
(adapted from Linton et al., 1985, see also Vlaeyen et al.: Fear of pain/movement, 1995, 2000)

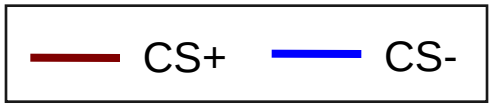

Control muscle
Relevant muscle
left m. flexor digitorum
right m. trapezius
change from baseline
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
Cs+p1
Cs+p5
Cs-p1
Cs-p5
CBP
HC
Habituation
Acquisition
Ext1
Ext2

Chronic Pain Patients



Healthy Controls

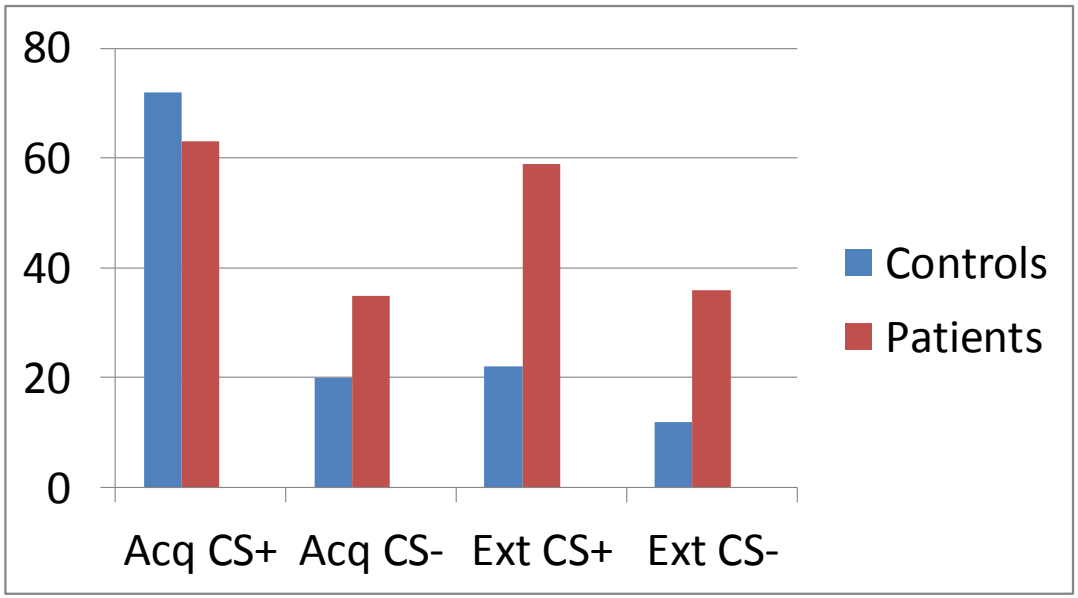




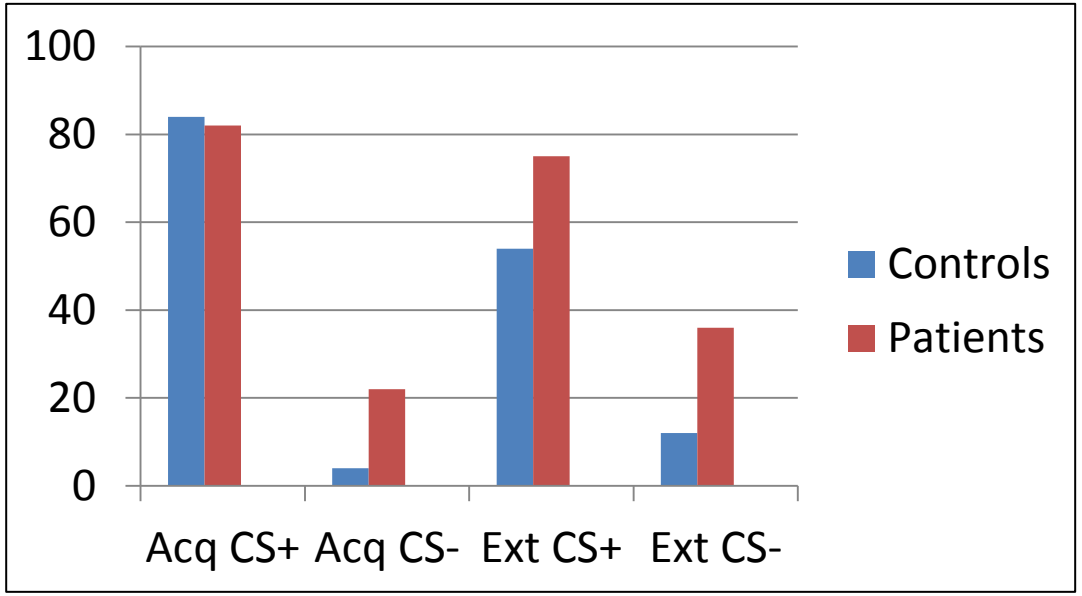
Schneider et al., Pain, 2004

Chronic pain

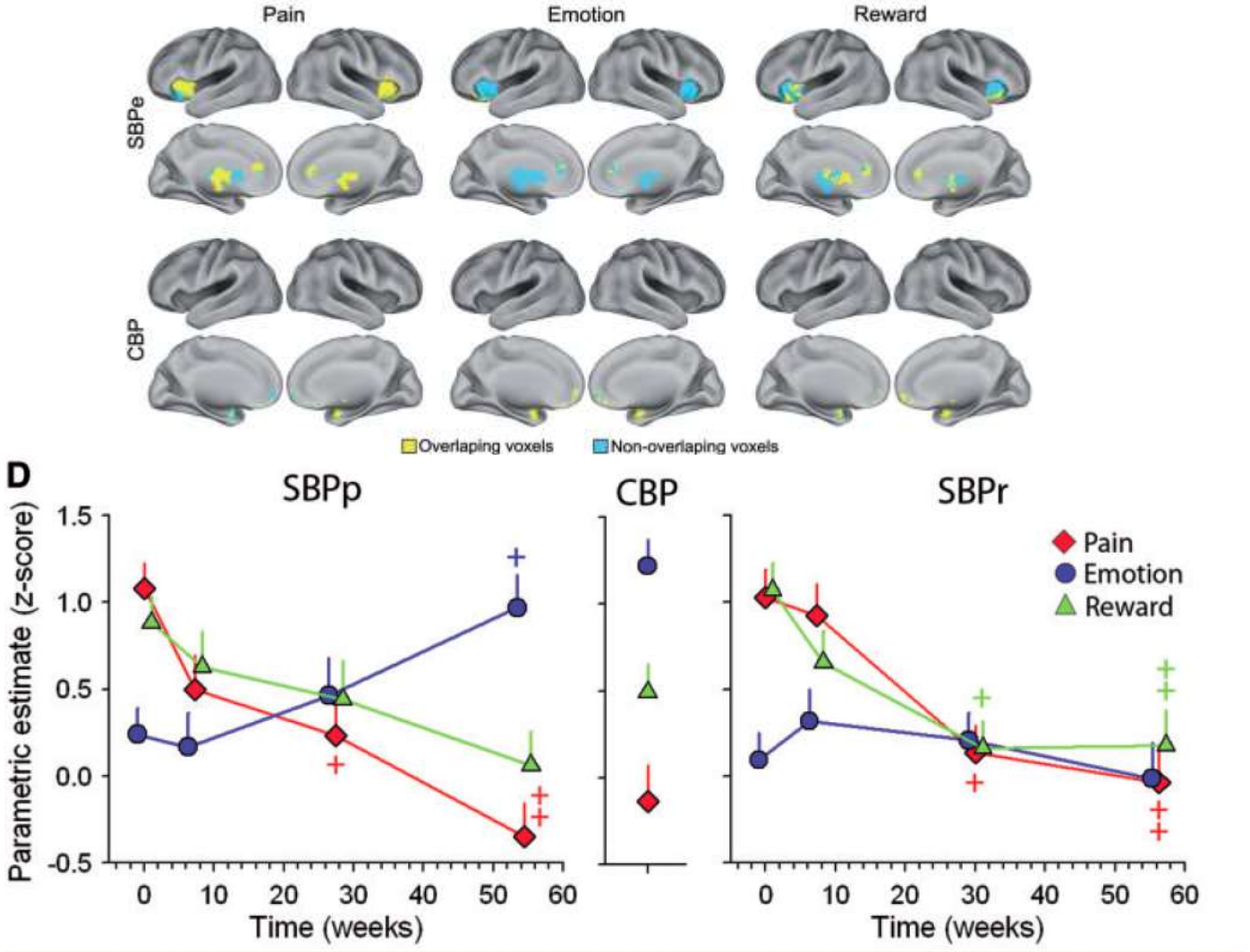
Prediction
-> Hypergivilance



Aversiveness
-> Negative Affectivity

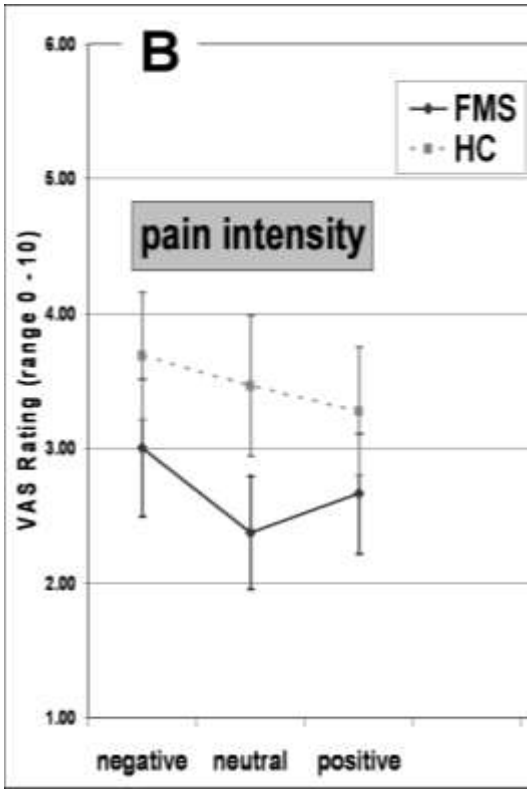


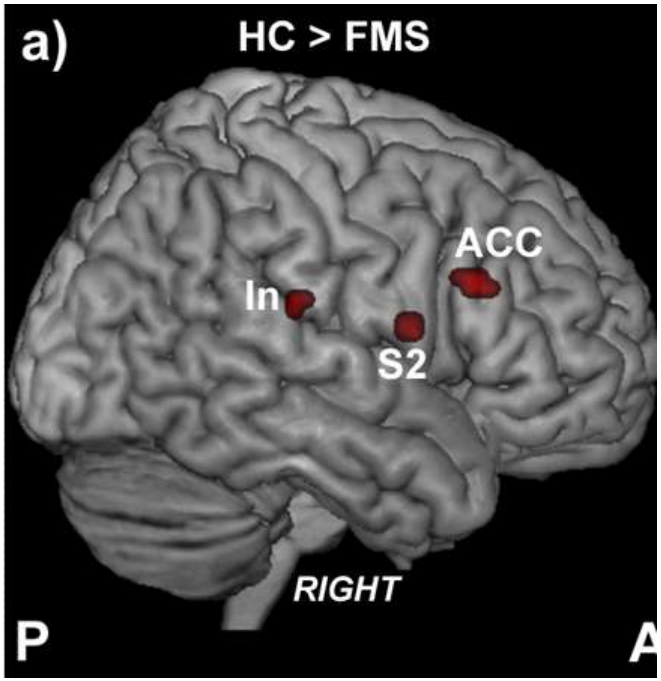
Transition from nociceptive to negative emotion networks in chronic pain



Hashmi et al., Brain, 2013

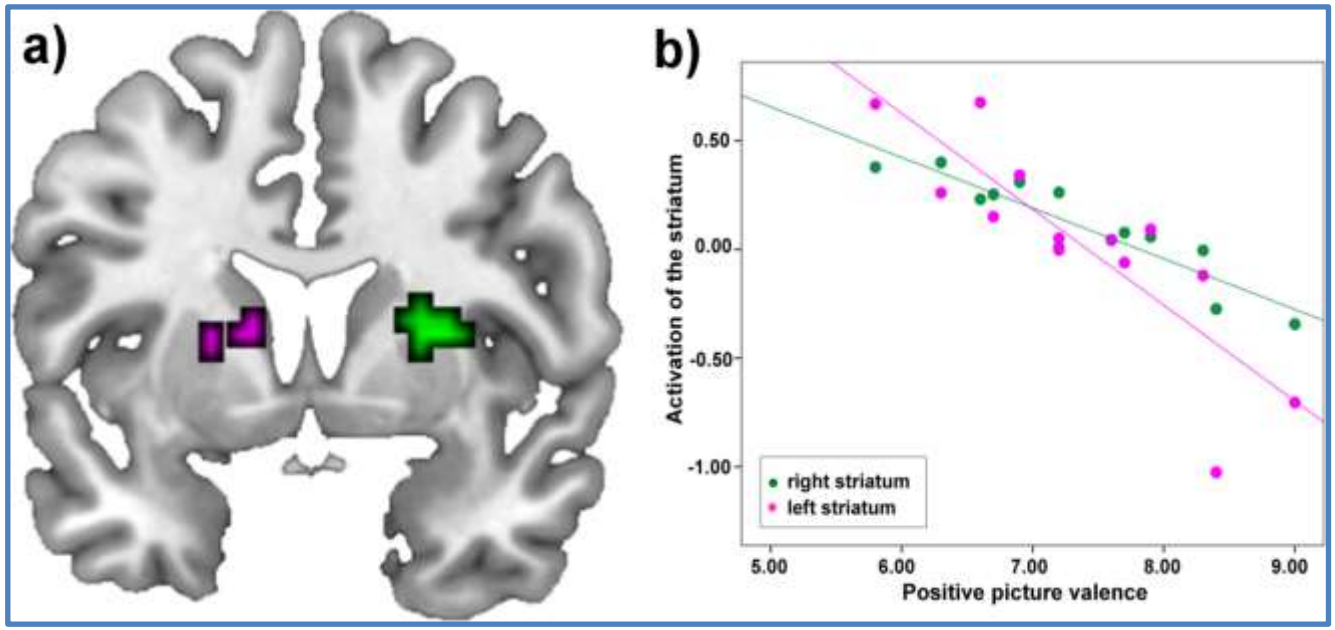
Pain is less modulated by positive emotions





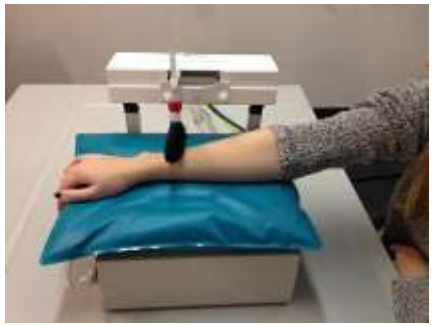
Kamping et al., Pain, 2013

Decreased striatal activity in chronic pain – disturbed emotional learning

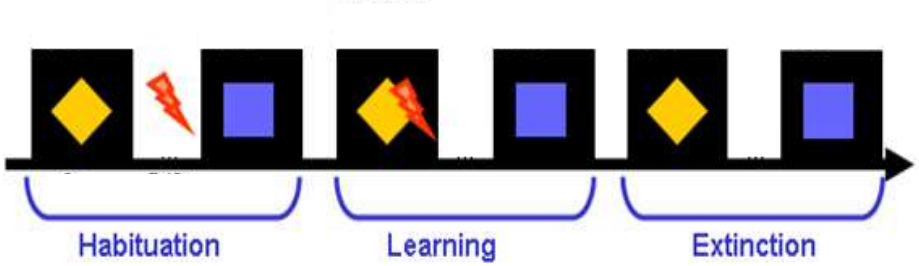


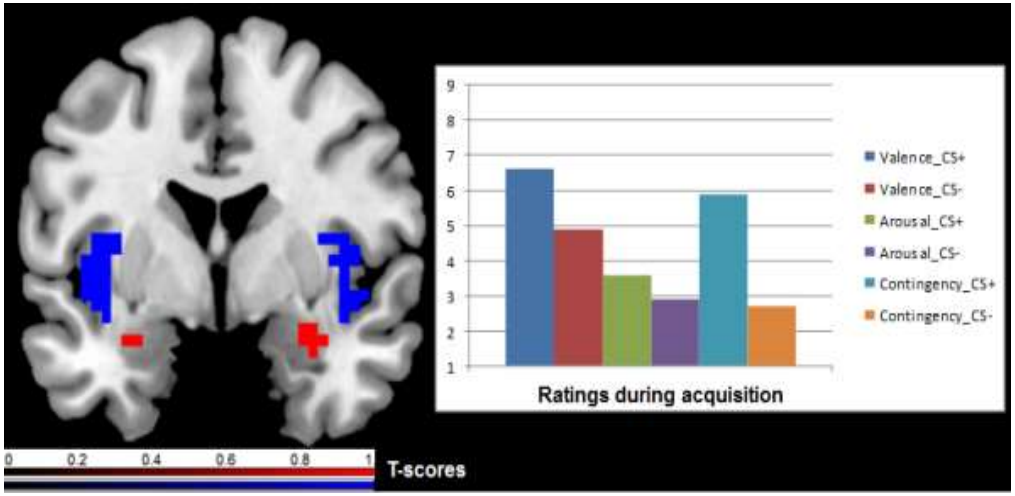
Kamping et al., Pain, 2013

Pleasant touch versus pain



Respondent conditioning during fMRI: pain / pleasant touch as USs

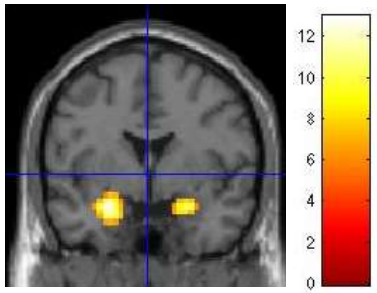




Interaction of reward processing and aversive learning-related brain activation

Significant positive correlations of regions of interest during aversive learning (CS+unpaired > CS-) and reward anticipation (big win > no win)

Learning-related amygdala activation correlated positively with reward-related activation in the



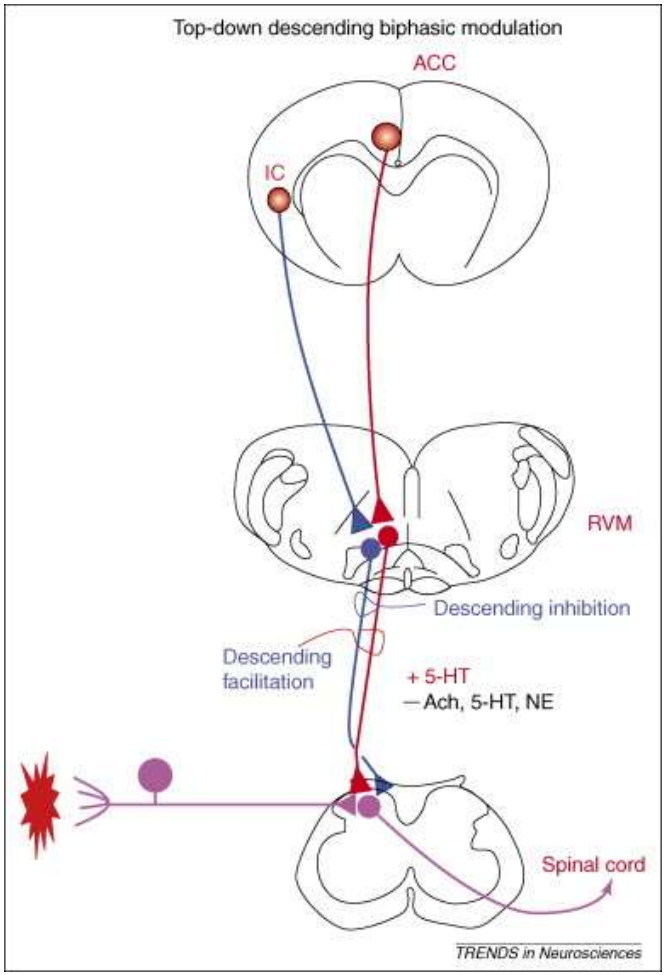
- amygdala
- striatal regions
- insula
- orbitofrontal and prefrontal regions, including the anterior cingulate

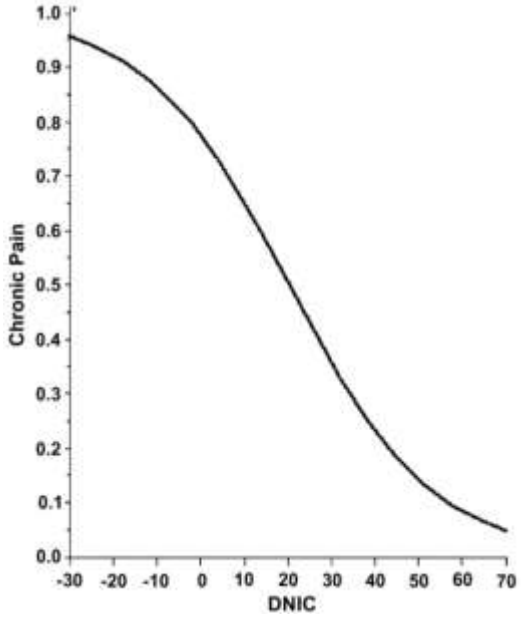
p < .001 FWE-corr., cluster > 10 voxels, N = 39 (21 female)

Before pain onset - may adapt with chronicity

Nees et al., in prep.

The role of stress – modulation of descending inhibition and facilitation

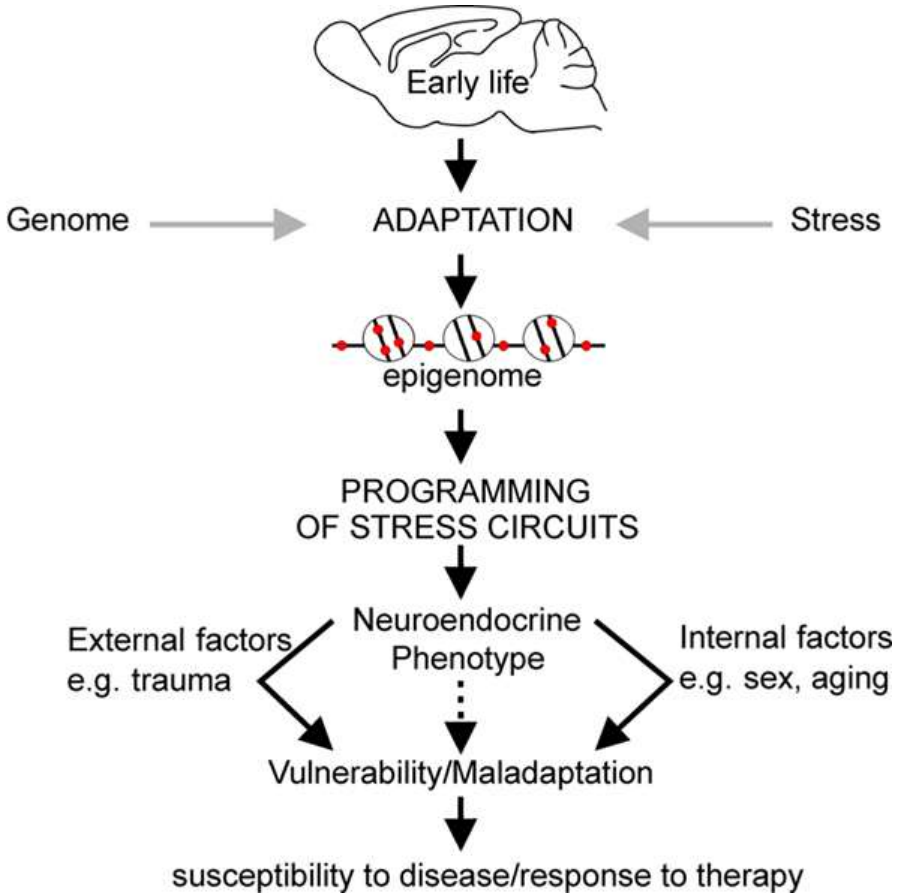




Yarnitzki et al., Pain, 2008

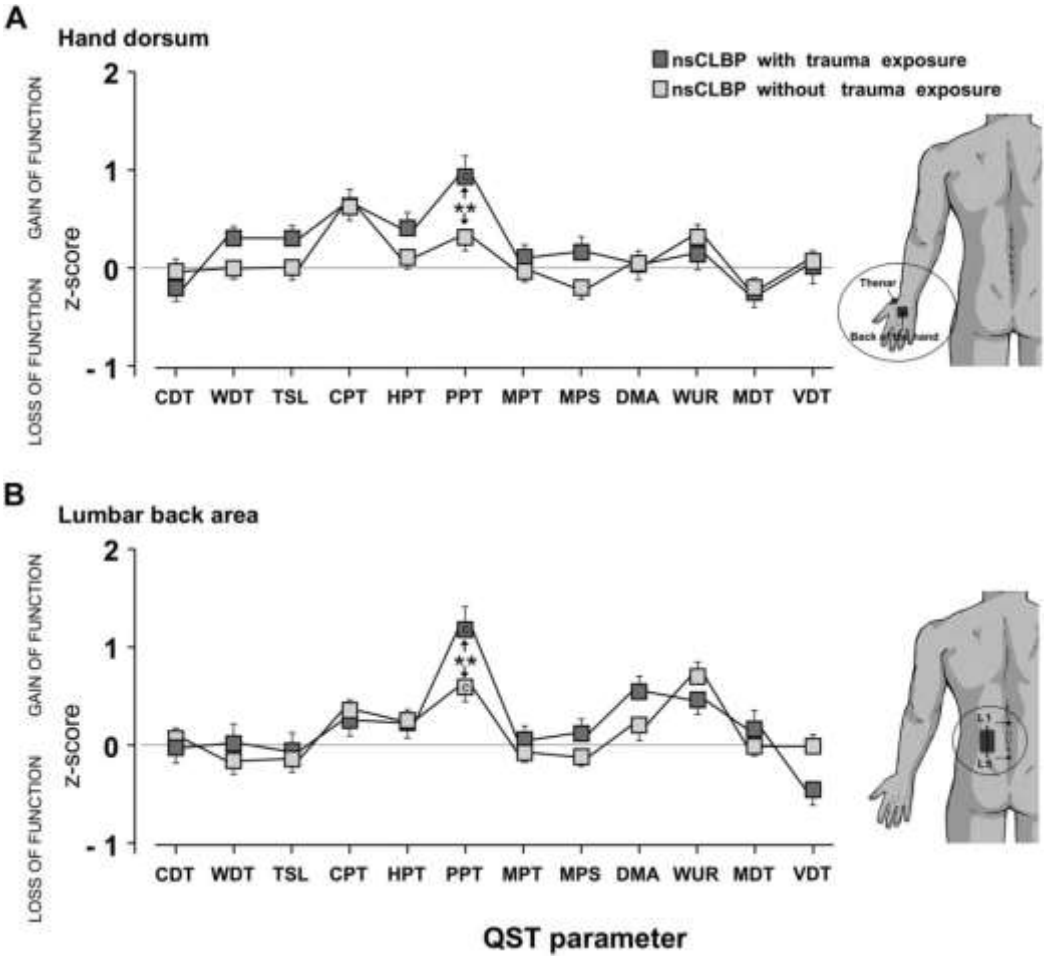
Le Bars
Willer et al.
Butler & Finn
Lautenbacher

Stress-Circuits



Acute stress: hypoalgesia /stress-induced analgesia
Chronic stress: hyperalgesia
Stress alters goal-directed to habitual behavior -> implicit behavior

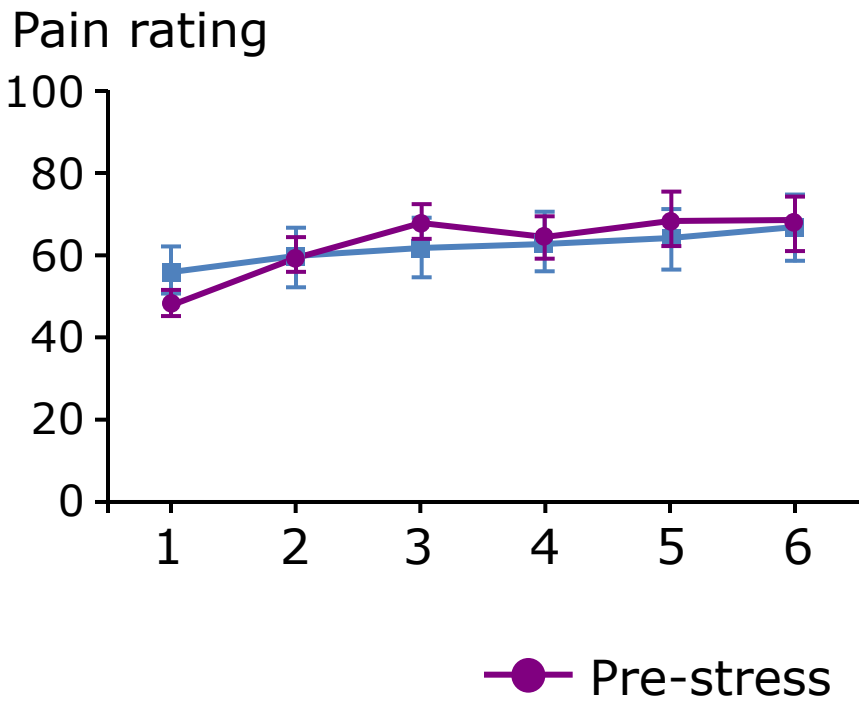
Distinct quantitative sensory testing profiles in nonspecific chronic back pain subjects with and without psychological trauma



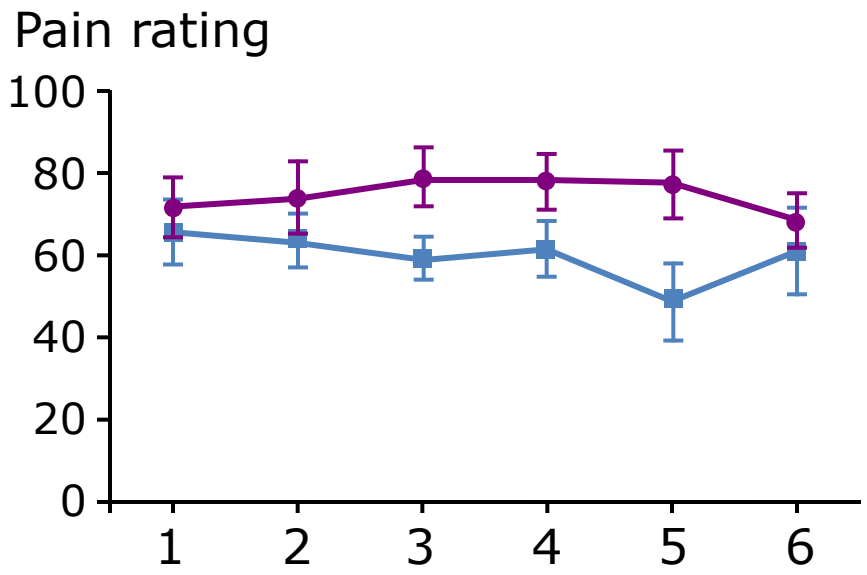
Tesarz, Gerhard, Leisner, Janke, Treede, & Eich, Pain, 2015

Stress-Analgesia

VAS ratings in patients with fibromyalgia



VAS ratings in healthy controls



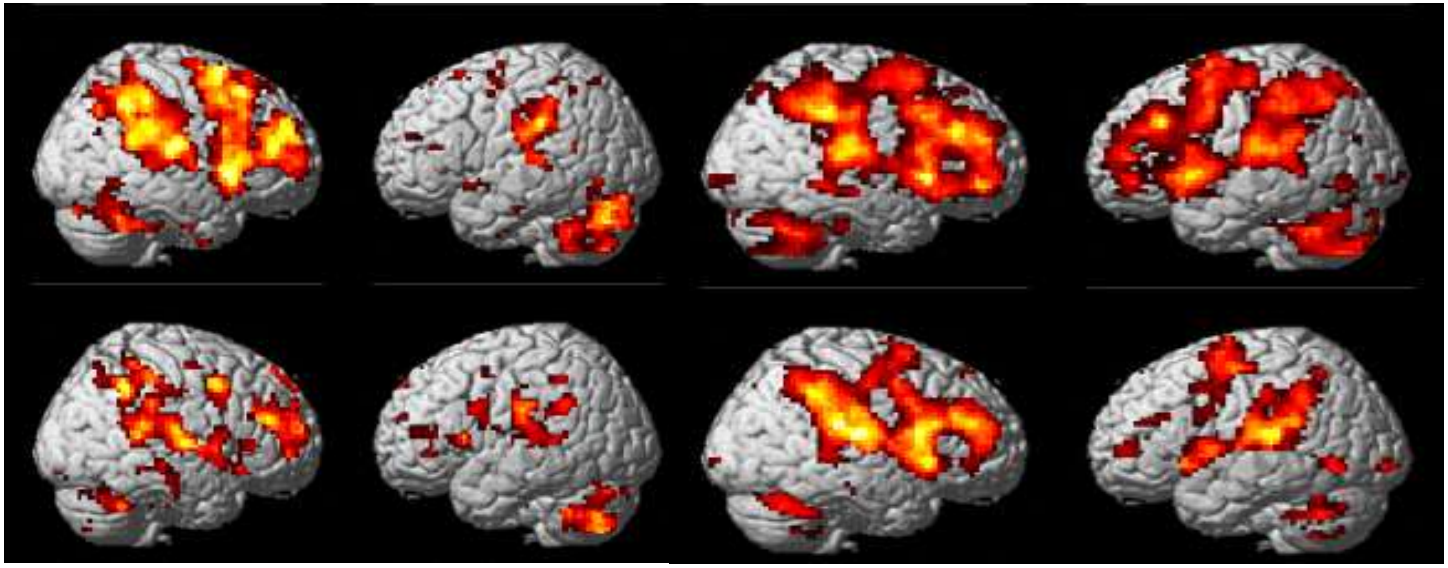
Yilmaz et al., Pain, 2010
Diener et al., J Aff Dis, 2012
Diers et al., 2016

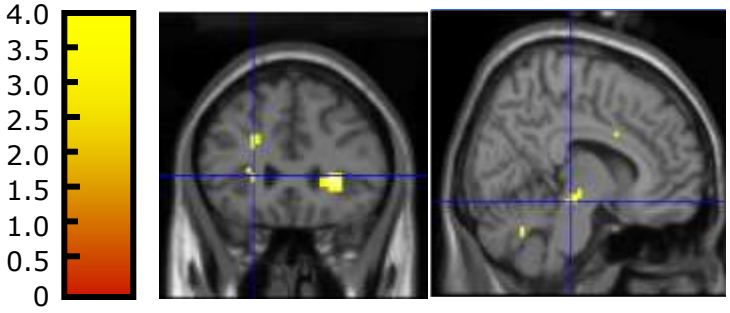
Healthy Controls

Fibromyalgia

Pre Stress

Post Stress

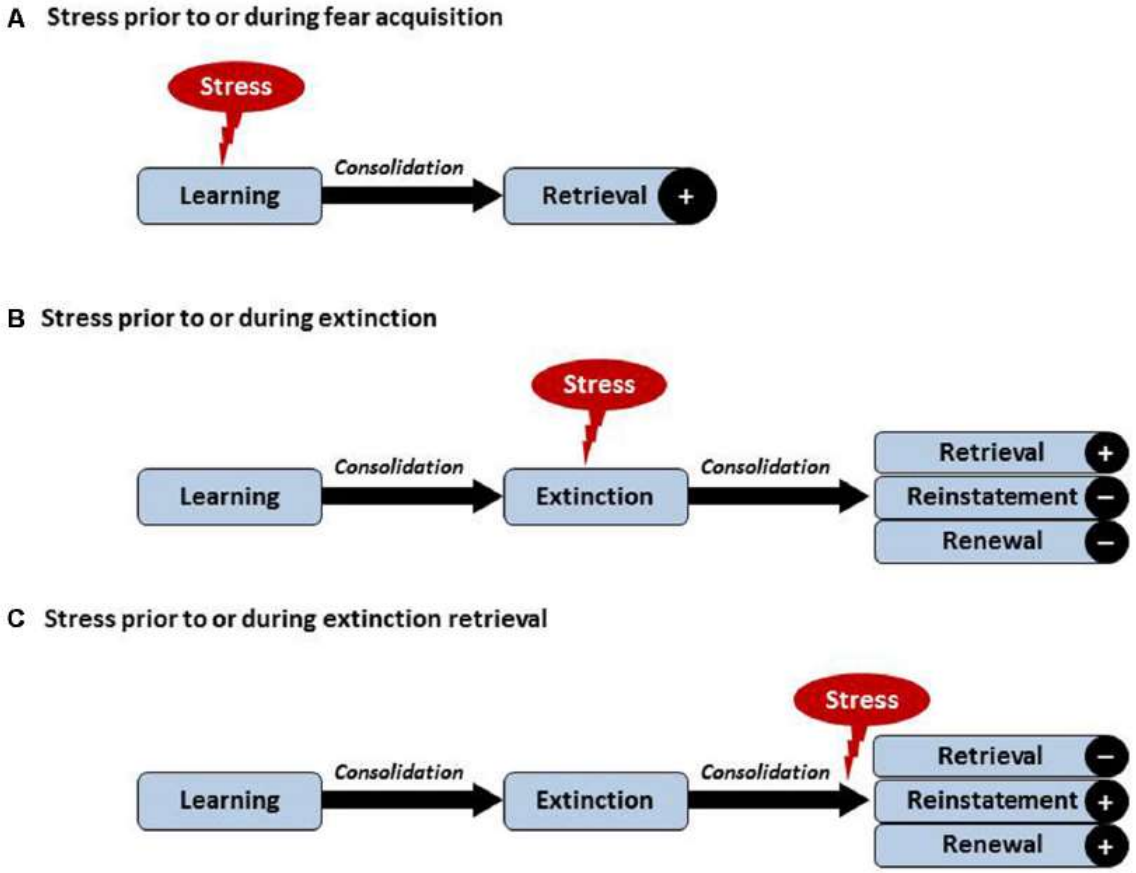




Insula

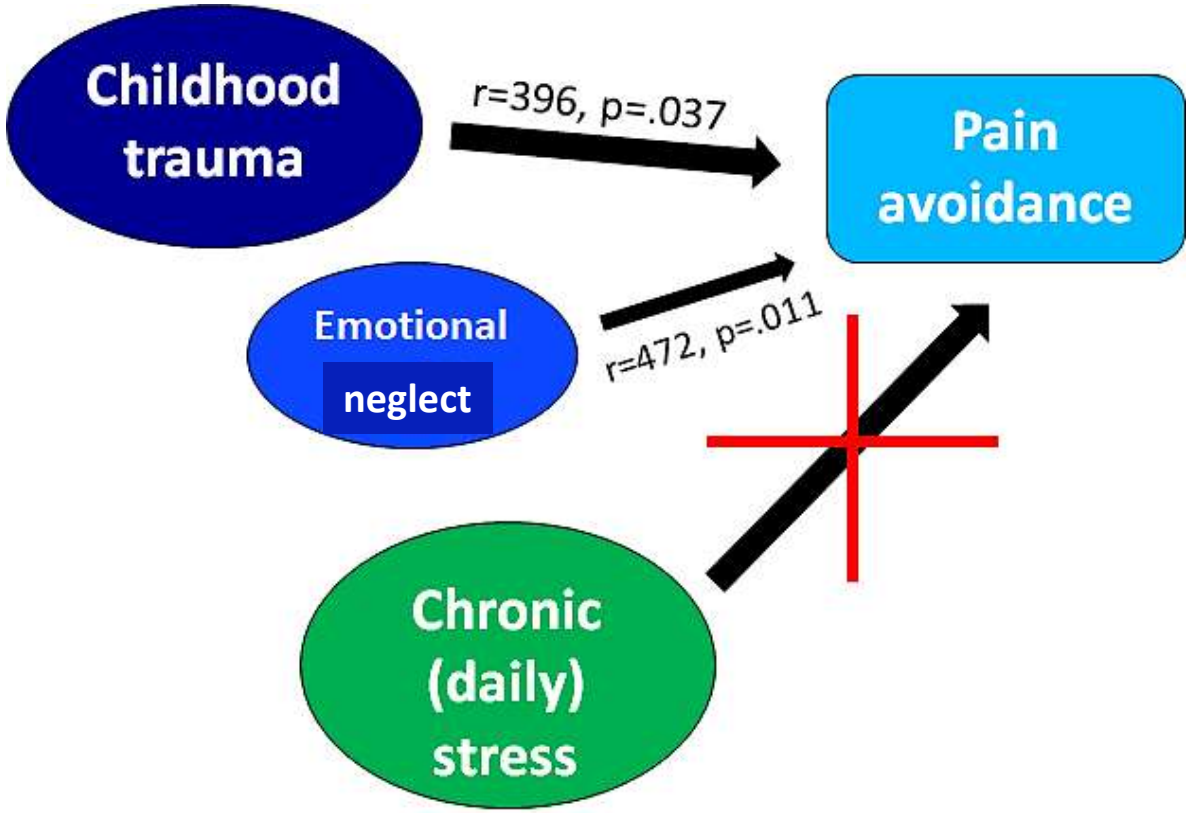
PAG

Contributions of stress to pain-related fear and learning:



Elsenbruch & Wolf, Front Beh NS, 2016

Association between pain avoidance and childhood trauma in chronic pain



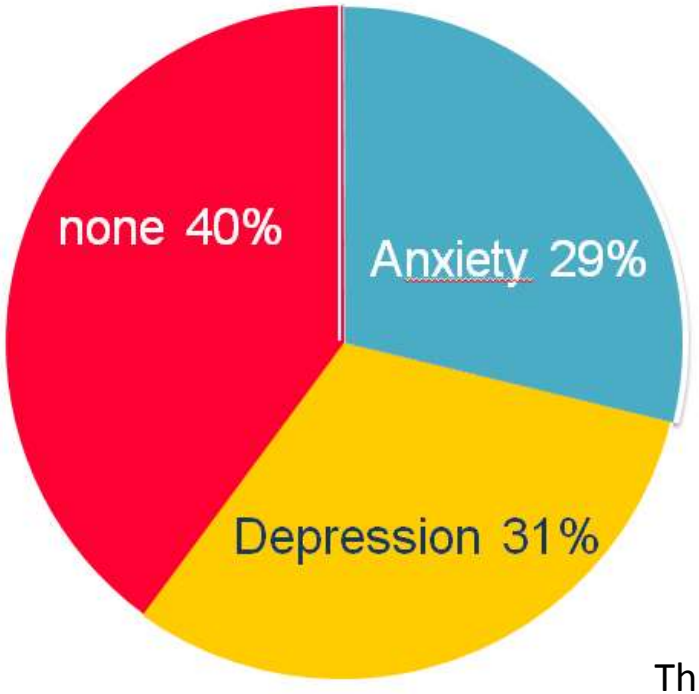
(Usai et al., in preparation; Löffler et al., in preparation)

Chronic back pain:
Best predictors (1-3 years later)

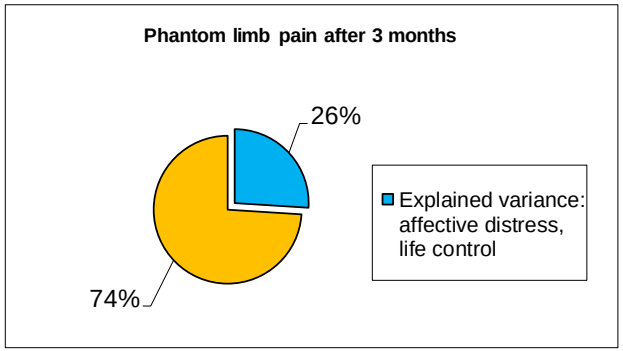
	pain	function
Fear of movement	.11	-.25
Catastrophizing	.57	-.51
Depression	.67	-.41

Boersma &Linton, BRAT, 2005;
Hasenbring et al., Spine, 1994

Comorbid Psychopathology in Chronic Pain

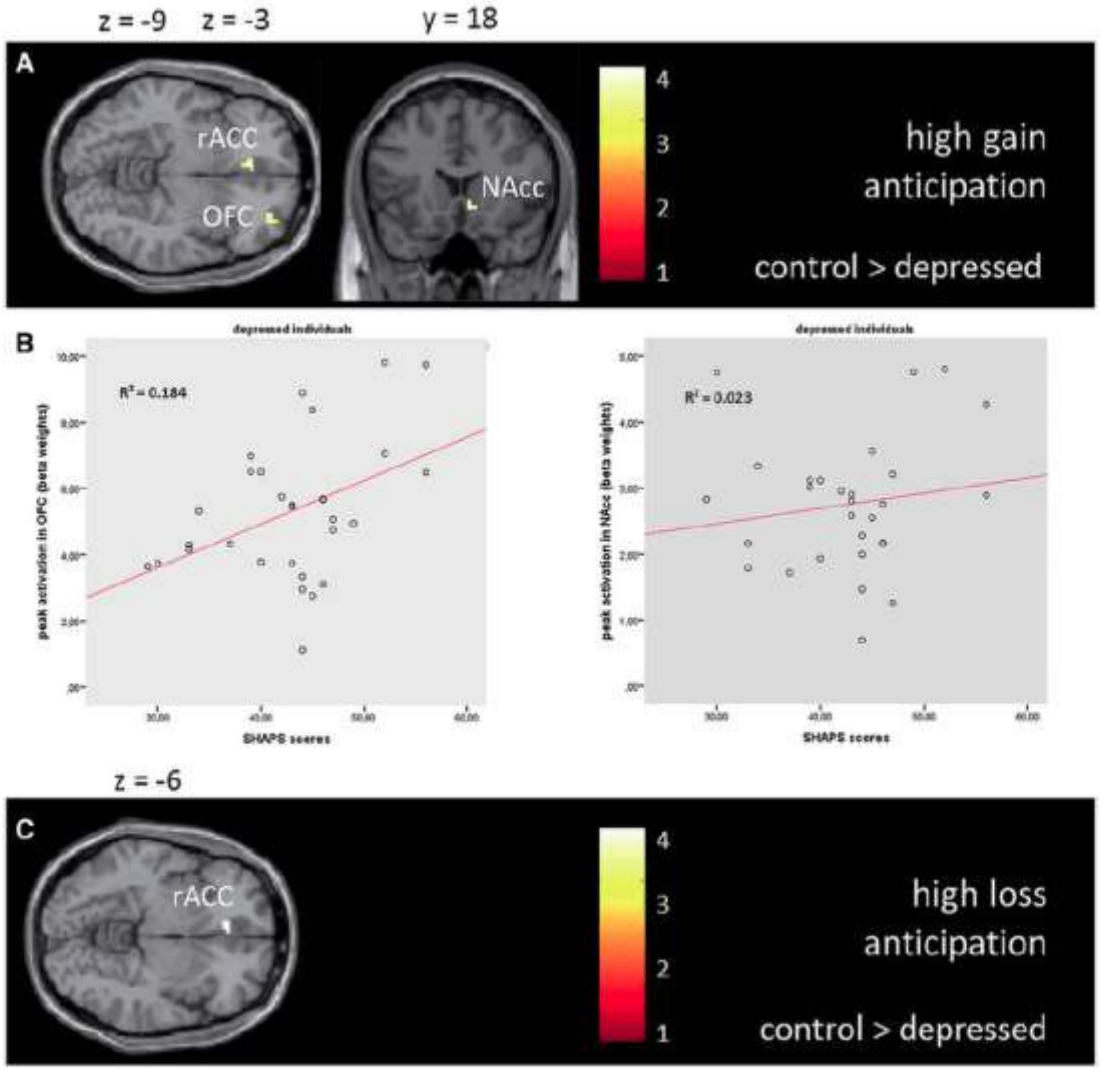


Thieme et al., Pssom. Med., 2004



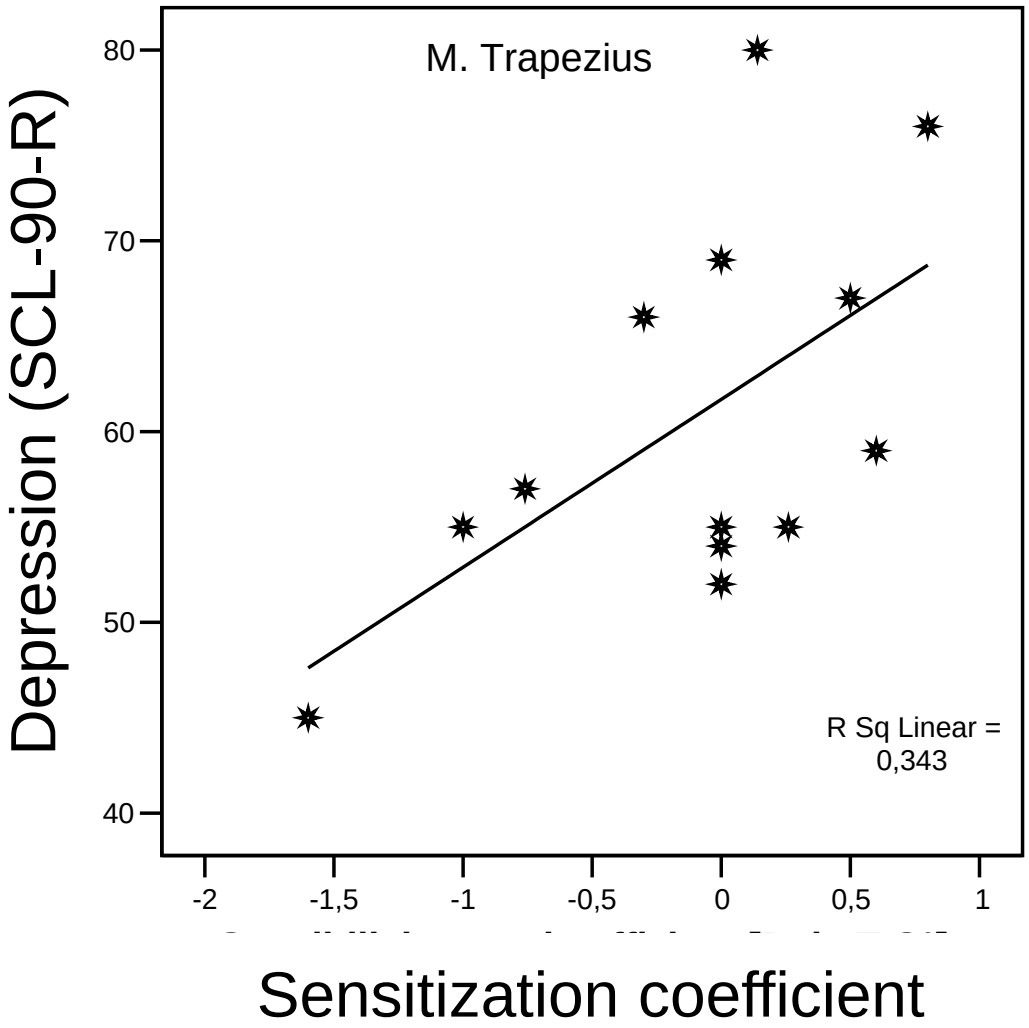
Larbig et al., in prep.

Blunted processing of reward and loss in depression

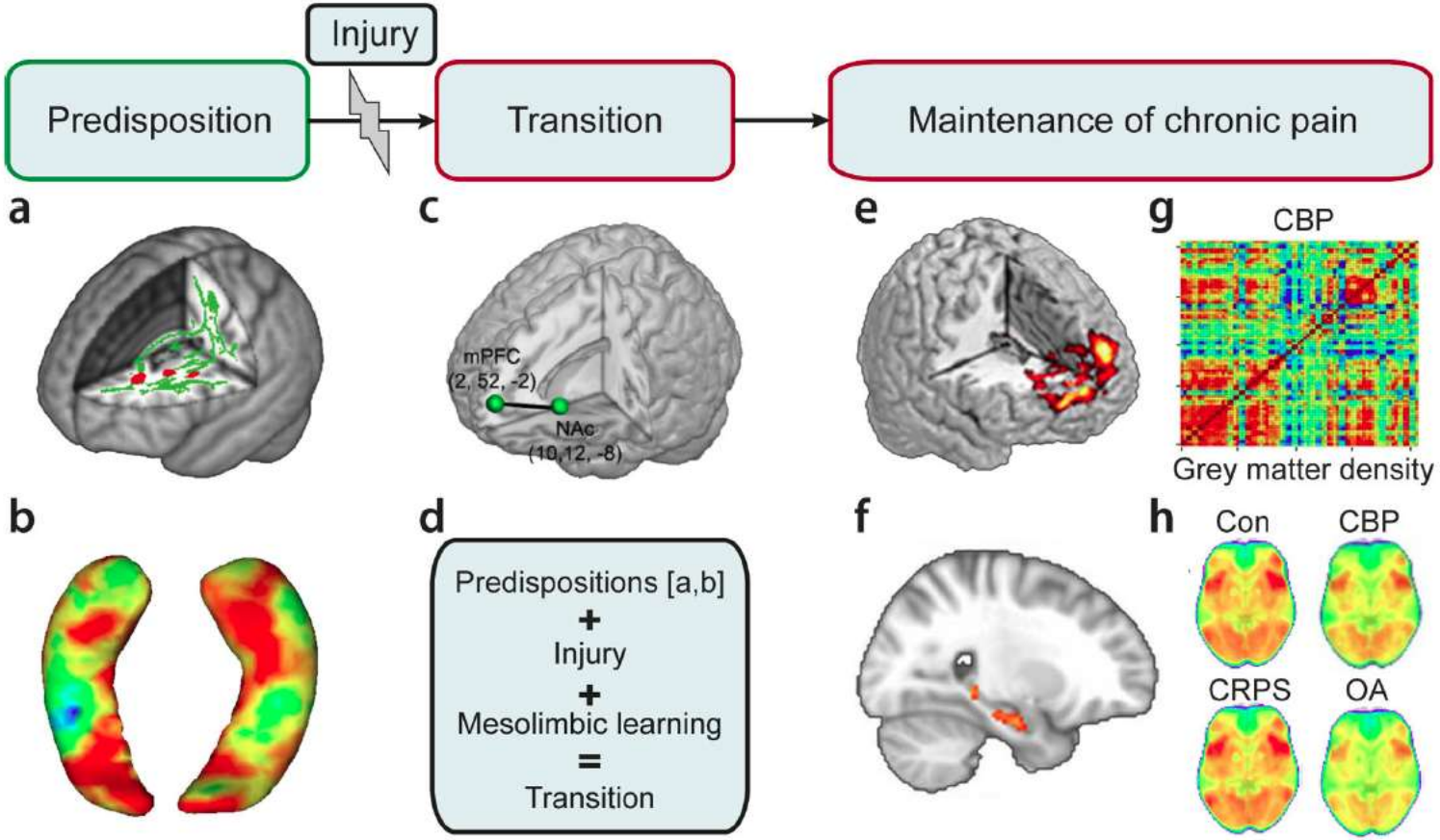


Ubl, Kuehner, Kirsch, Ruttorf, & Flor, SCAN, 2015

Depression and Sensitization are related

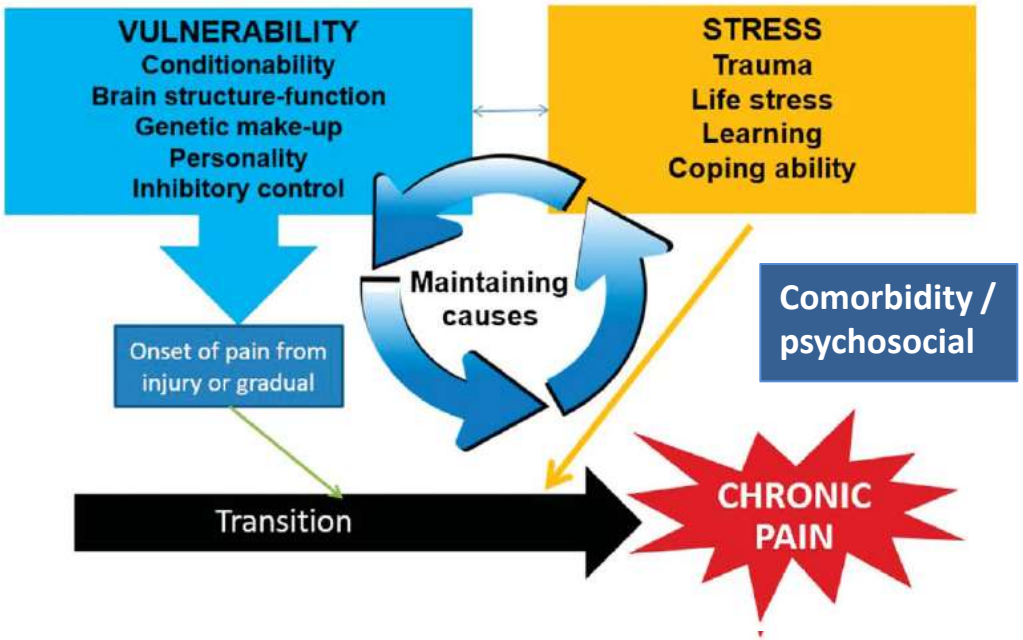


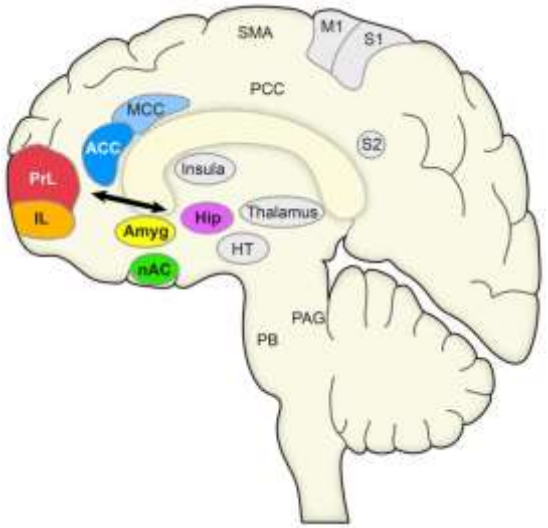
Brain changes indicative of phase of chronicity



Baliki & Apkarian, Neuron, 2015

Ongoing collaborative research





- Influence of appetitive (reward) and aversive (fear) processing / learning on chronicity
- Impact of stress
- Role of comorbidity / psychosocial / personality factors

➡ *Antecedence or consequence ?*

➡ *Underlying circuits and their plasticity ?*

Pain treatment: reversal of aversive, enhancement of appetitive learning and related brain plasticity

pharmacological:

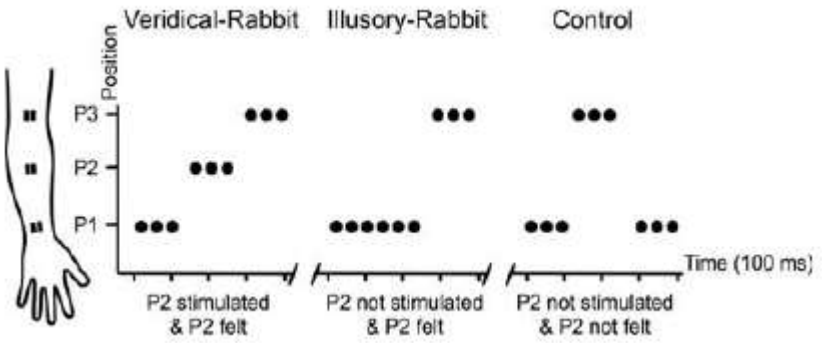
- NMDA receptor agonists/antagonists
- GABA agonists
- opiates
- anticonvulsants
- anticholinergic medication?
- AMPA antagonists
- cannabinoids

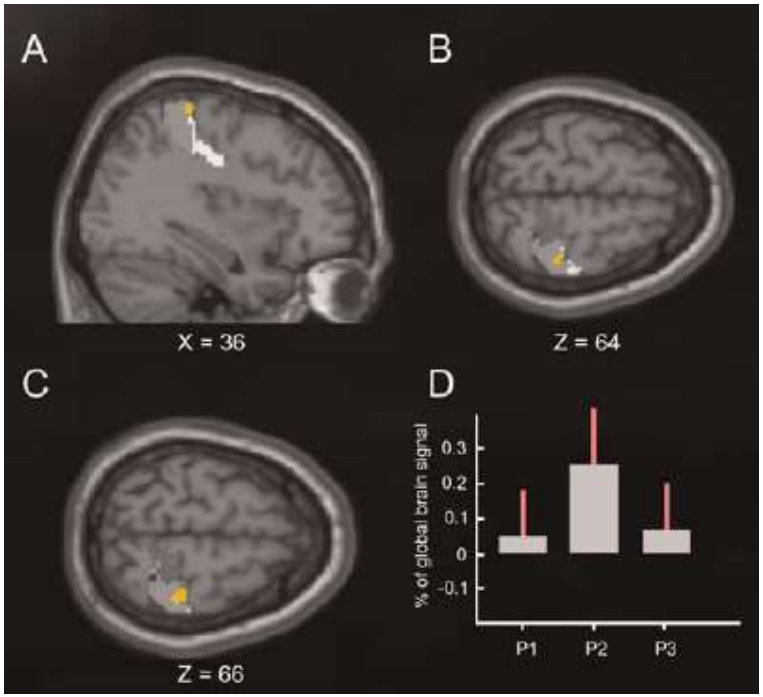
behavioral/stimulation:

- behavioral training
- sensory discrimination
- biofeedback/brain computer interface
- imagery
- mirror treatment
- transcranial/ DC stimulation

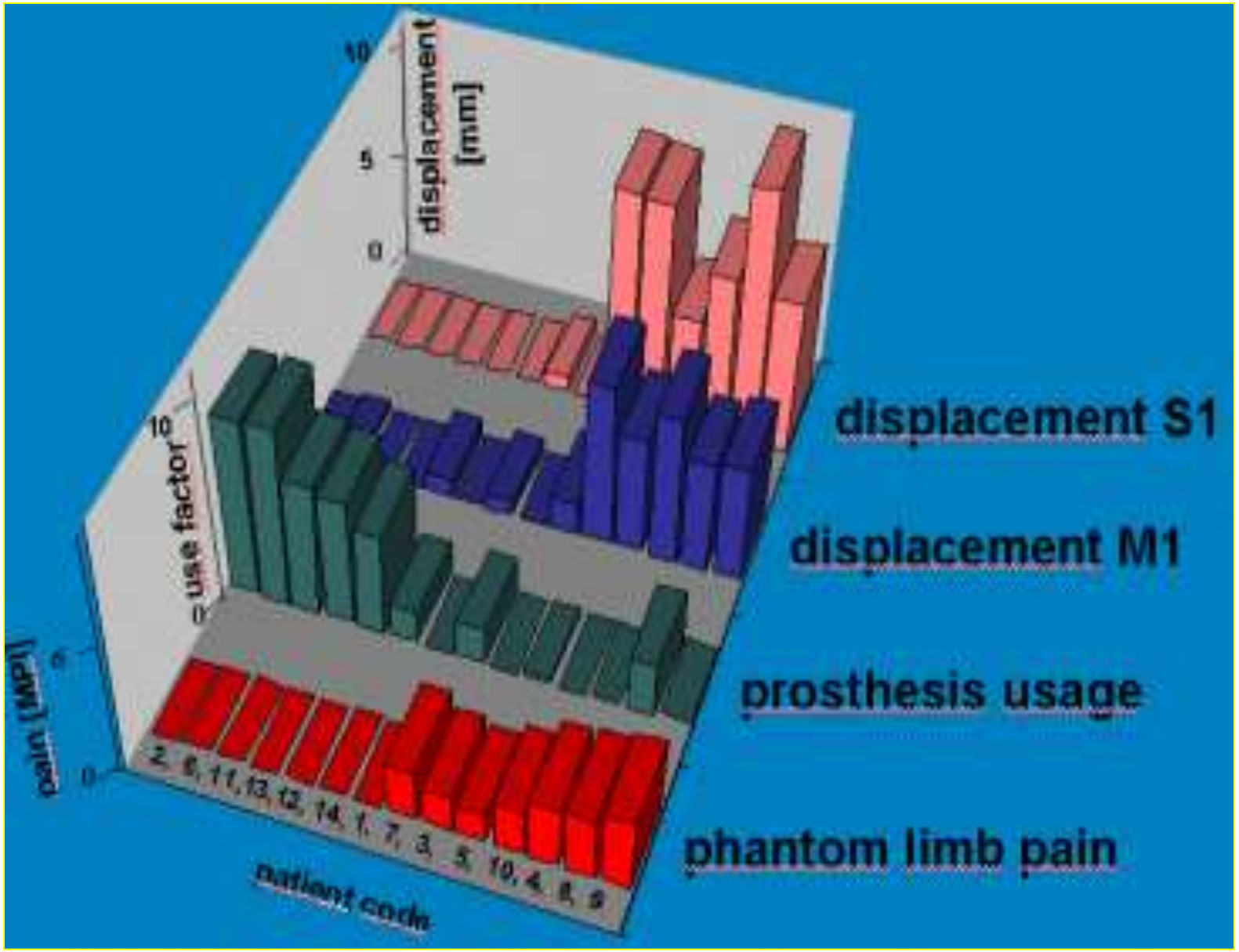
combination

The cutaneous rabbit: the brain processes the perceived not the physical reality

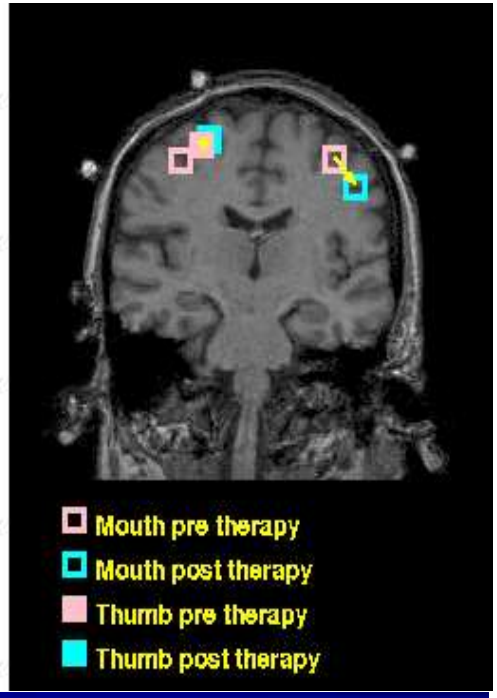


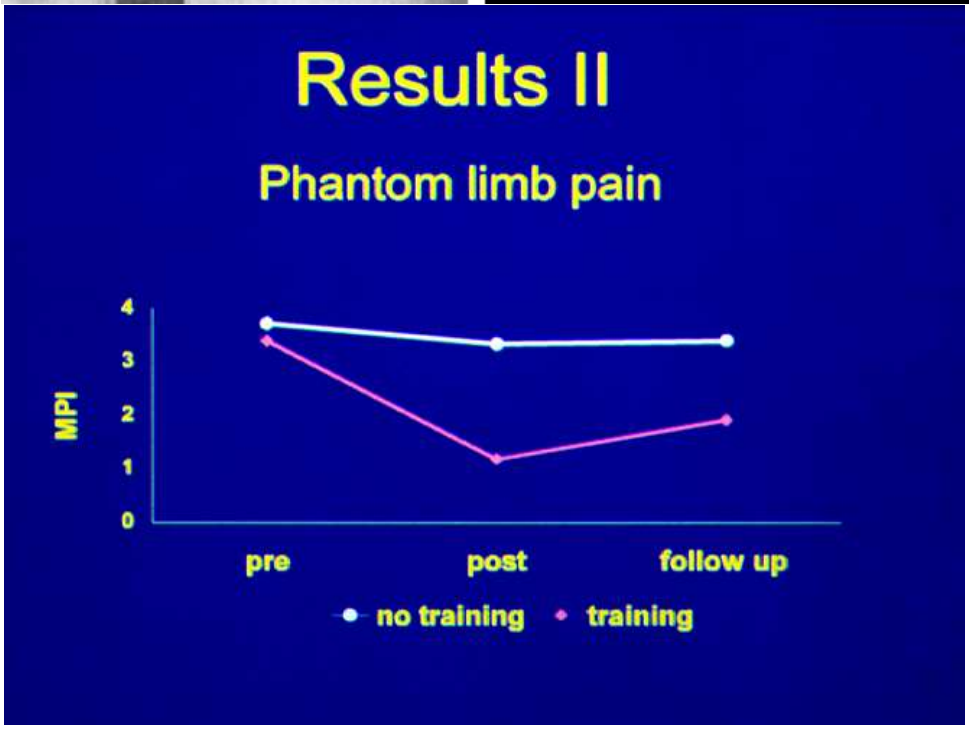


Blankenburg et al., PLOS Biol, 2006



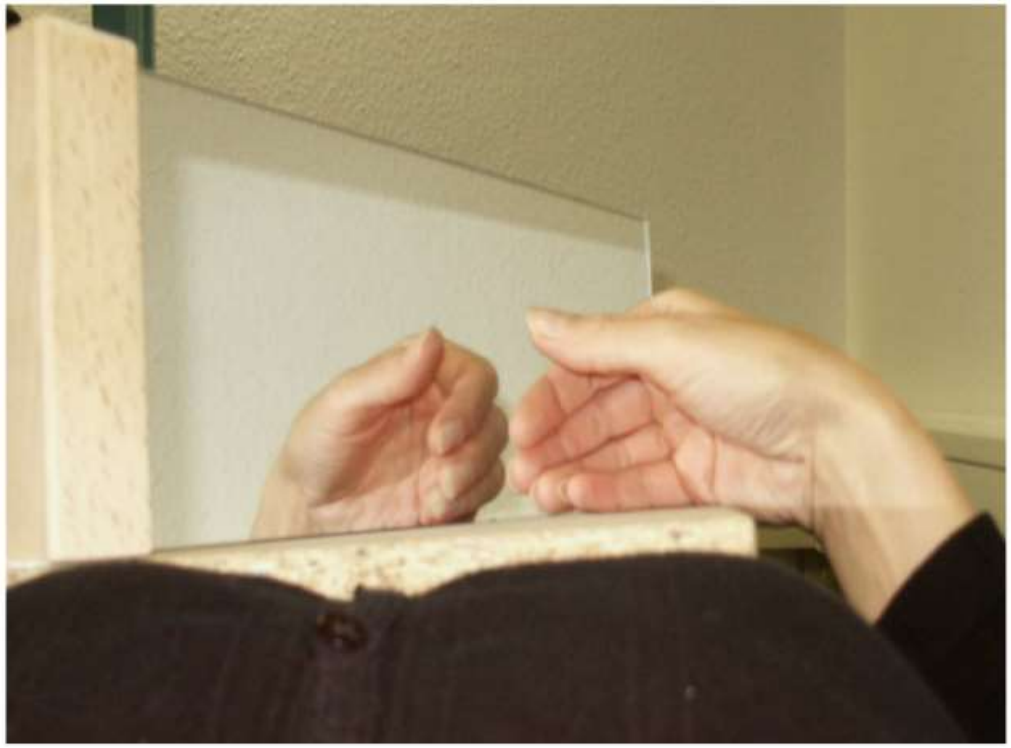
Lotze et al., Nature Neuroscience, 1999



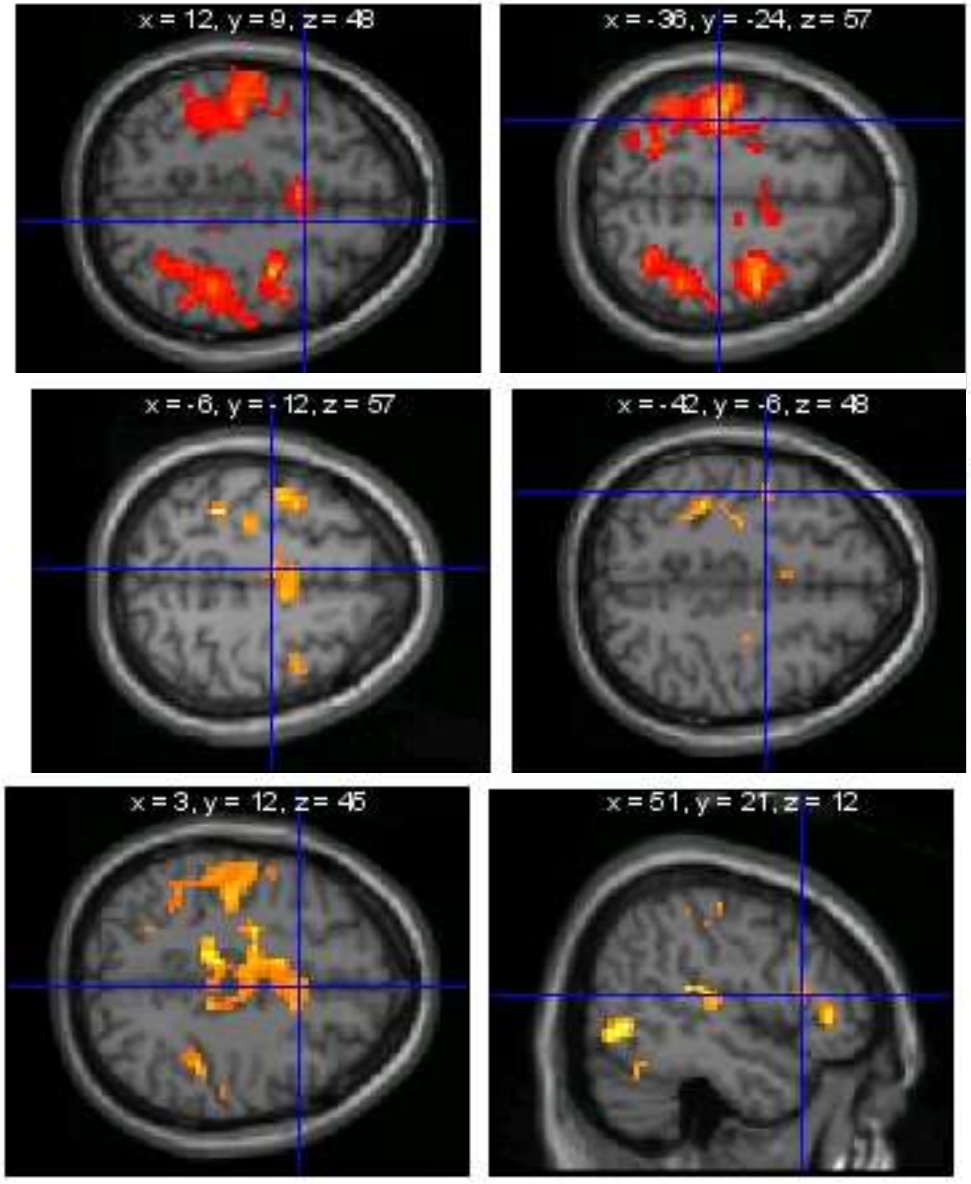


Flor et al.,
Lancet, 2001

Mirror treatment



Mirror trial



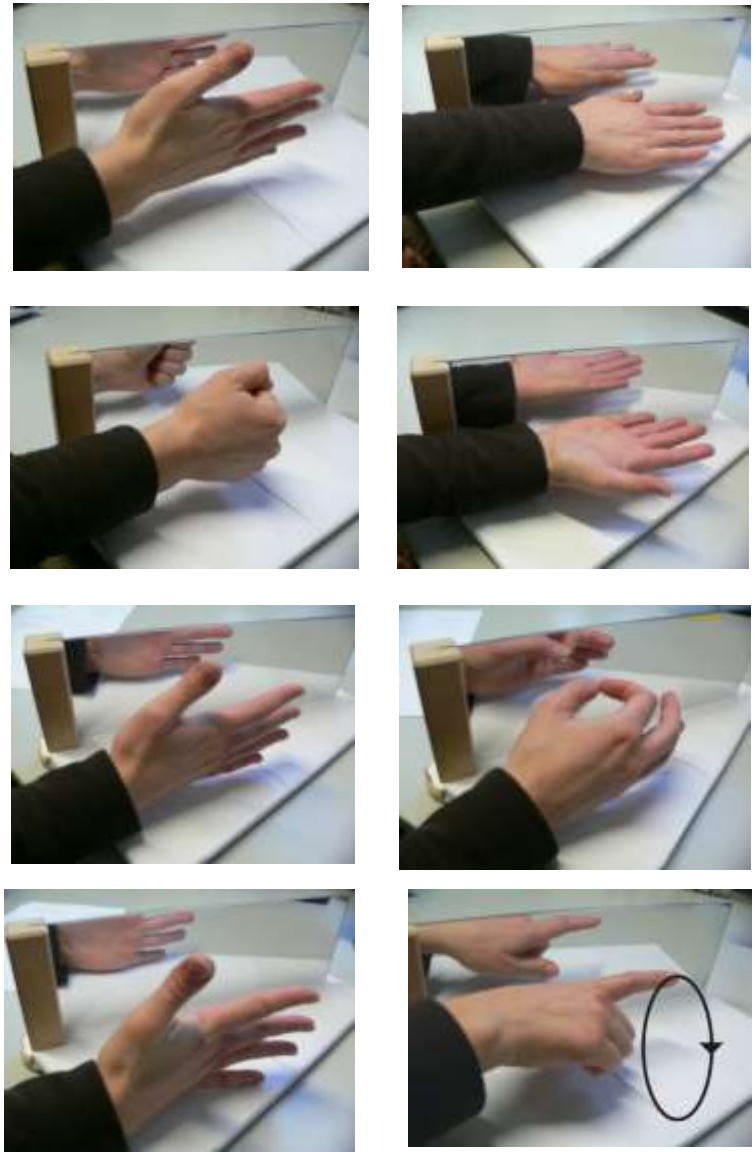
No phantom pain

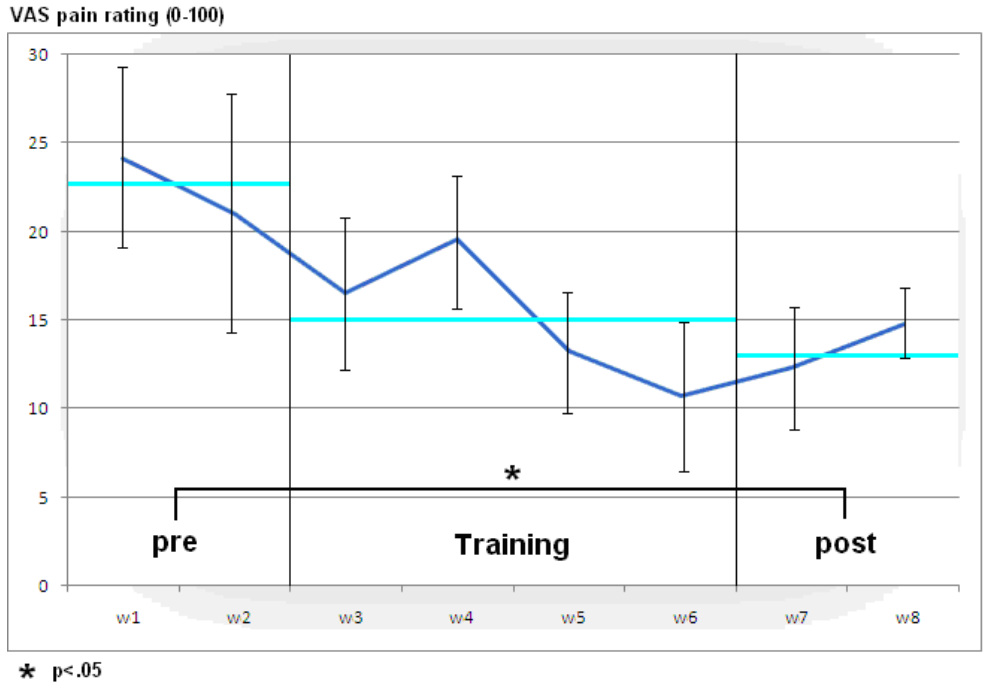
Phantom pain

Healthy

Diers et al., Pain, 2010;
Brain Res, 2015

Mirror Training

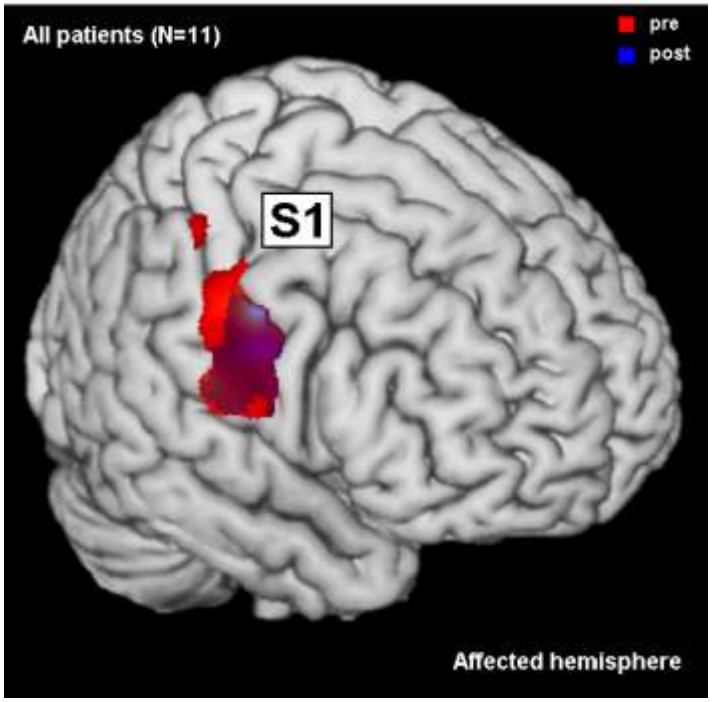


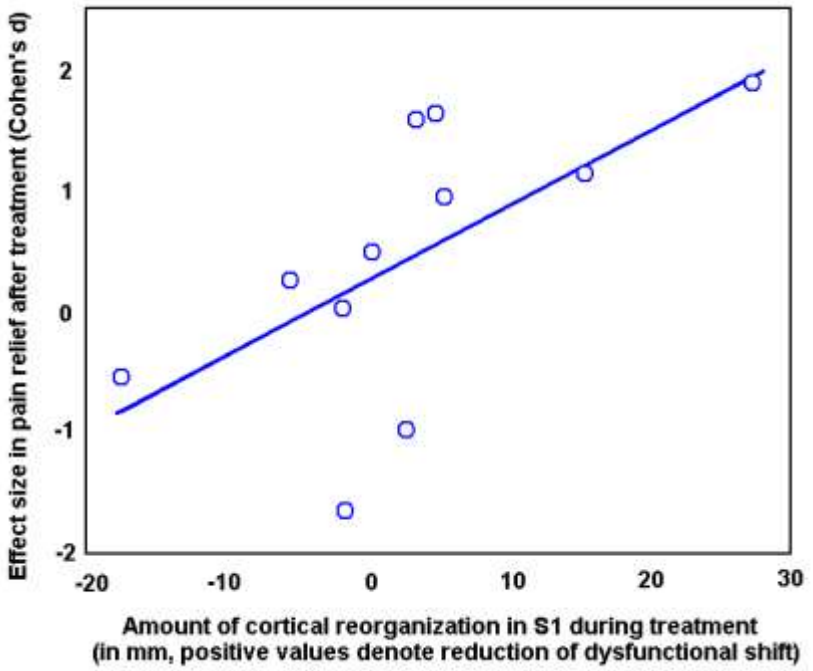


* p<.05

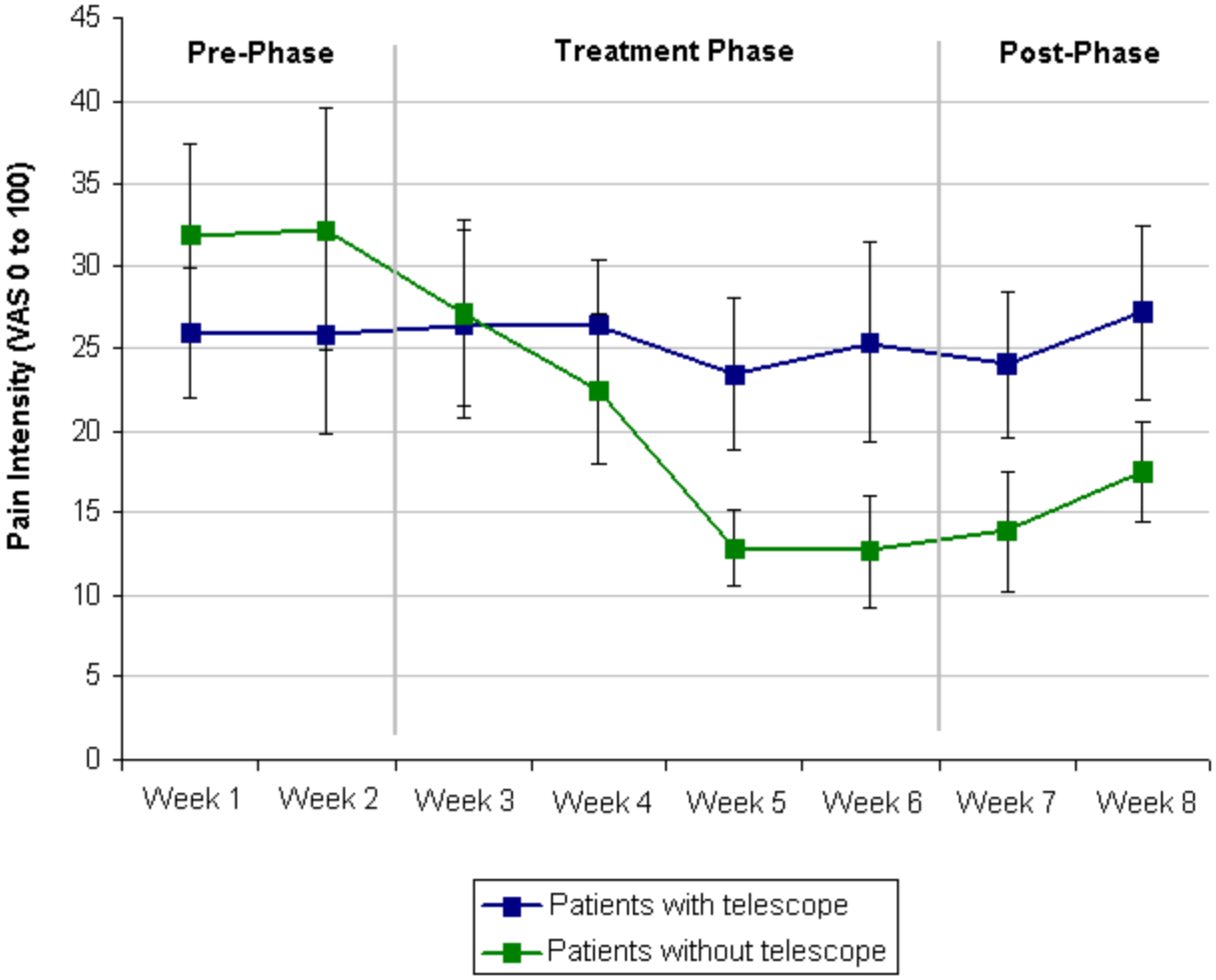
Foell et al., Eur J Pain, 2014

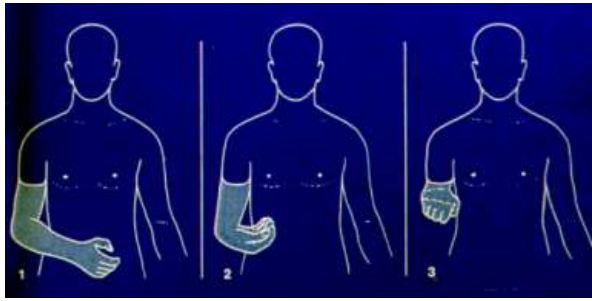
Pain reduction normalizes brain activation



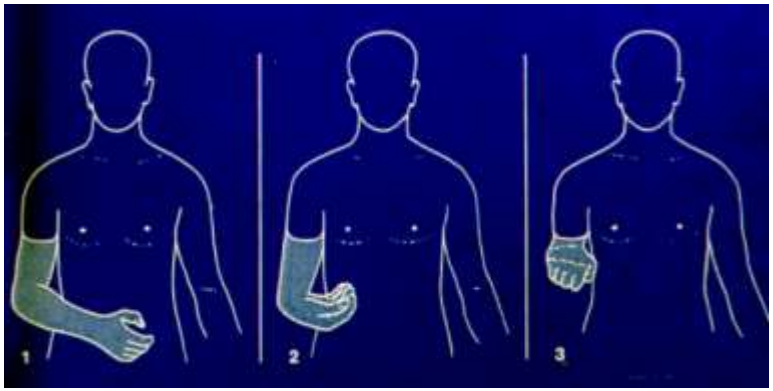


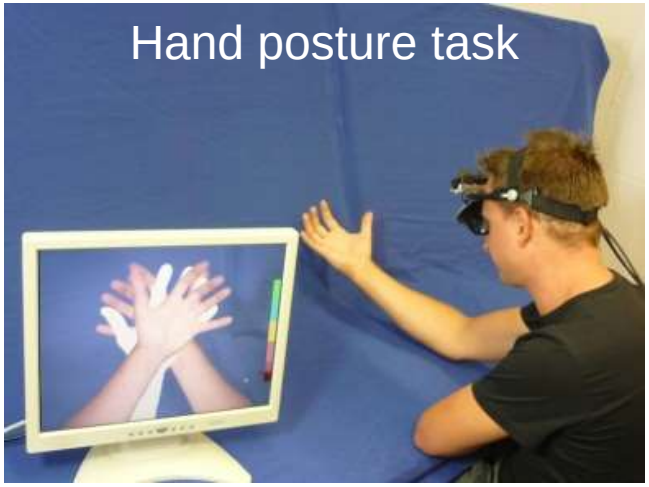
Body distortion predicts negative outcome

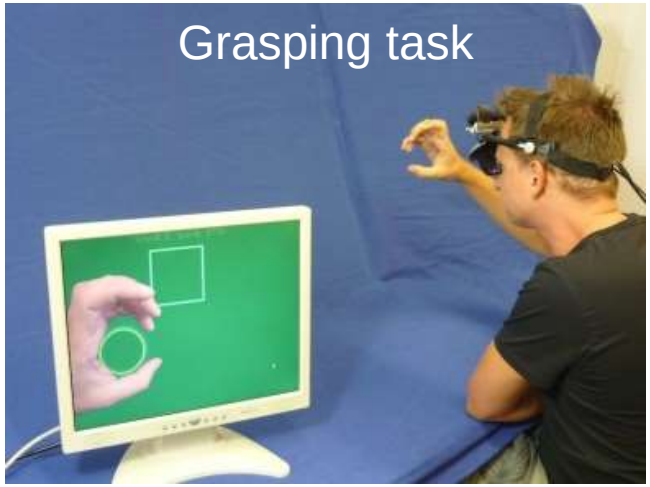




Training in augmented/virtual reality







Trojan et al., Beh Res Meth, 2015

Behavioral extinction training

- Training of pain-incompatible healthy behaviors
- Exposure
- Reduction of pain expressions
- Work with the spouse on reinforcement of healthy behaviors
- Training of pleasant activites
- Training of abilities (social, work)
- Medication reduction
- Discrimination training

Positive activity diary

Monday

date: ___.___.___

0	1	2	3	4	5	6	7	8	9	10

O= not at all true 10 = exactly true

I am pain-free today

I feel fit and active

Things are easy for me tooday

I am in a good mood today

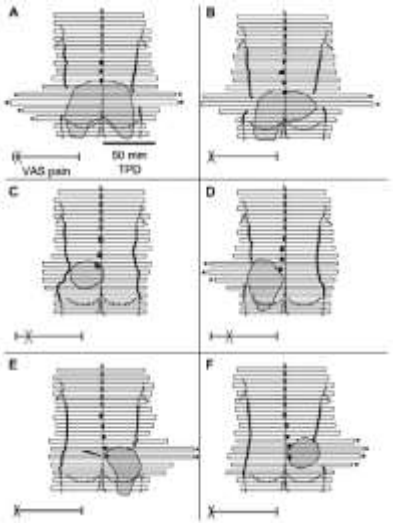
I have slept well today

I trust that the treatment will work

Write down one thing that was fun for you today

Ich bin spazieren gegangen.

Bitte kreuzen Sie pro Aussage Ihre Tagesverfassung an (0 = trifft gar nicht zu, 10 = trifft voll zu).

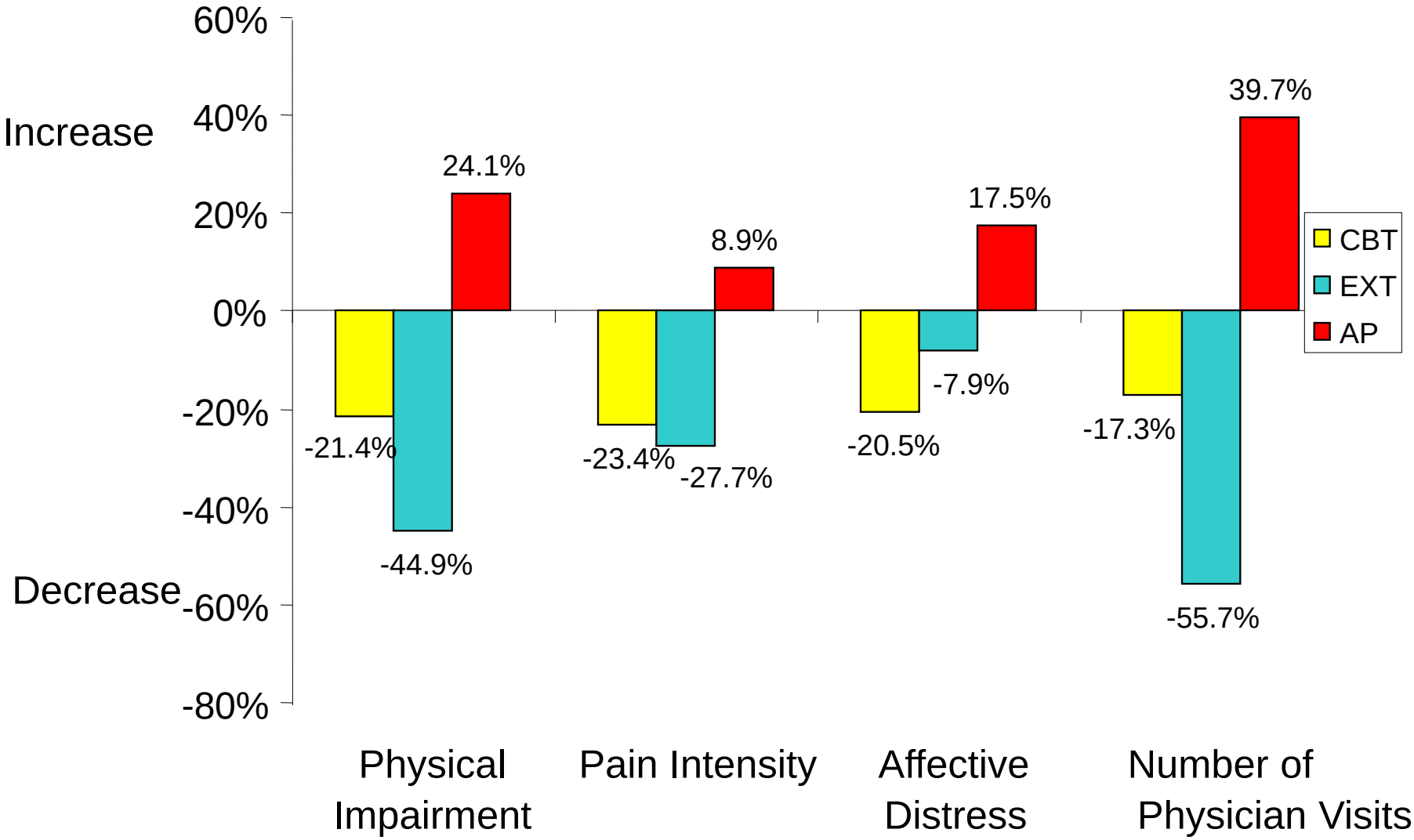


Video feedback of pain behaviors
Training of healthy behaviors
Discrimination training
Biofeedback

- Massed training
- Many different situations
- Training at home
- Training with significant other
- Reminders

Immediate reinforcement of healthy behaviors
Immediate punishment of pain behaviors

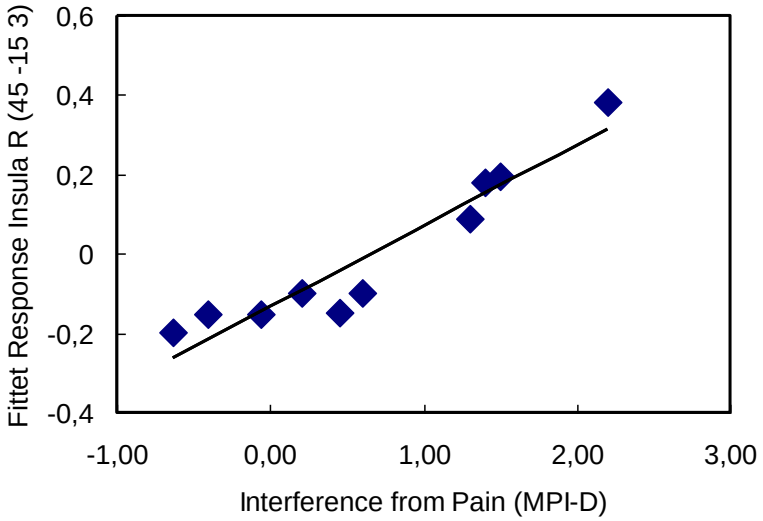
Extinction training

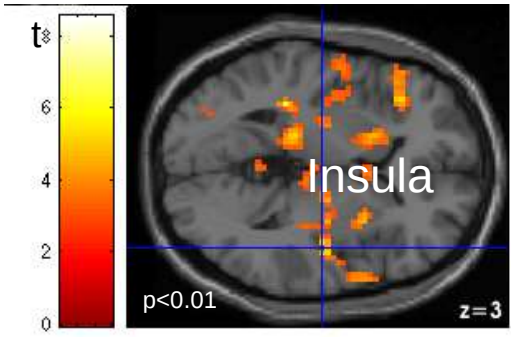


Thieme et al., Arthr Res Ther, 2006

Treatment-induced brain changes

higher reduction in interference from pain - positive correlation with activation in the bilateral posterior insula and contralateral SI





Diers et al., Exp Brain Res, 2012

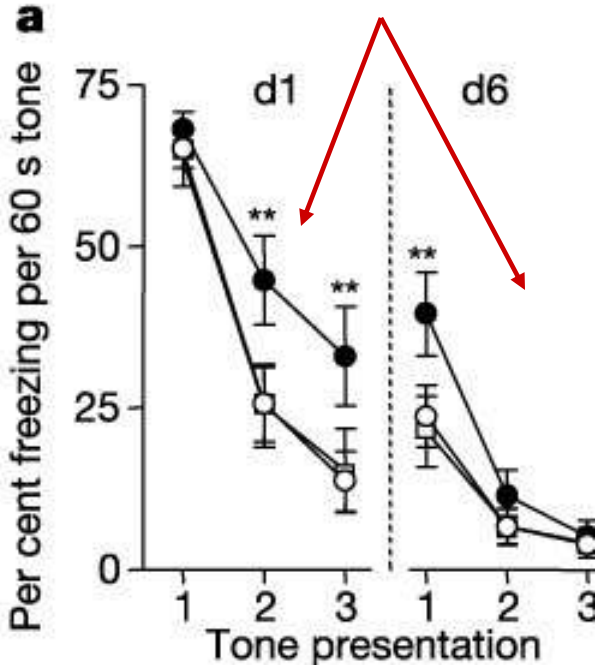
Behavioral extinction and pharmacotherapy

- Extinction training and cannabis
- Extinction training and placebo
- Extinction training
- Standard treatment

Chronic musculoskeletal pain

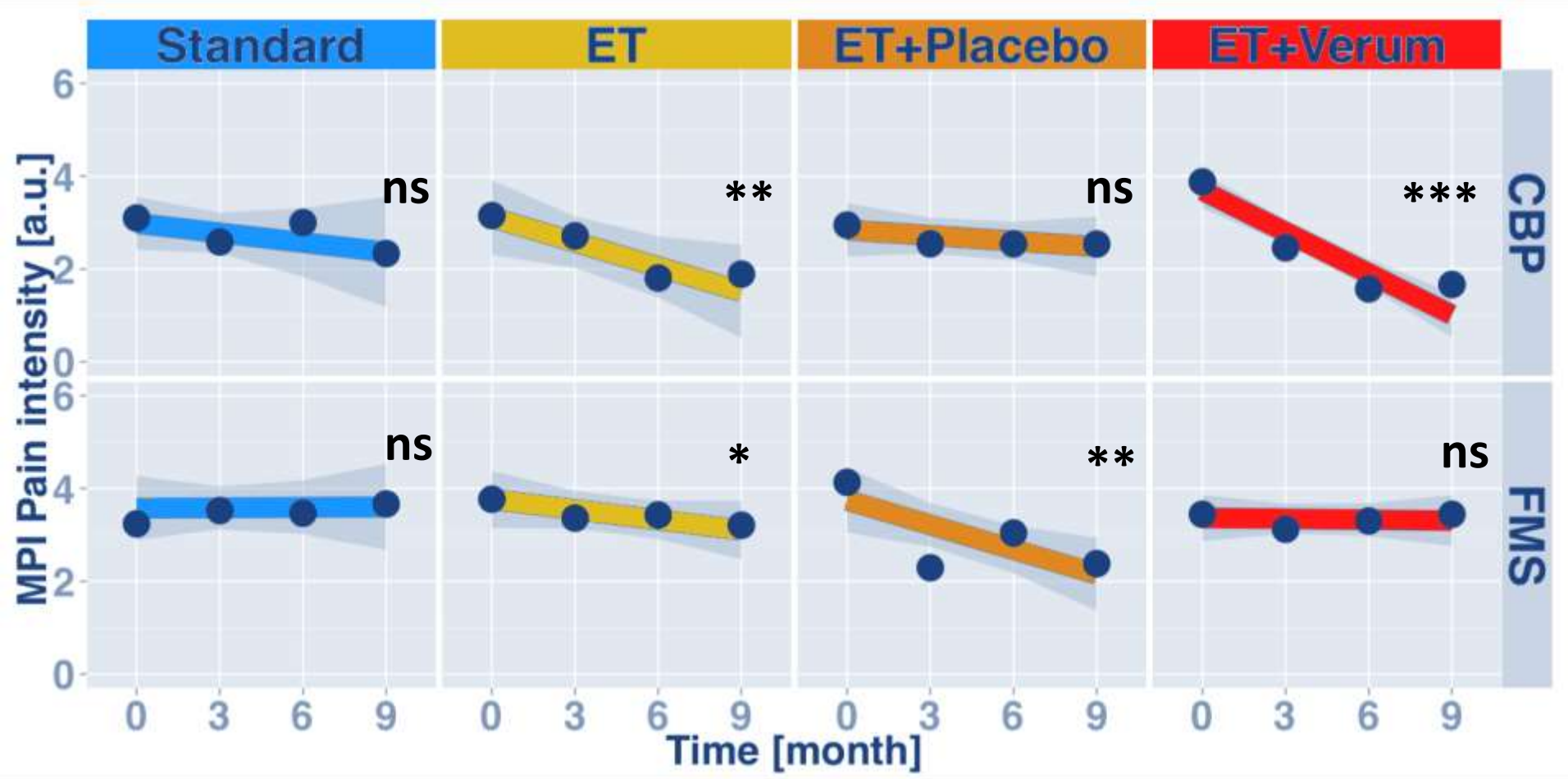
(chronic back pain and fibromyalgia)

CB1 receptor antagonist

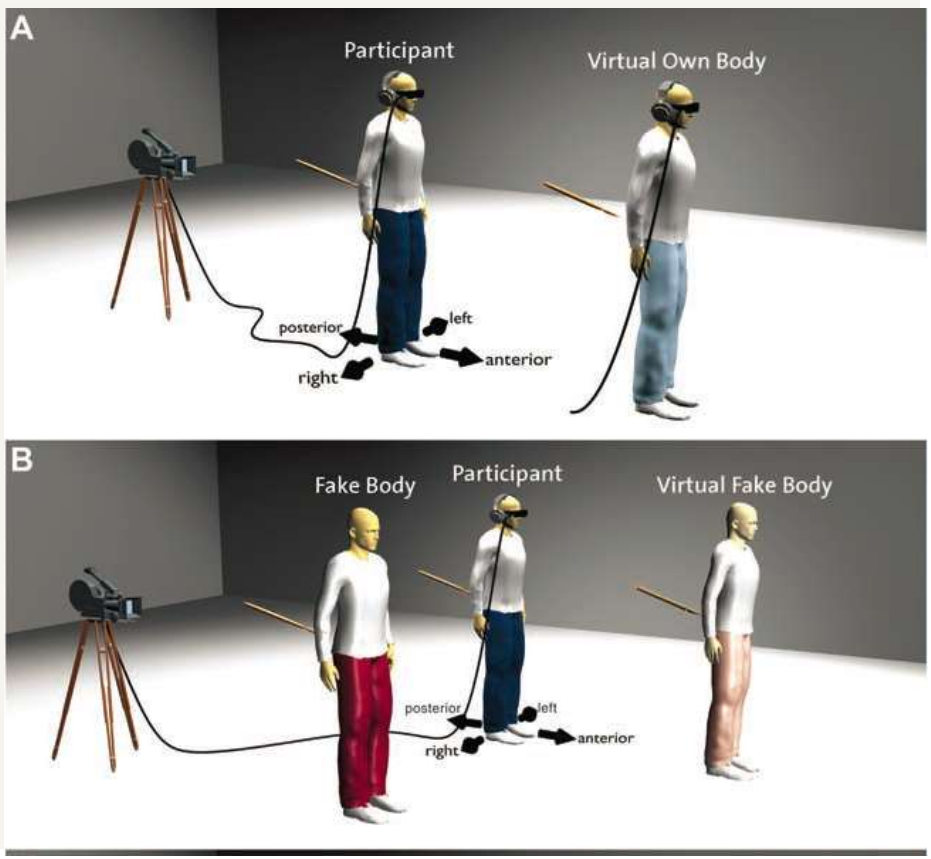


Marsicano et al, Nature, 2002

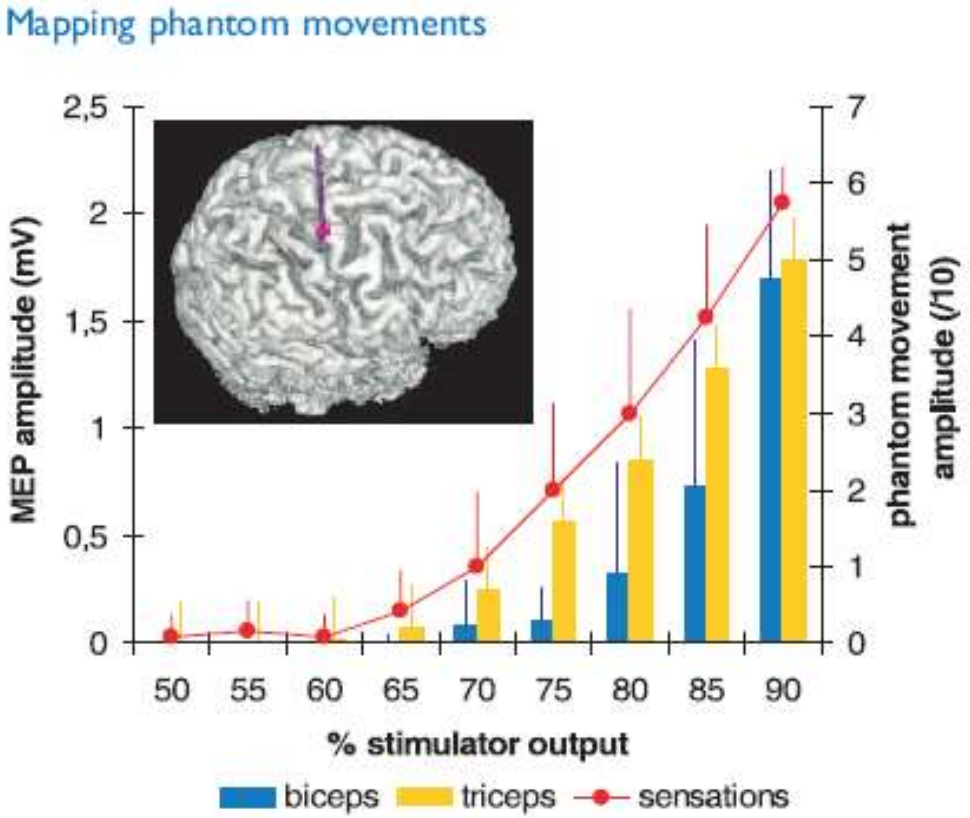
Change in clinical pain intensity: Extinction training and cannabis

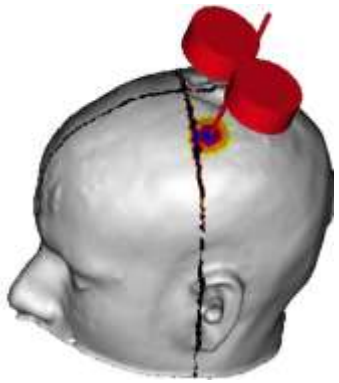


Thieme, Kleinböhl et al., in prep.

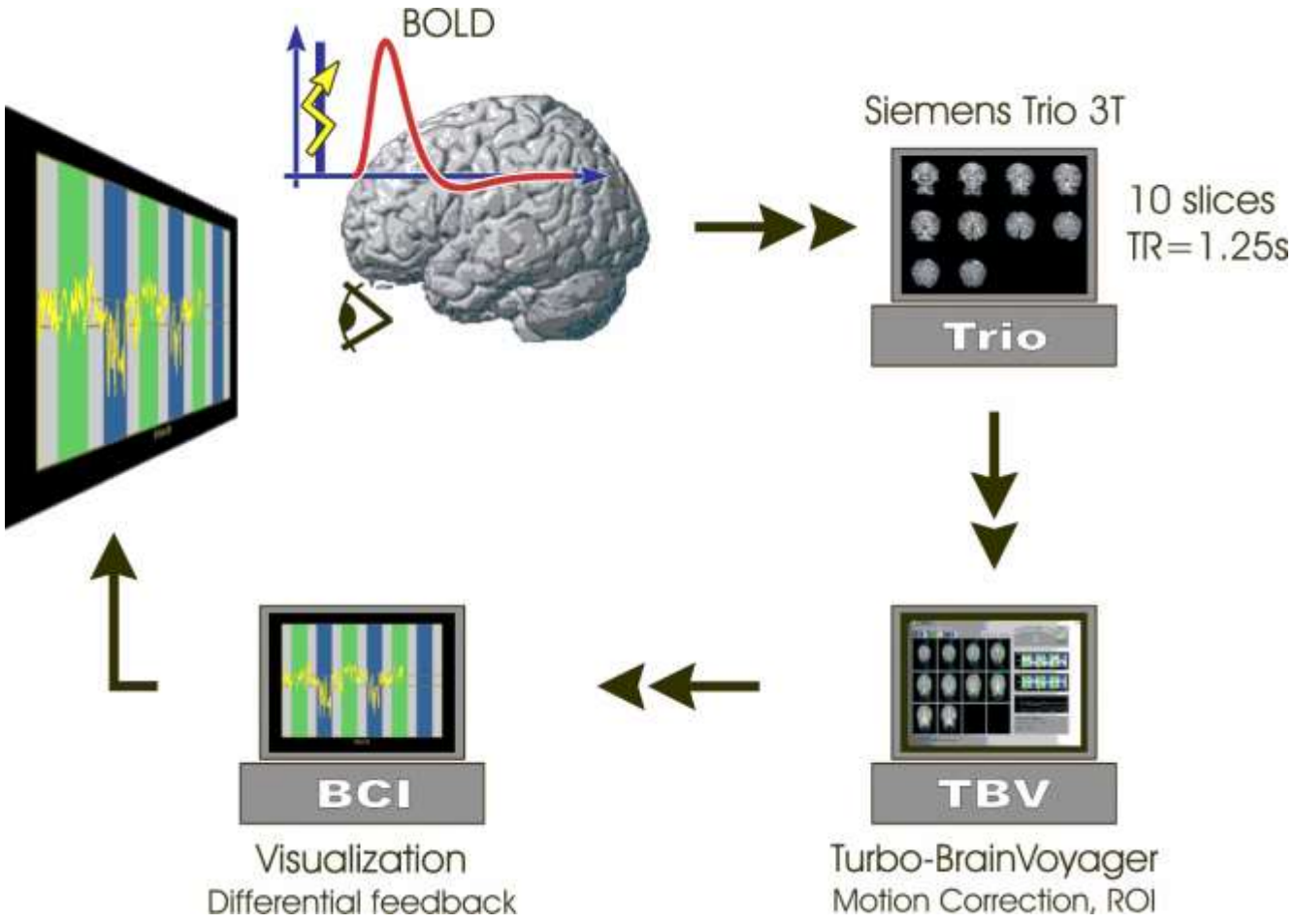

A
Participant
Virtual Own Body
posterior
left
anterior
right
B
Fake Body
Participant
Virtual Fake Body
posterior
left
anterior
right

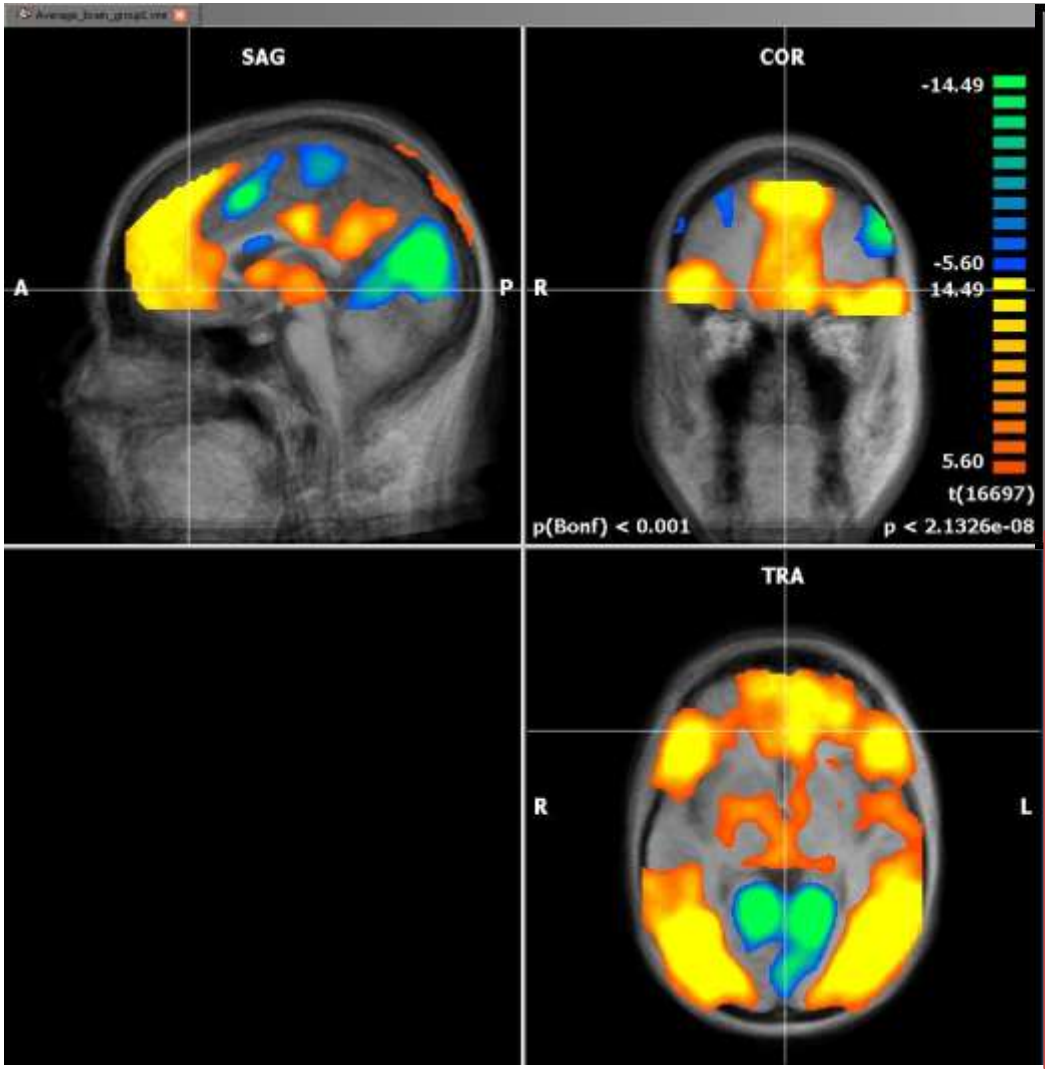
Transcranial magnetic and DC/AC stimulation

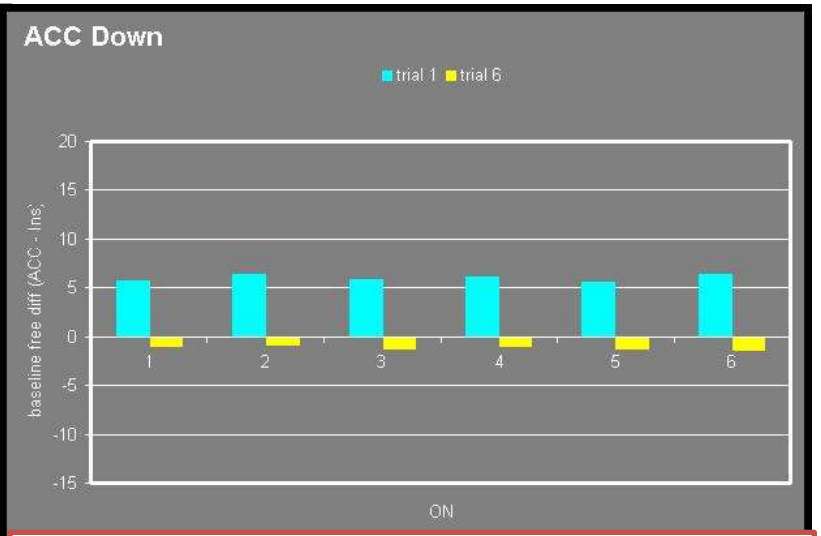


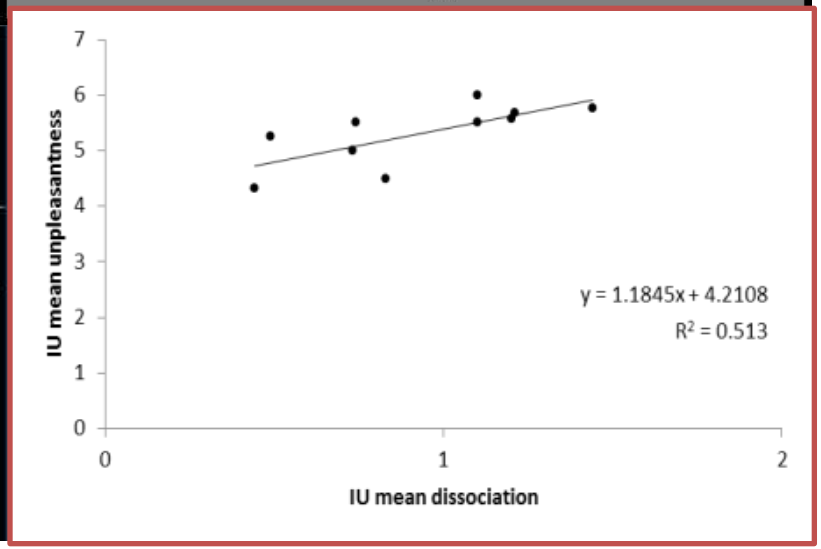


Brain-computer interface: real time fMRI







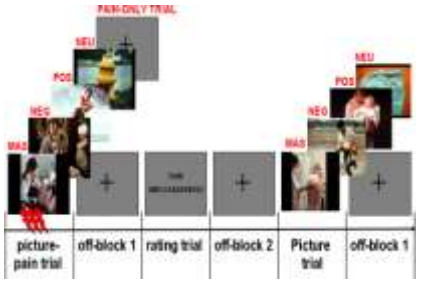


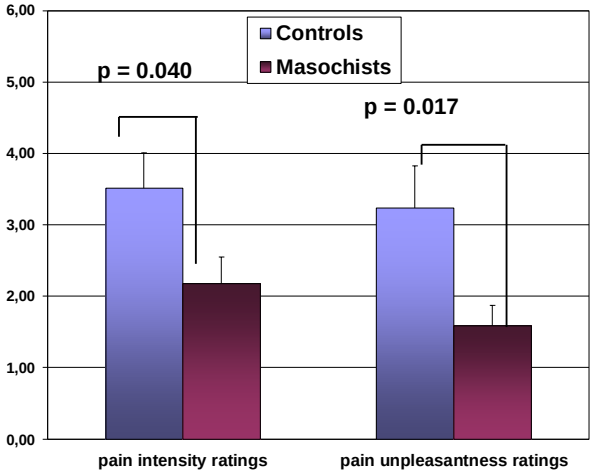
Rance et al., Hum Brain Map, 2014

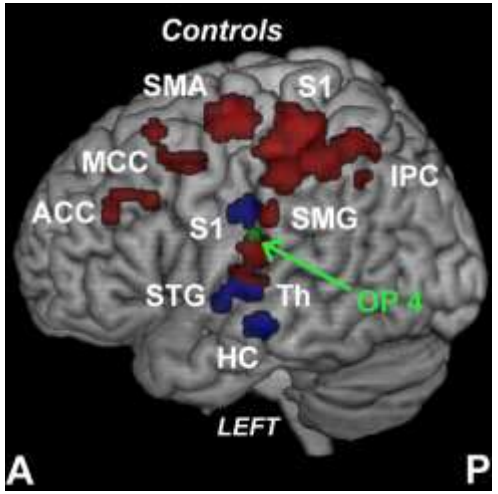
Resilience

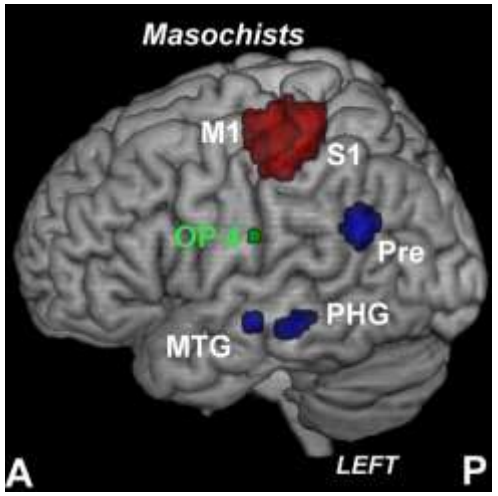
Groups:

- Masochists
- Borderline personality disorder
- Amputees without phantom pain
- Congenitally pain-insensitive persons
- Persons with chronic pain who never see a doctor
- People with optimism









Kamping et al., Pain, 2016; Defrin et al., Eur J Pain, 2015; Bekrater-Bodmann et al., Pain, 2015

Summary

- Chronic pain is related to maladaptive learning and related plastic changes in the brain
- Stress and comorbid mental disorder modulate learning
- Behavioral trainings (also combined with pharmacological interventions) that target maladaptive learning prevent or reverse these maladaptive memory traces and pain and can induce beneficial plasticity

Thanks to team members and the funding agencies

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Thank you for
your attenntion!