What has fMRI revealed about central sensitization and chronic pain?

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Definitions and Ontology of Central Sensitization

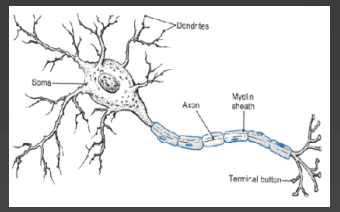
IASP Definitions:

- "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"
- "neurophysiological term that can only be applied when both input and output of the neural system under study are known, e.g., by *controlling the stimulus and measuring the neural event*"
- "Clinically, sensitization may only be inferred *indirectly* from phenomena such as *hyperalgesia* or *allodynia*"
- Other pain-related phenomena linked to central sensitization: temporal summation, reduced conditioned pain modulation, reduced habituation, cortical amplification, increased receptive field size (plasticity in cortical representations) – ***how to assess with neuroimaging?***

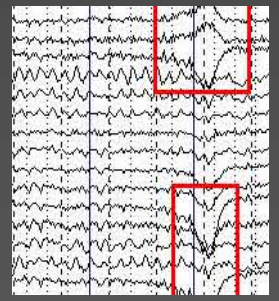
Functional Neuroimaging Modalities:

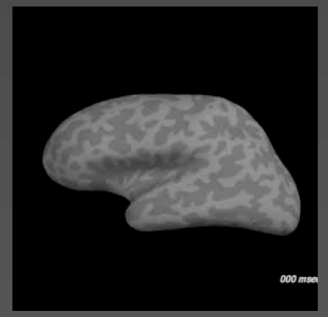
Hemodynamics, Metabolism, Electrophysiology, Neurochemistry

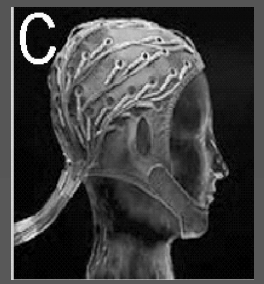
Neural Activity



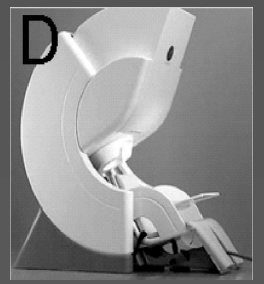
Electromagnetic Response







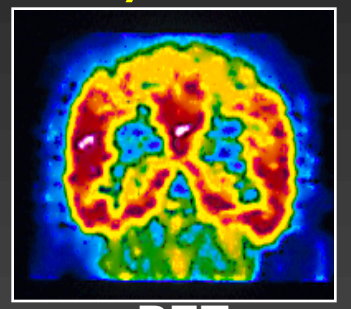
EEG



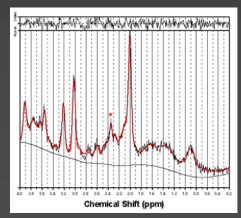
MEG

Neurotransmitter Response

↑ Glu, GABA, endorphin
↑ Receptor (e.g. μ-opioid) Binding



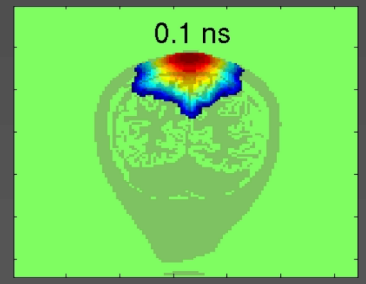
PET



H-MRS

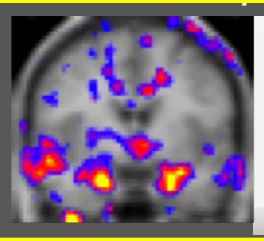
Hemodynamic Response

↑ Blood Flow
↑ Blood Volume
↑ Blood Oxygenation

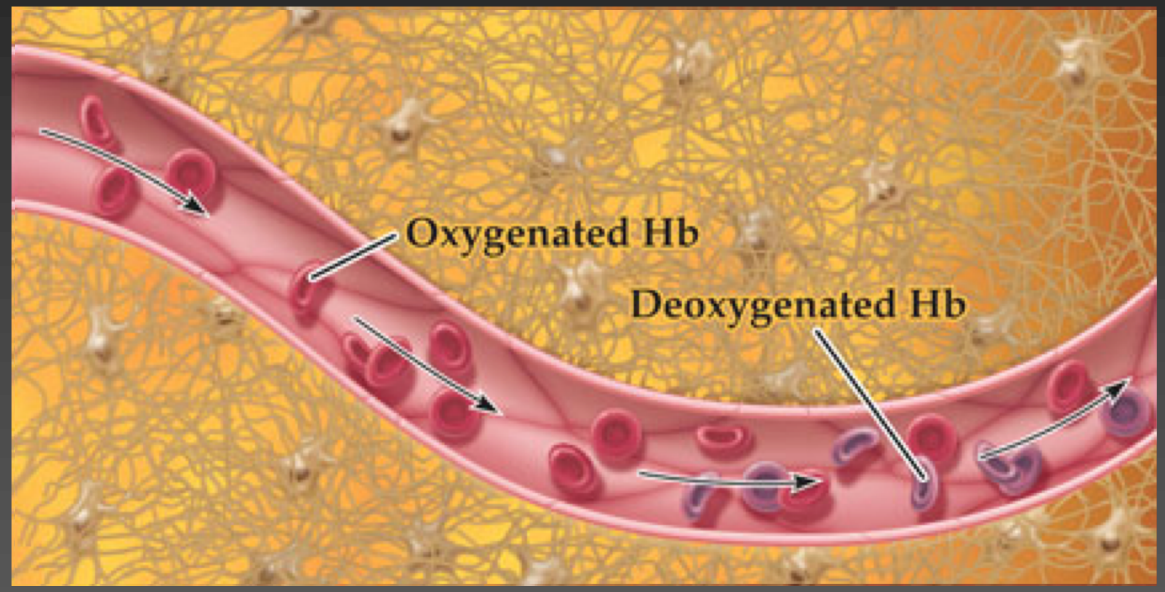


Optical

fMRI



fMRI Contrast: BOLD – Blood Oxygenation Level Dependent



Basal State

- basal neuronal activity
- basal blood flow
- basal [HbO_2], [Hbr]
- basal MRI signal

Activated State

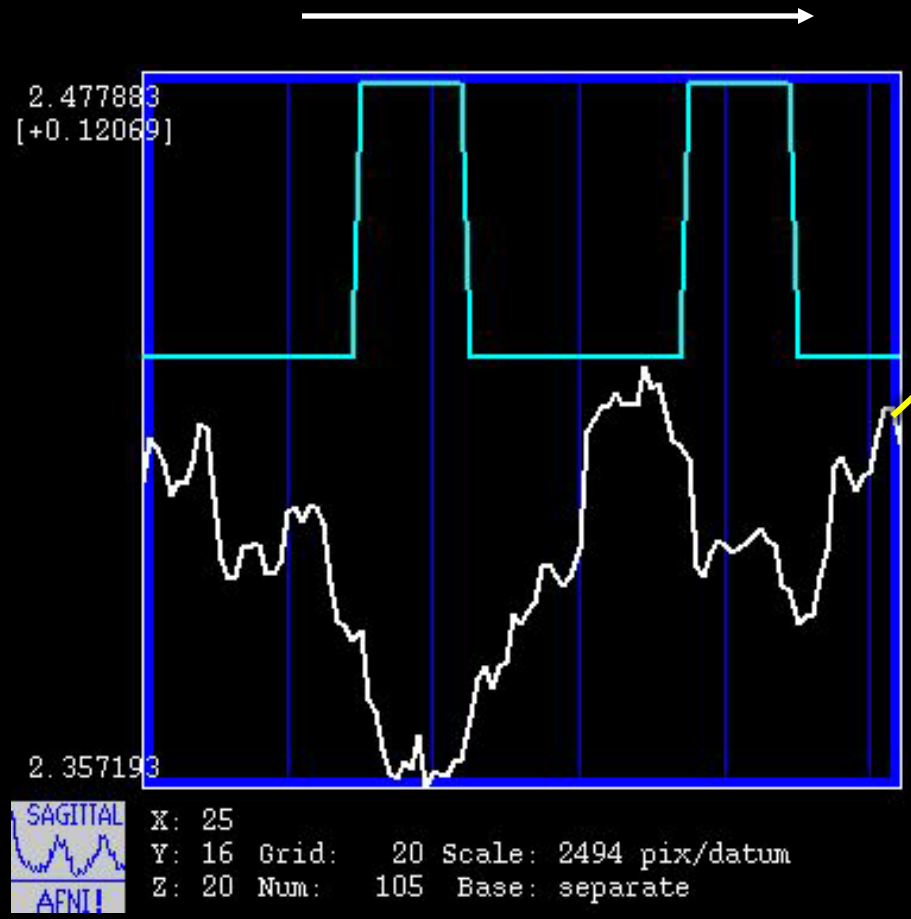
- Increased blood flow
- Incr. [HbO2], decr. [Hbr] → lower field gradients around vessels
- Increased MRI signal (from lower field gradients)

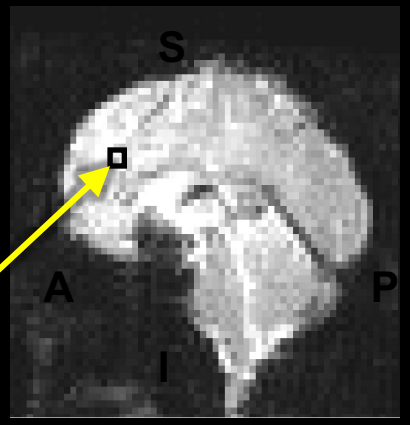
↑ Activation → ↑ HbO_2/deoxy-Hb → ↑ T2* → ↑ fMRI signal

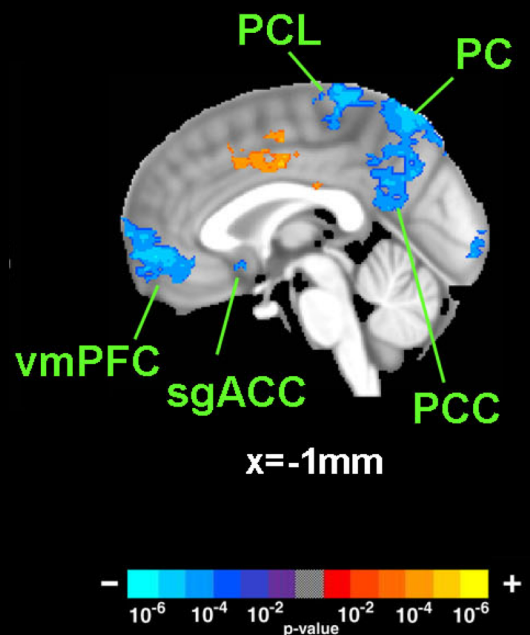
What Does fMRI Data Look Like?

…a time series of MRI signal brightness

MRI signal from one of ~40,000 brain voxels







fMRI meta-analysis of evoked pain and sensitization, >200 studies

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Functional reorganisation in chronic pain and neural correlates of pain sensitisation: A coordinate based meta-analysis of 266 cutaneous pain fMRI studies

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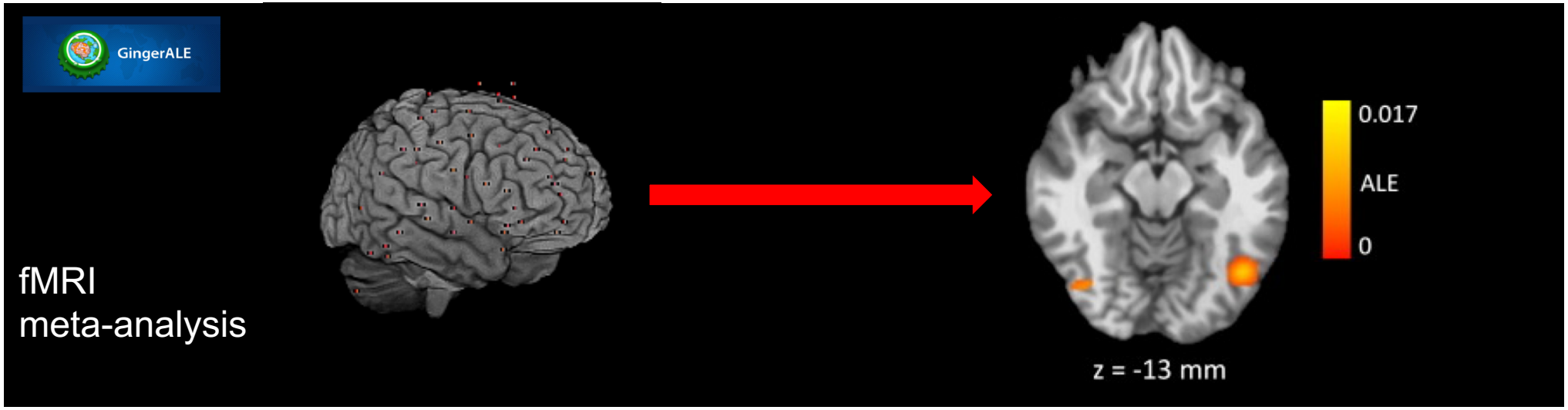
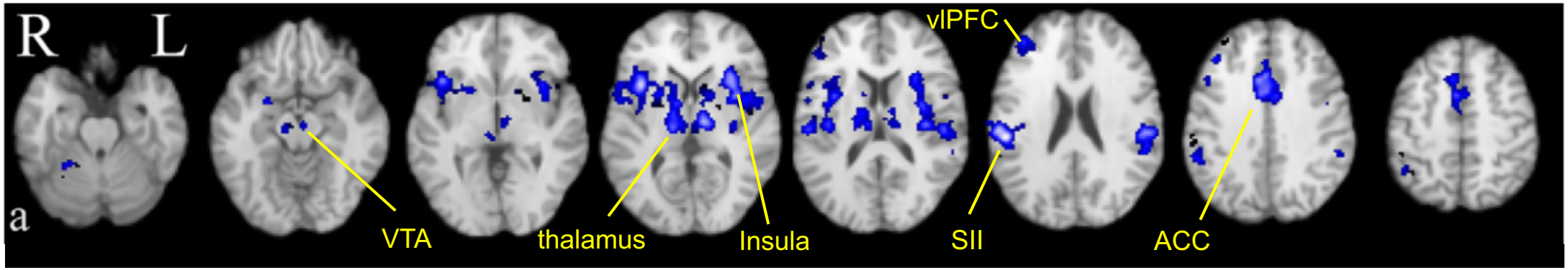
Table 1
Study groups included in the CBMA (in grey: main groups; in white: sub-groups).

Group	Detail	Population	Papers	Studies Extracted	Study numbers after merging	Coordinates extracted	Subjects
HC	All HC	HC	154	180	155	2780	2278
$MECH_{HC}$	Mechanical	HC	24	28	25	391	325
$THERM_{HC}$	Thermal	HC	104	120	104	1855	1520
$ELEC_{HC}$	Electrical	HC	28	33	30	534	453
$RIGHT_{HC}$	Right Stimulus	HC	64	75	65	1200	951
$LEFT_{HC}$	Left Stimulus	HC	77	85	79	1249	1176
$REST_{HC}$	Pain vs. rest	HC	76	91	78	1296	1128
$INNOC_{HC}$	Pain vs. innocuous	HC	66	75	67	1216	912
$CUED_{HC}$	Cued	HC	33	36	34	577	587
$NCUED_{HC}$	Non-cued	HC	121	145	123	2199	1691
CP	All CP	CP	32	38	32	514	506
$NEUR_{CP}$	Neuropathic	CPP	16	21	16	322	177
MSK_{CP}	MSK	CPP	8	9	8	125	122
FM_{CP}	FM	CPP	8	9	8	81	207
CS_{CP}	Clinical Site	CPP	16	19	16	321	192
OS_{CP}	Remote Site	CPP	16	19	16	193	309
$OS\text{-}FM_{CP}$	As OS but excluding all FM studies	CPP	8	11	8	126	102
$ALDN_{CP}$	Allodynic	CPP	11	12	11	199	143
NOX_{CP}	Noxious	CPP	23	27	23	333	400
$MECH_{CP}$	Mechanical CPP	CPP	20	21	20	289	381
$HYPER_{HC}$	Hyperalgesia	HC	9	11	11	188	116

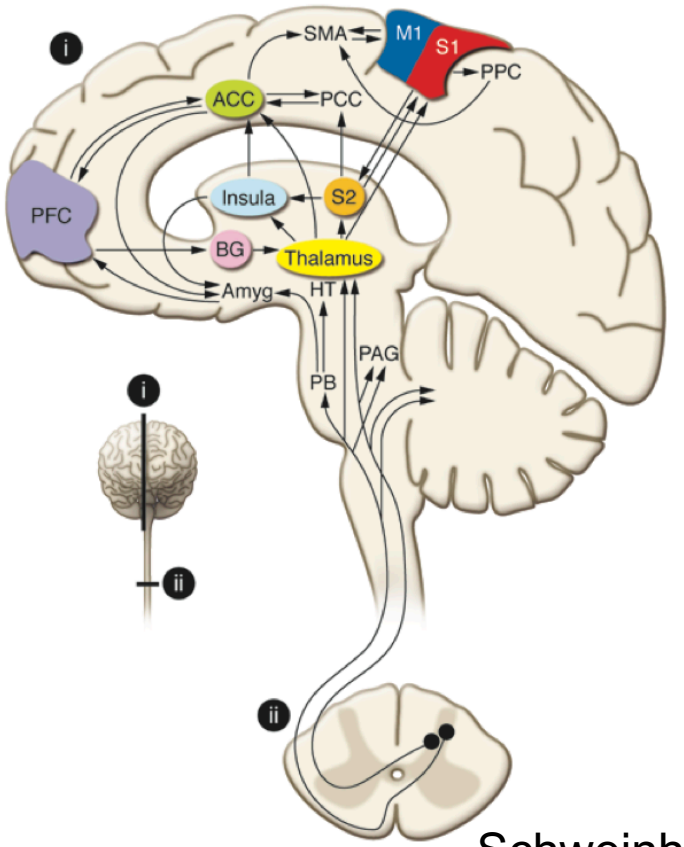


Evoked pain fMRI meta-analysis: Healthy Controls

HC



Tanasescu et al., 2016



- For healthy adults, many ascending nociception-processing regions activated, including insula – integration between sensory and affective dimensions of pain
- Pain modulatory areas (e.g. vlPFC, VTA) also activated

Schweinhardt et al., 2010

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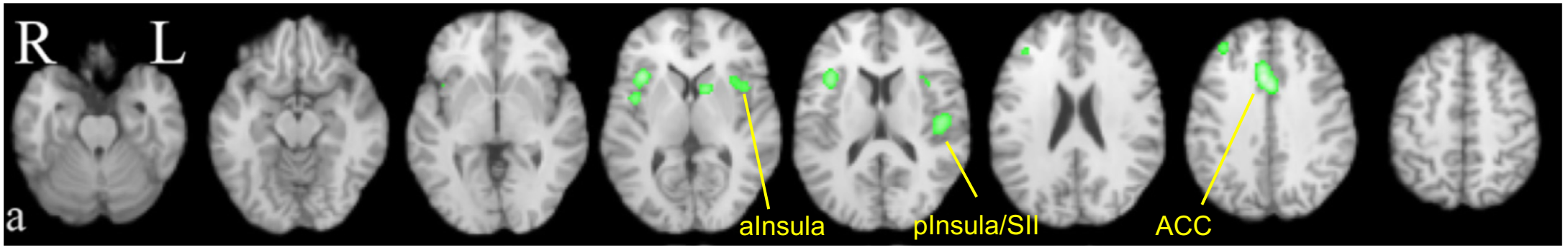
Evoked pain fMRI meta-analysis: experimental hyperalgesia, model for CS

HC (capsaicin-induced hyperalgesia > normalgesia, N=11 studies)



- While localization between normalgesia and hyperalgesia in healthy controls did not differ… combining direct contrasts reported in studies (i.e. sensitive to differences in response intensity) did show greater activation in insula, cingulate, SII
- Thus, for experimentally induced central sensitization → *generalised upregulation of pain and salience processing brain areas (insula, SII, ACC)*

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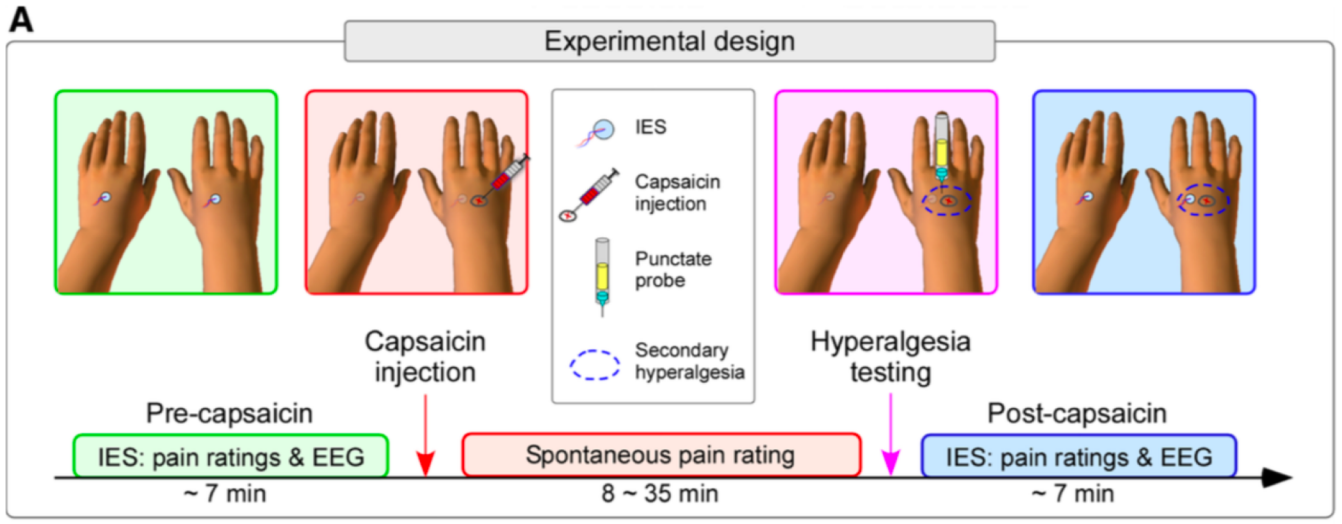
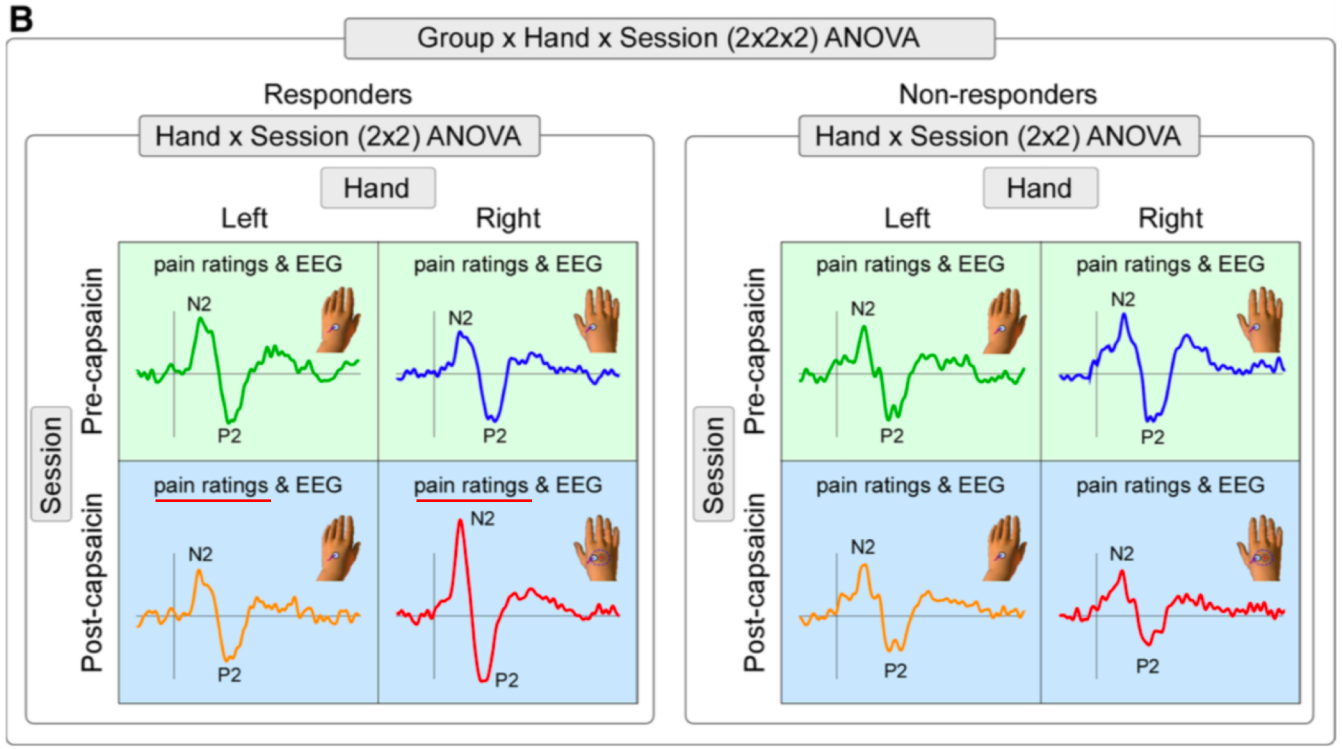
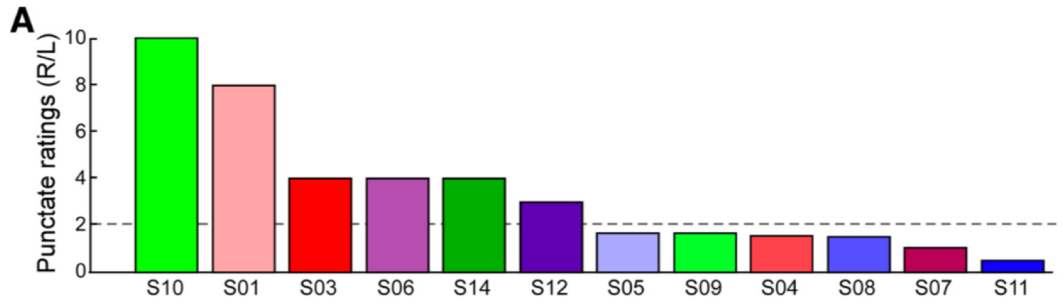
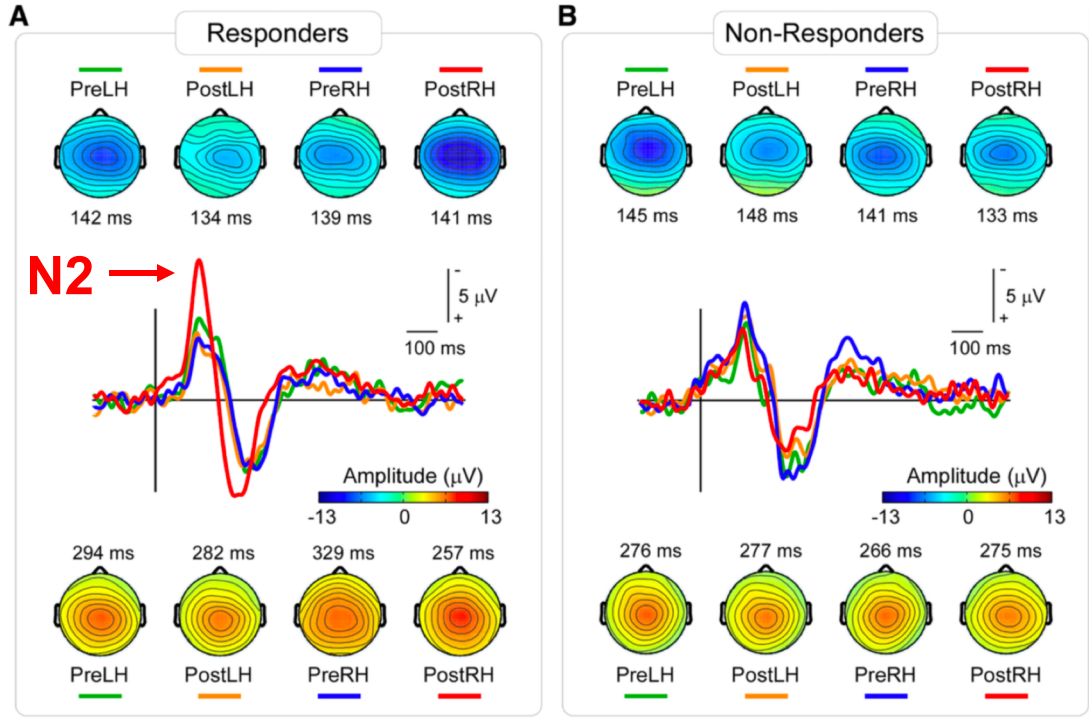
Consistent with EEG for capsaicin-induced central sensitization









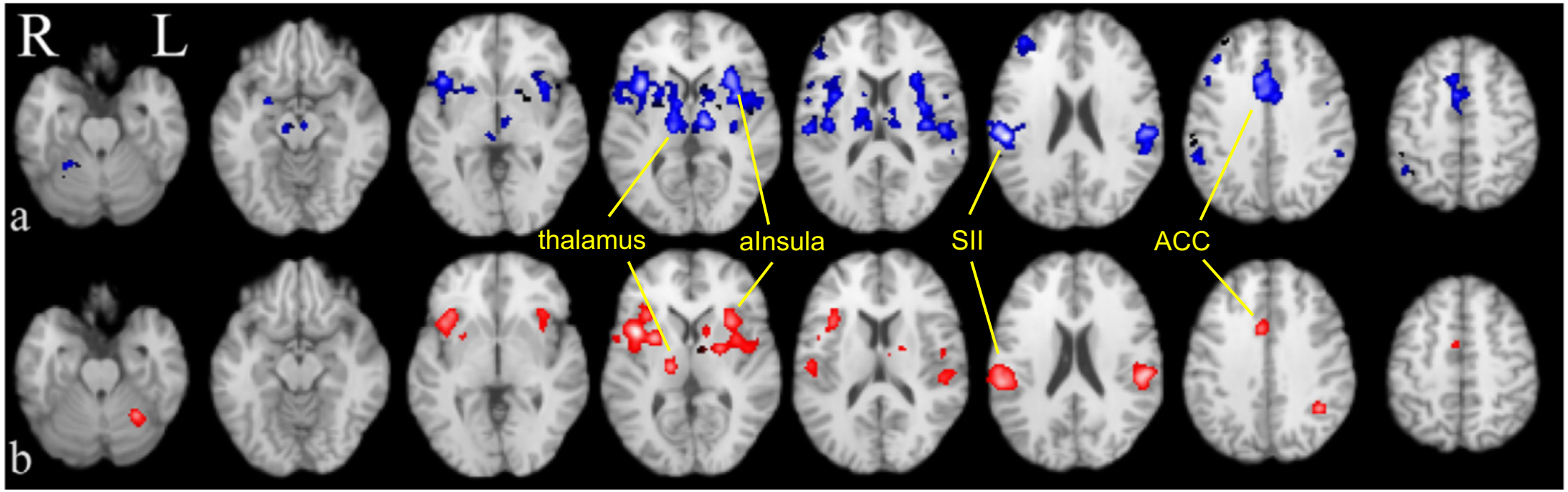
Liang et al. 2016

Central Sensitization → Increased N2 peak

Evoked cutaneous pain fMRI meta-analysis: Chronic Pain vs Healthy

HC

CP



"remarkably similar activation patterns in healthy controls … and chronic pain patients"

CP vs. HC key findings:

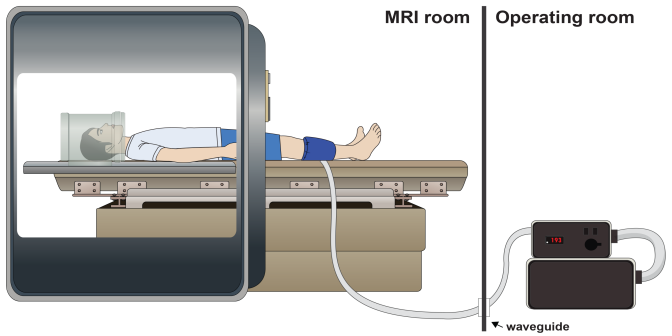
- No significant differences in *spatial localization* of nociceptive processing
- No significant differences in *intensity* of activation (combining CP-HC contrasts)
- No significant differences for subgroup of FM vs. HC studies (N=8)

?

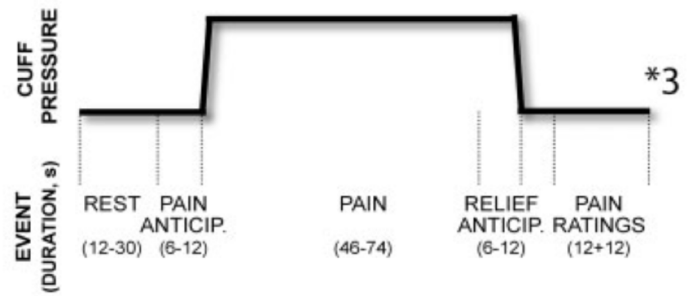
Tanasescu et al., 2016

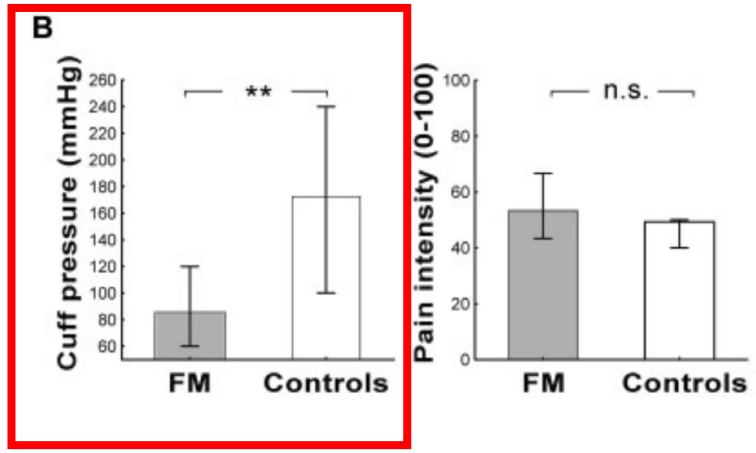
No FM vs HC difference in deep pressure-pain evoked fMRI response

- N=31 FM, N=14 HC
- *Percept-matched* pain

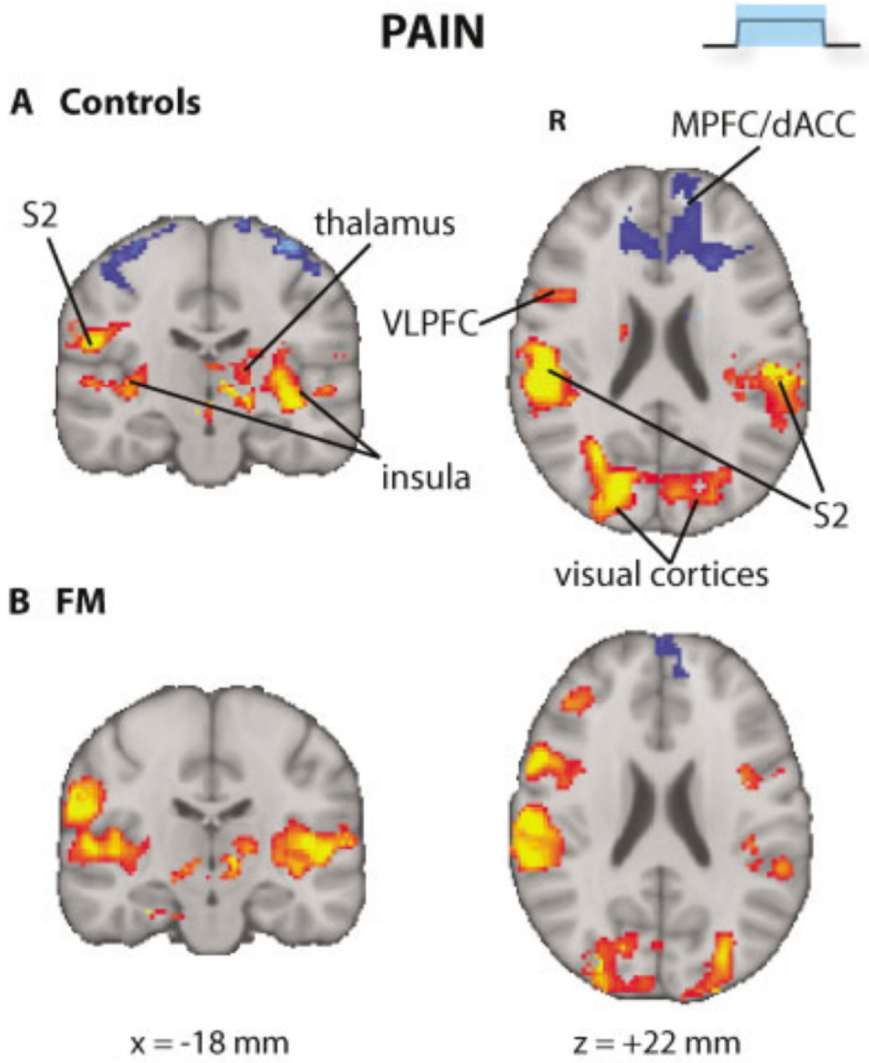


deep tissue evoked pain





Loggia et al. 2014



Clear (widespread) hyperalgesia…

Why no difference in brain response?

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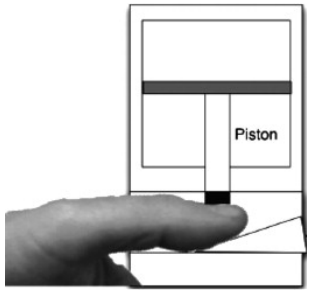
Stimulus-matched vs. percept-matched pain response in FM

- Stimulus-matched thumbnail pressure pain (4.5 kg/cm^2 for both FM and HC) vs. percept-matched (HC: ~6 kg/cm^2) pain
- Stimulus matched: FM > HC, Percept-matched: FM=HC



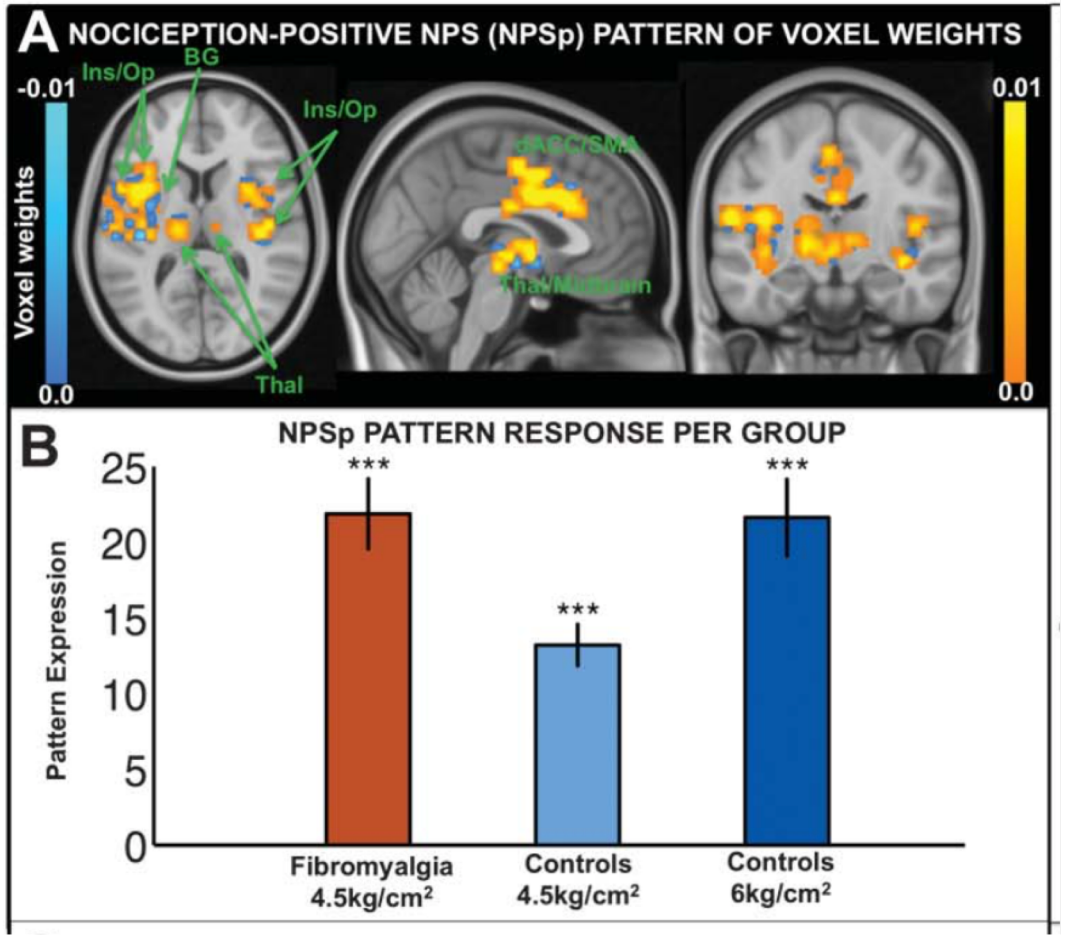
Pressure=4.5 kg/cm^2

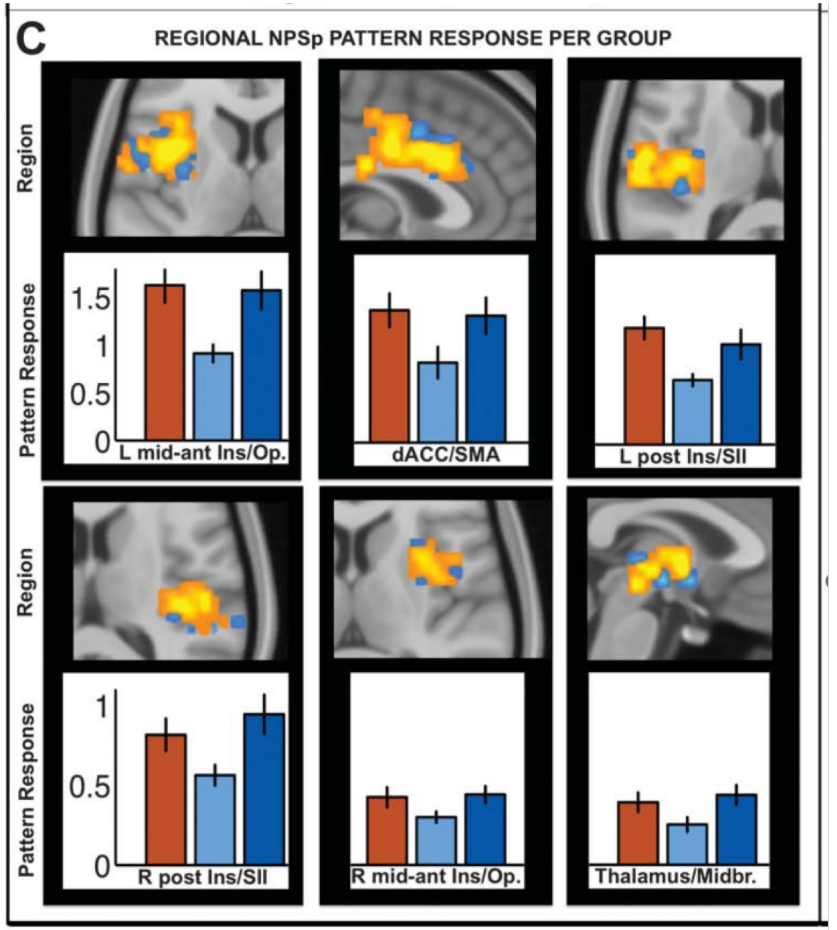
HC (N=35) 48.48 ± 18.31

FM (N=37) 71.71 ± 14.47

**Pain ratings for HC at pressure=6kg/cm^2 did not differ from FM pain ratings (p=0.54)*

Lopez-sola et al. Pain 2017





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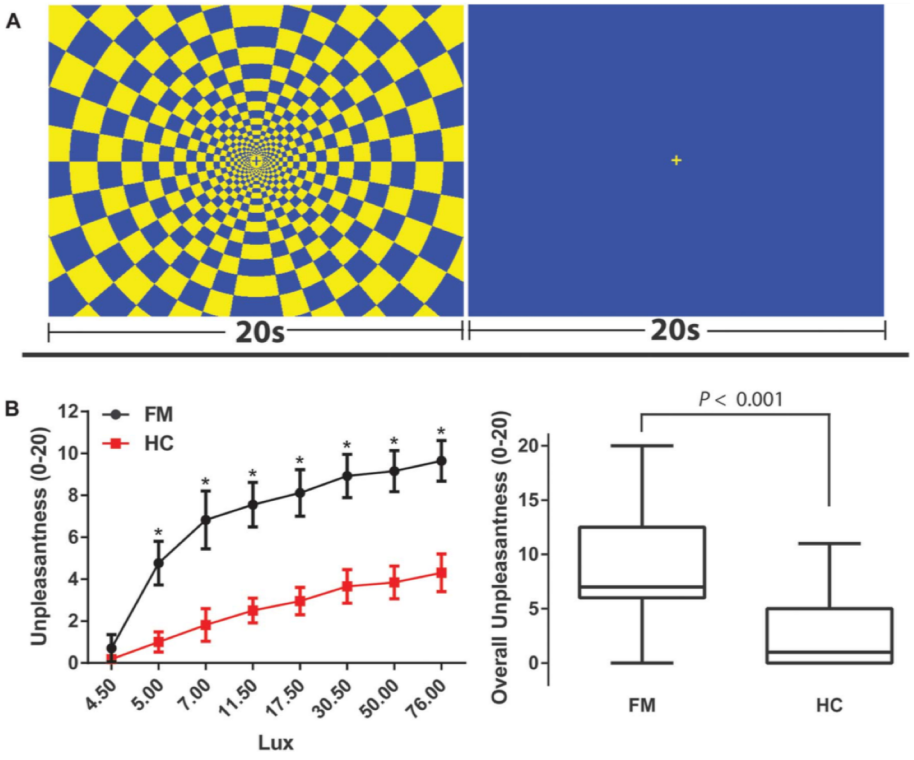
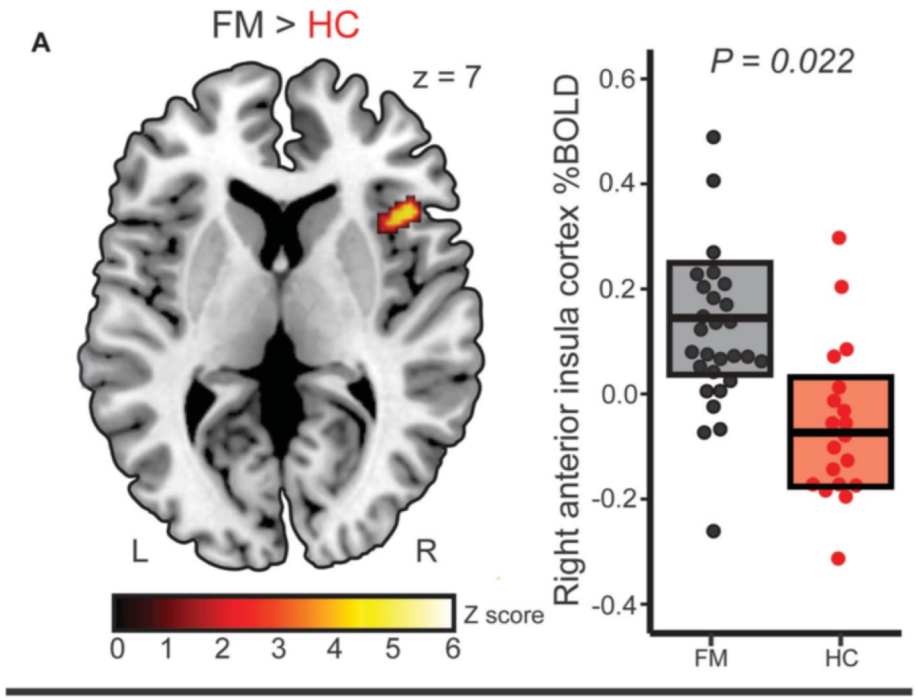
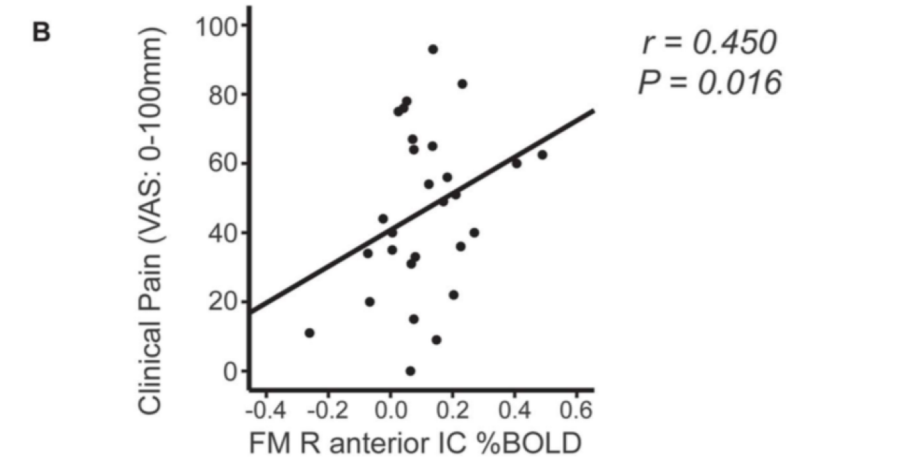
Amplified FM insula response to stimulus-matched visual stimuli

- N=25 FM, N=20 HC
- Stimulus-matched visual checkerboard stimulation
- FM show elevated unpleasantness ratings and right anterior insula response to 76 lux visual stimuli
- Greater clinical pain correlated with greater insula response







Harte et al. Pain 2016

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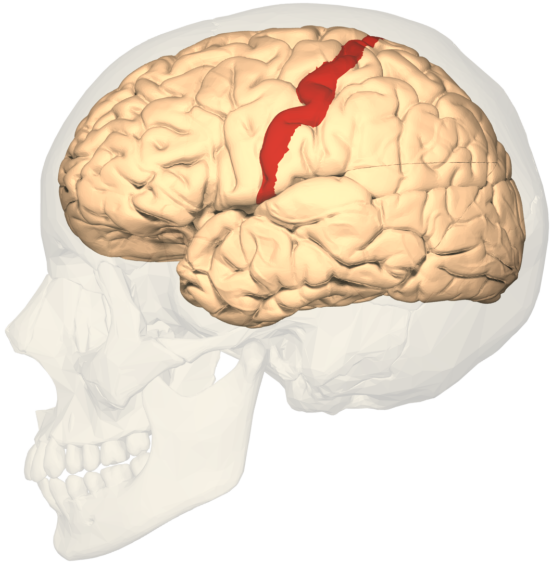
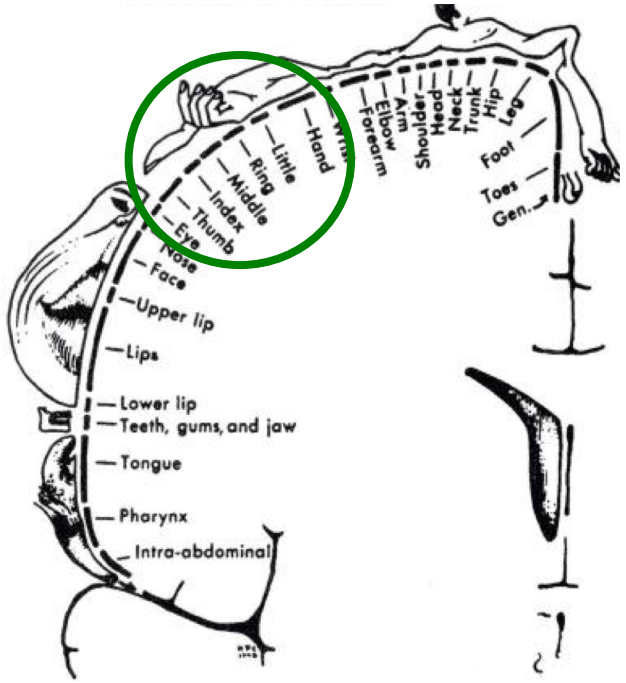
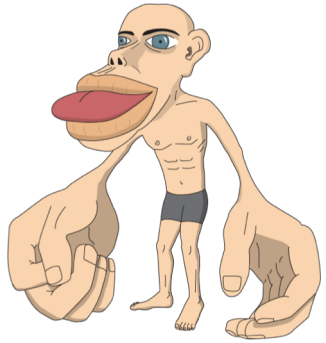
Other fMRI metrics of central sensitization: receptive fields / representations

- The somatotopic humuncular organization in post-central gyrus / primary somatosensory cortex, S1 (Penfield, 1937).







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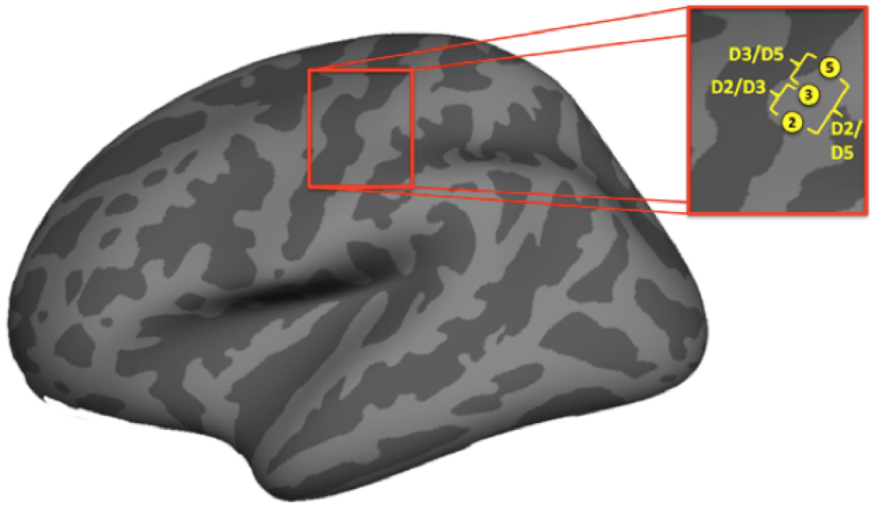
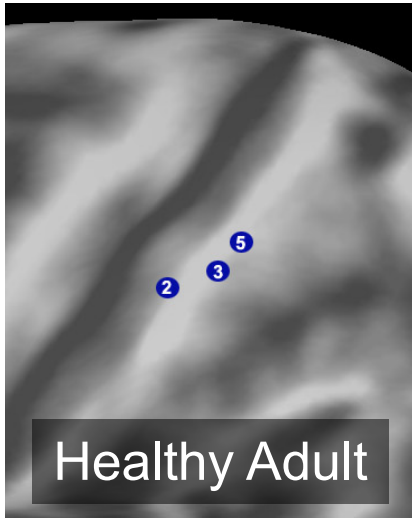
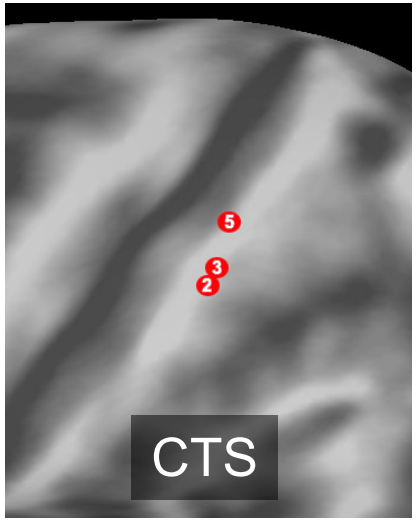
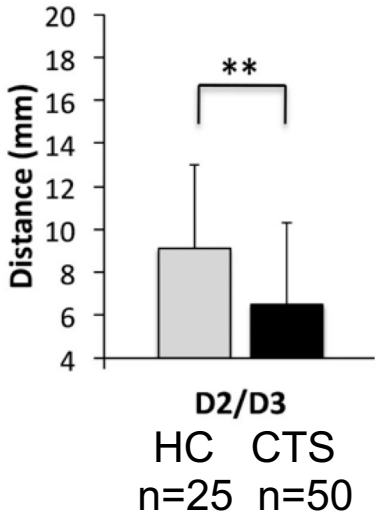
Increased / blurred cortical representations (S1) in neuropathic pain

- In chronic neuropathic pain (carpal tunnel syndrome, CTS), median nerve pathophysiology is linked with central plasticity in primary somatosensory cortex, S1

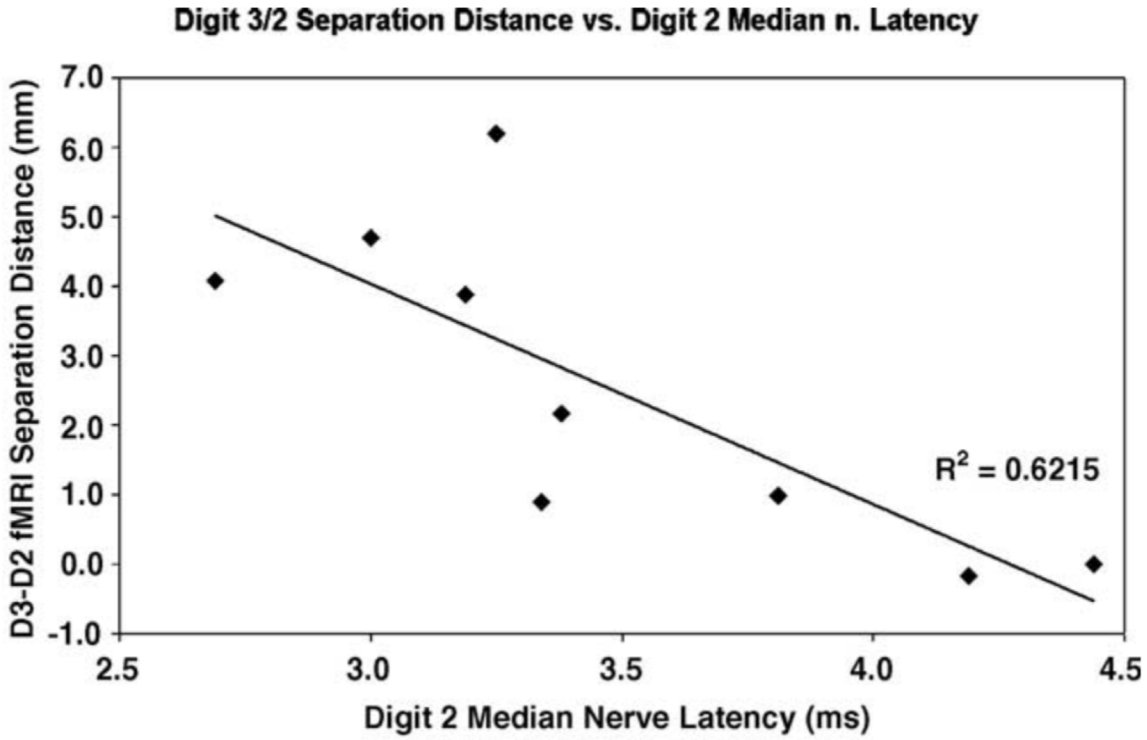








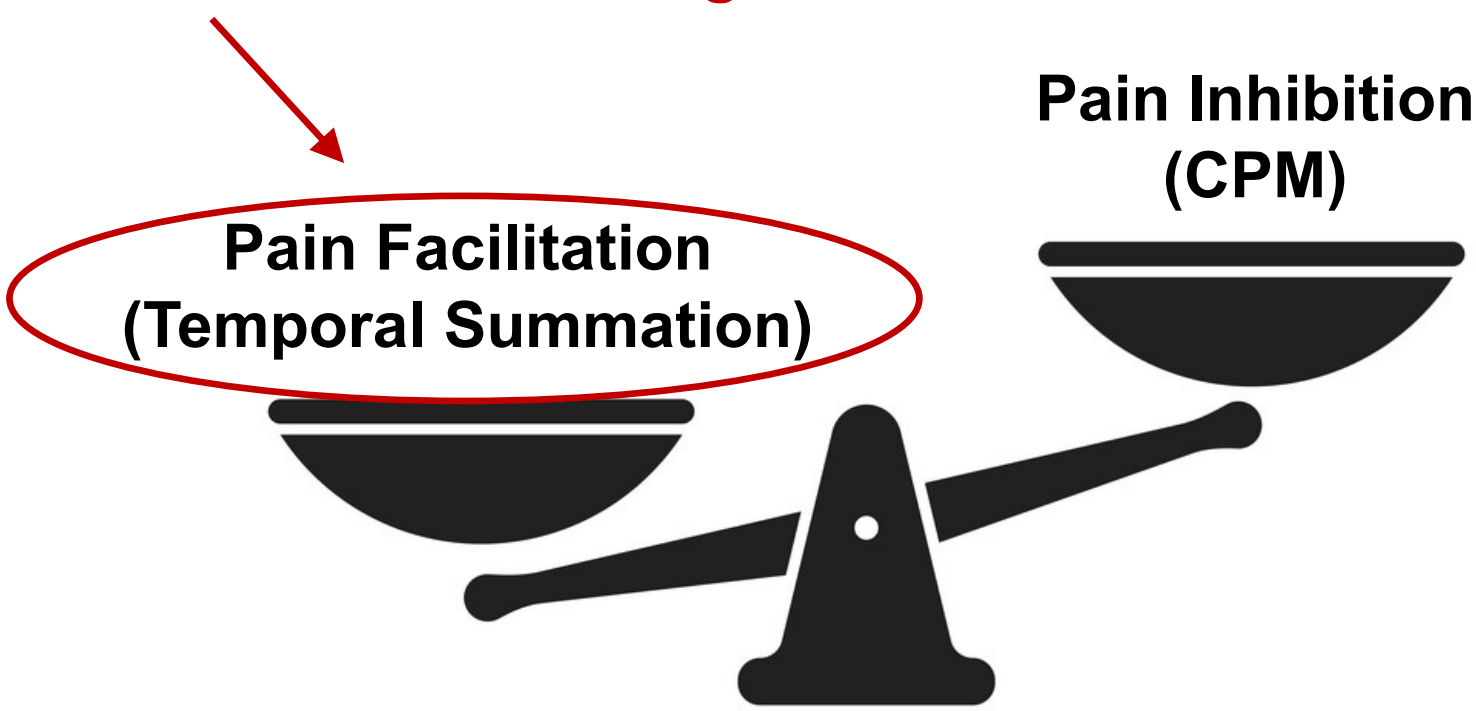
Maeda et al., Brain, 2014



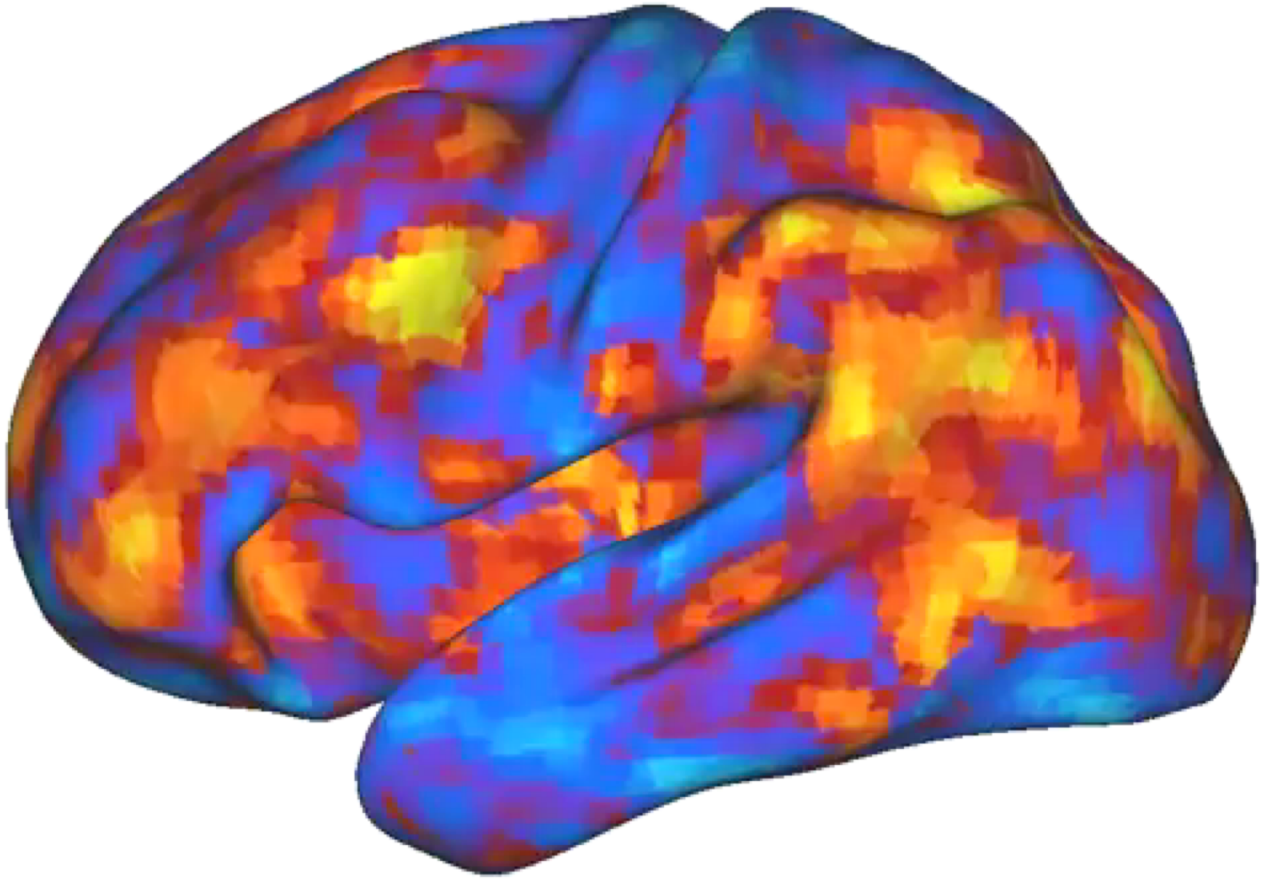
Napadow et al., NeuroImage 2006

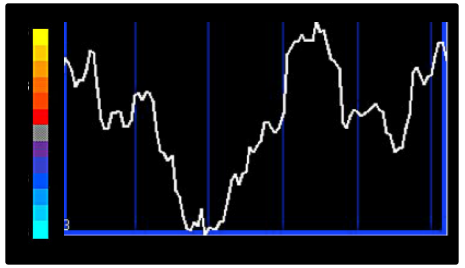
Other fMRI metrics of central sensitization: temporal summation and conditioned pain modulation (CPM)

Stimulus frequency (~0.33 - 1Hz) less amenable to fMRI event-related designs



More fMRI metrics → Functional Connectivity: fMRI Signal Fluctuates Synchronously within Distinct Brain Networks

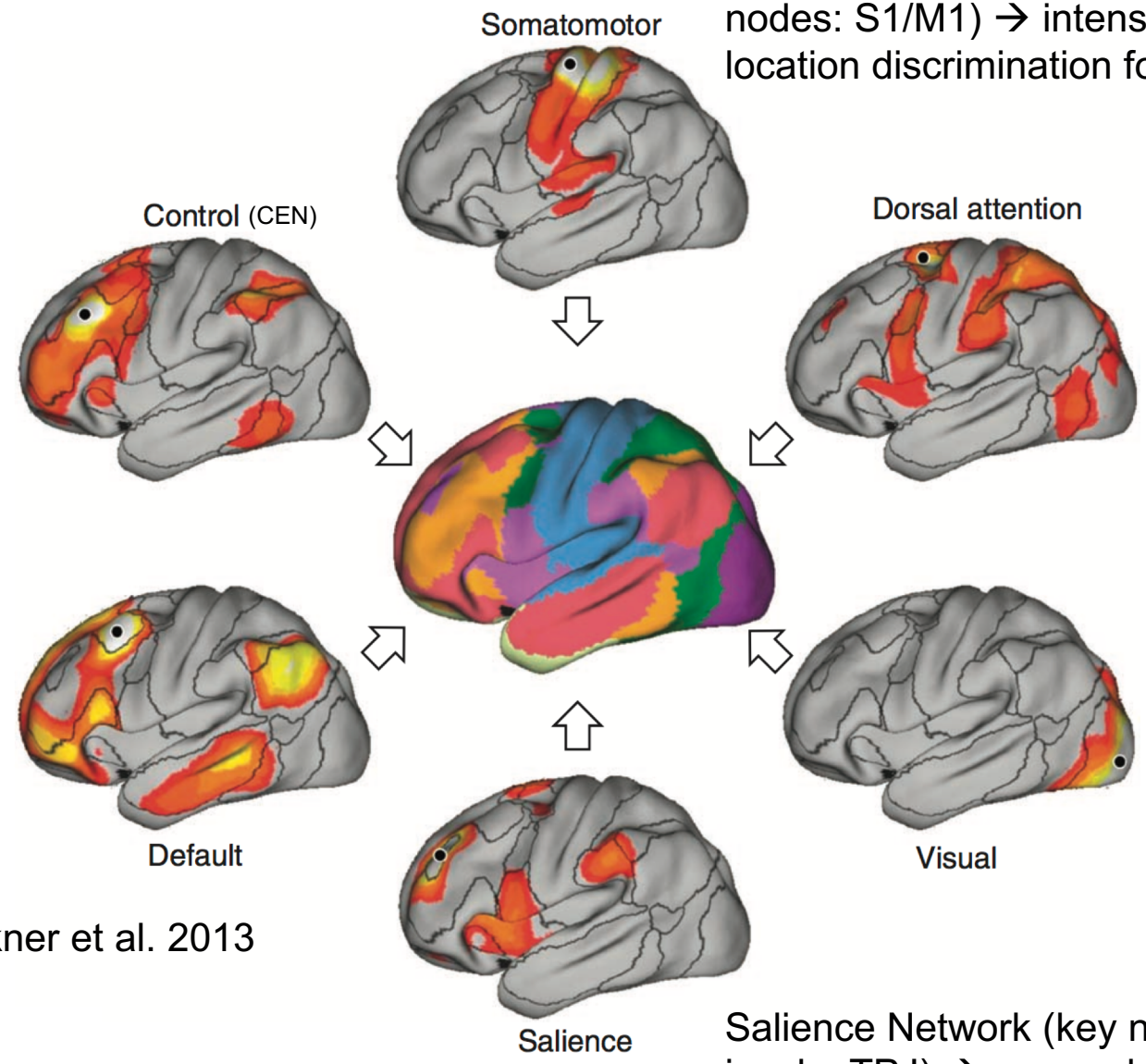




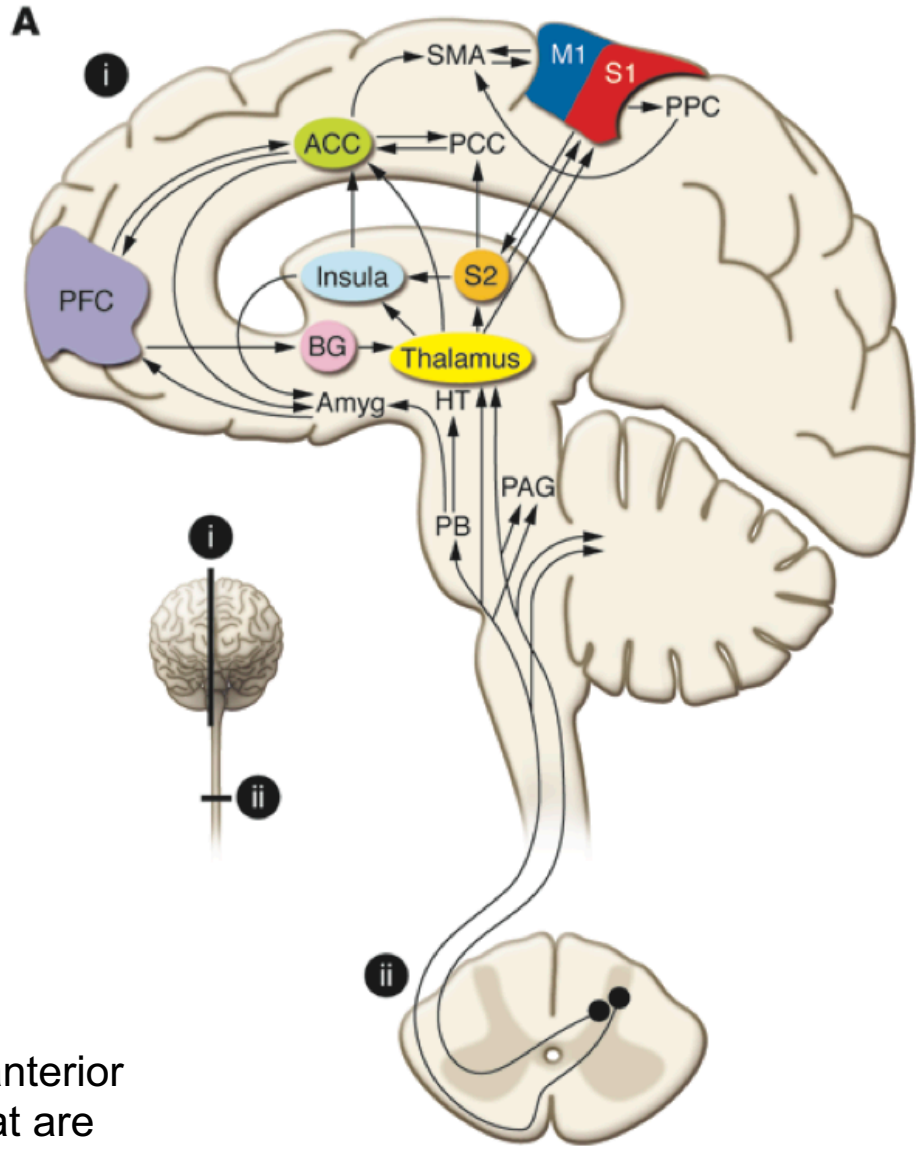
Vincent et al. 2008

Multiple primary and associative brain connectivity networks

Somatomotor Network (key nodes: S1/M1) → intensity, location discrimination for pain



Buckner et al. 2013



Salience Network (key nodes: ACC, anterior insula, TPJ) → responds to stimuli that are "salient" = stand out from other stimuli (e.g. pain)

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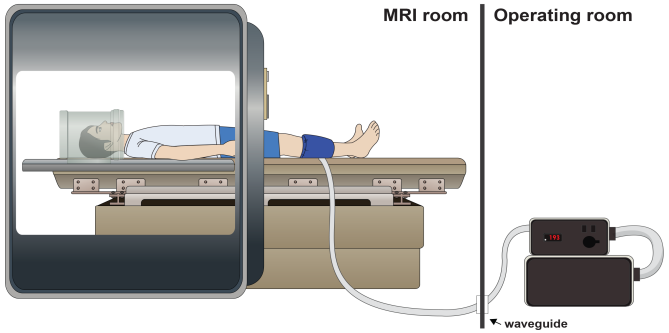
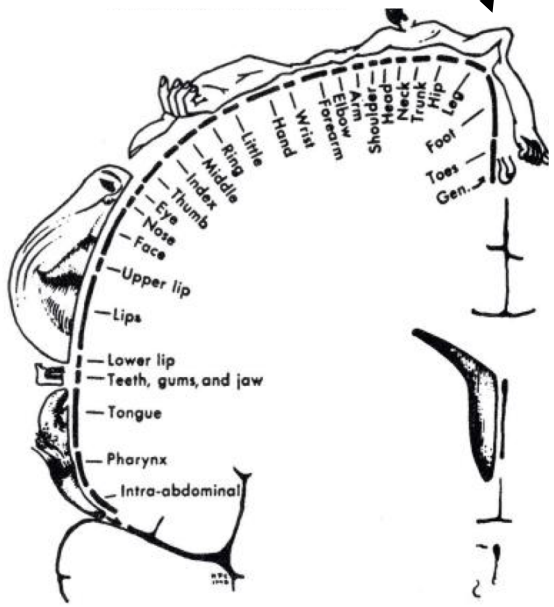
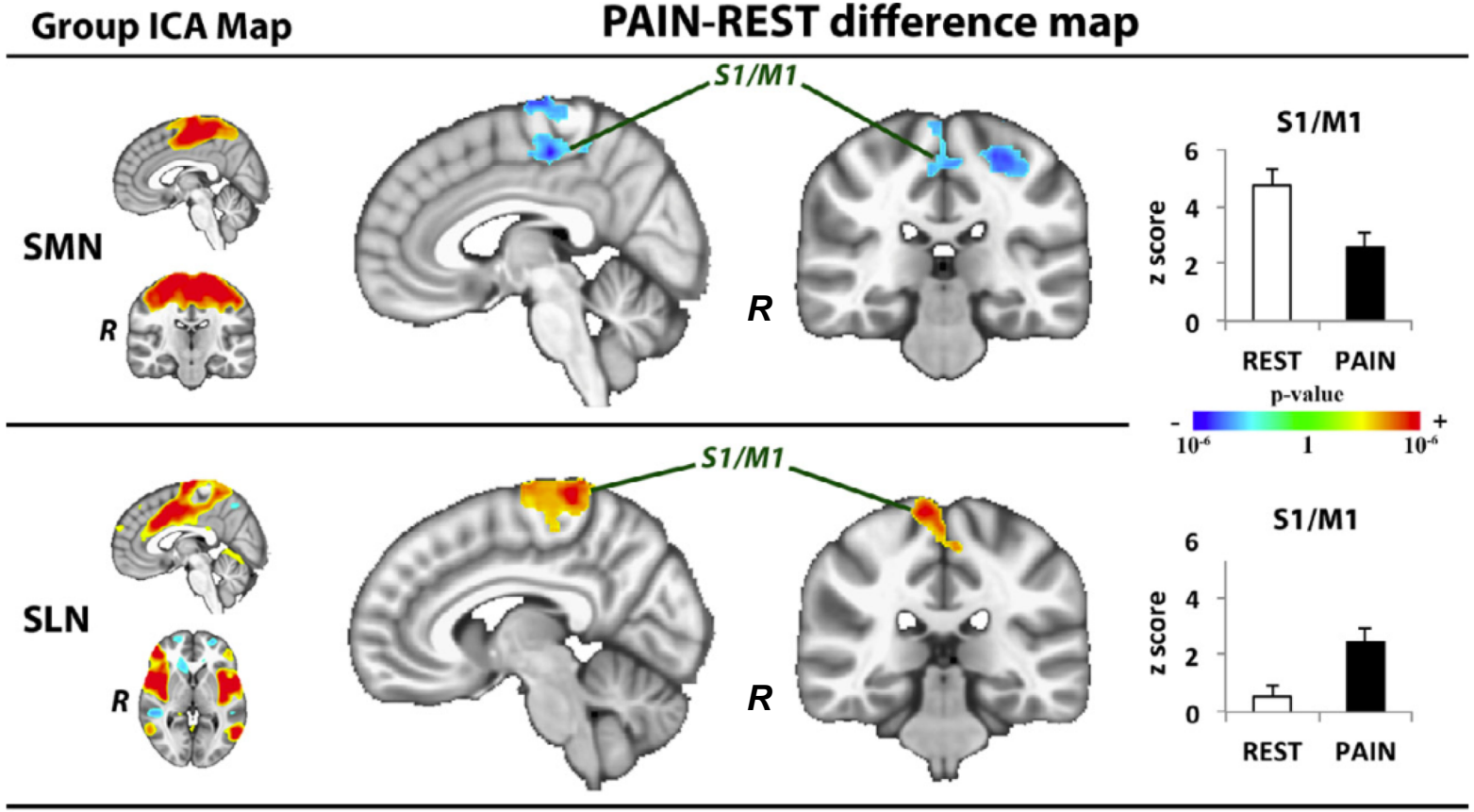
SMN and SLN connectivity shifts during sustained pain state



Sustained (6 minutes), deep tissue evoked PAIN (left leg) vs REST

S1 leg representation





Kim et al., Pain 2013

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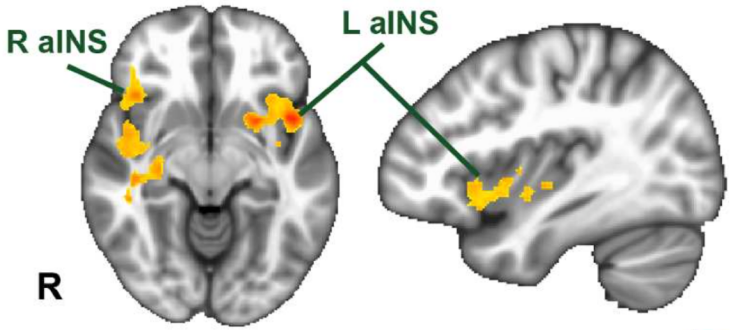
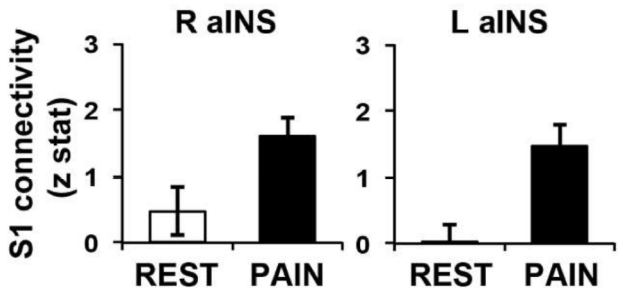
$S1_{leg}$ connectivity also shifts for FM, linked with temporal summation

Seed: leg

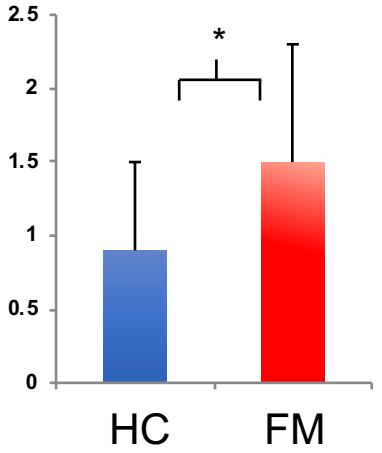
z=68mm

FM $S1_{leg}$ connectivity: PAIN vs. REST (6 minutes)

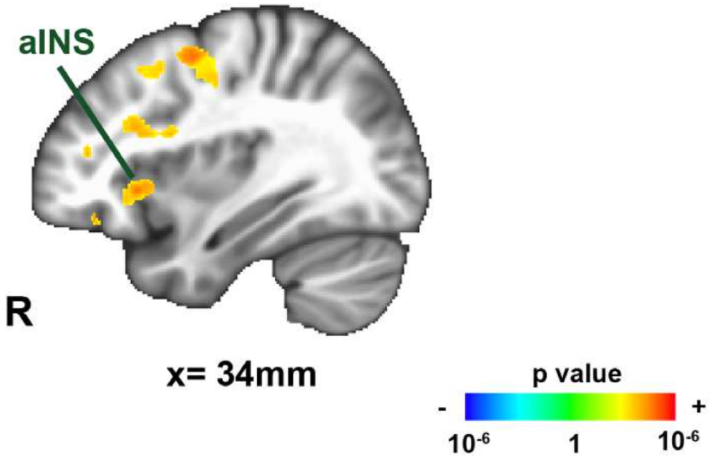


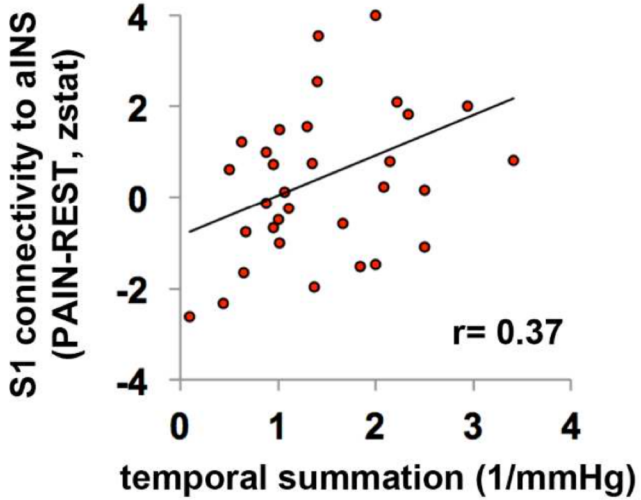


Temporal Summation (Last 2min - 1st 2min)



FM: PAIN altered $S1_{leg}$ connectivity vs. temporal summation





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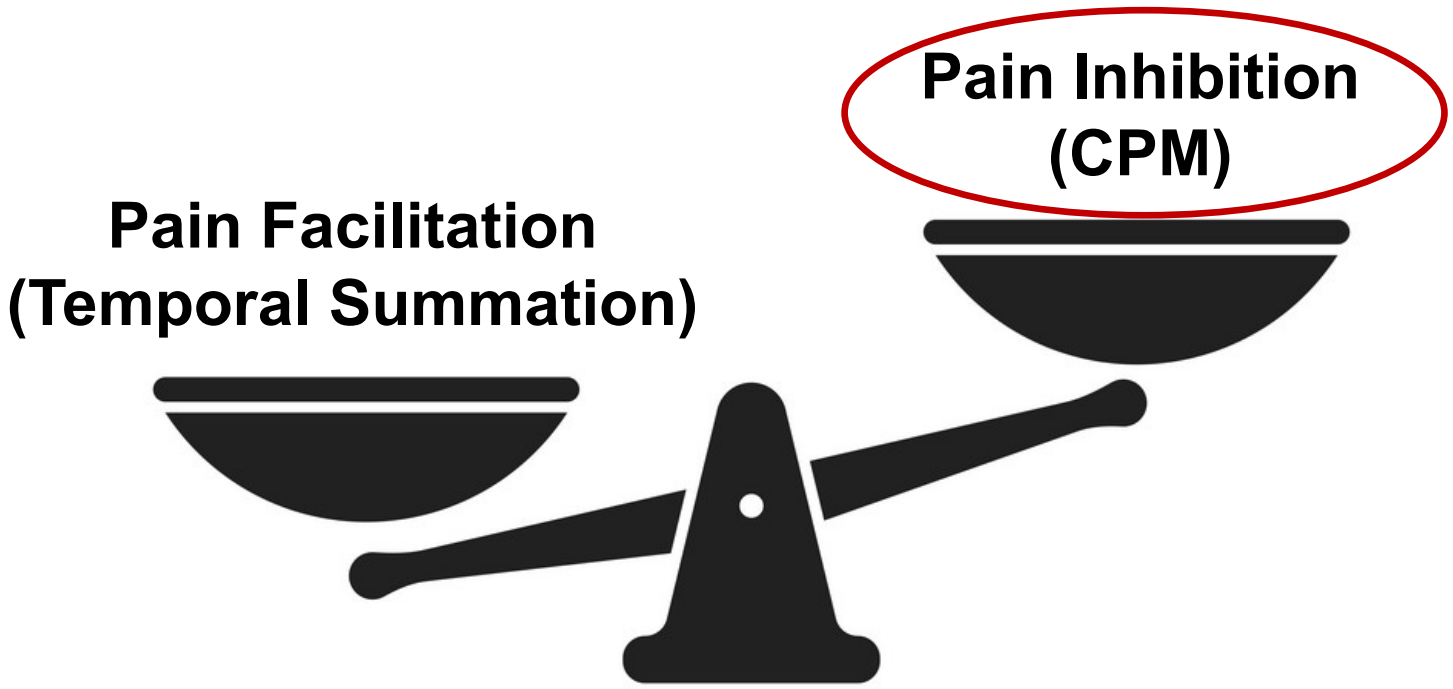
Kim et al., A & R 2015

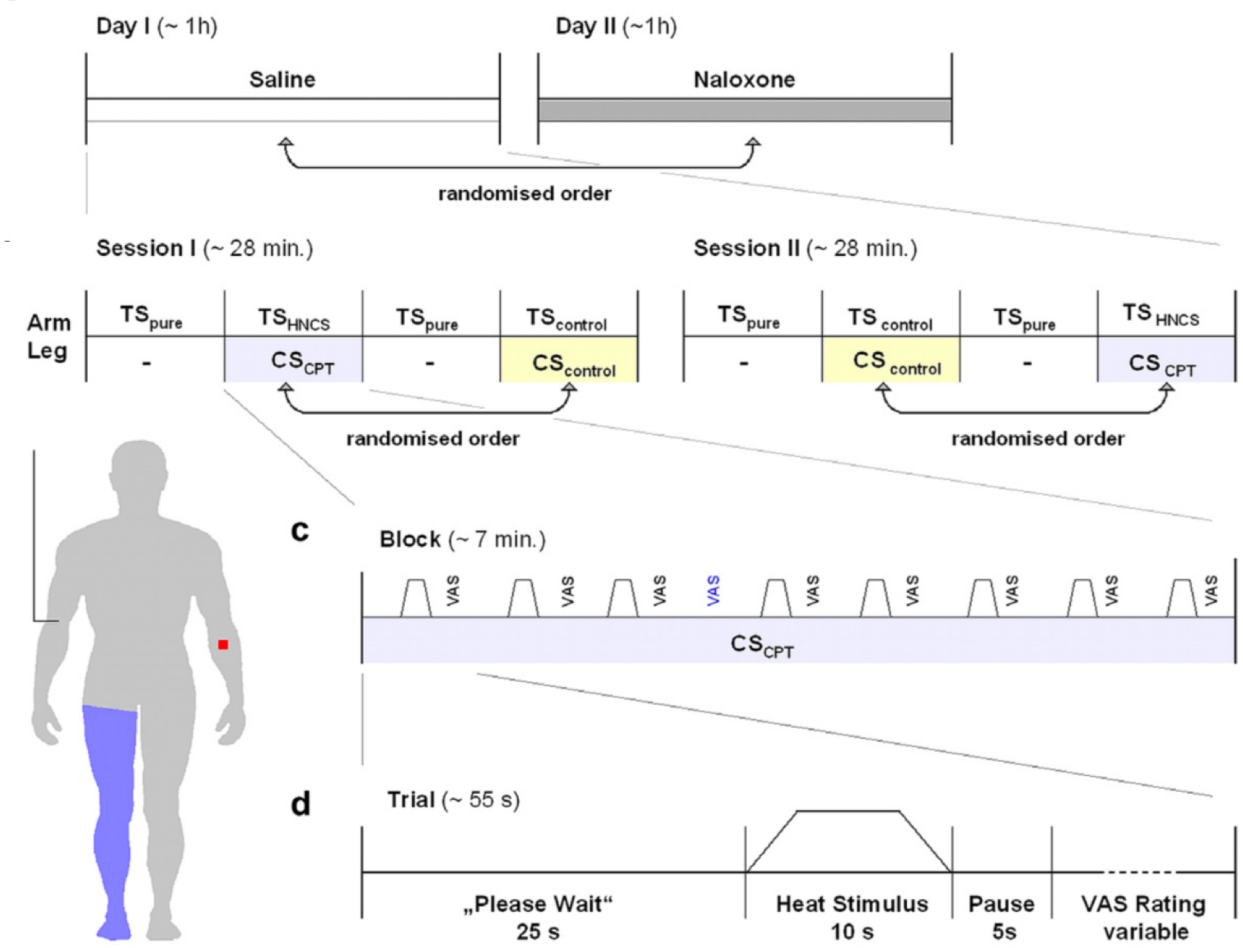
Other fMRI metrics of central sensitization: temporal summation and conditioned pain modulation (CPM)

Stimulus design for MRI scanner can be problematic

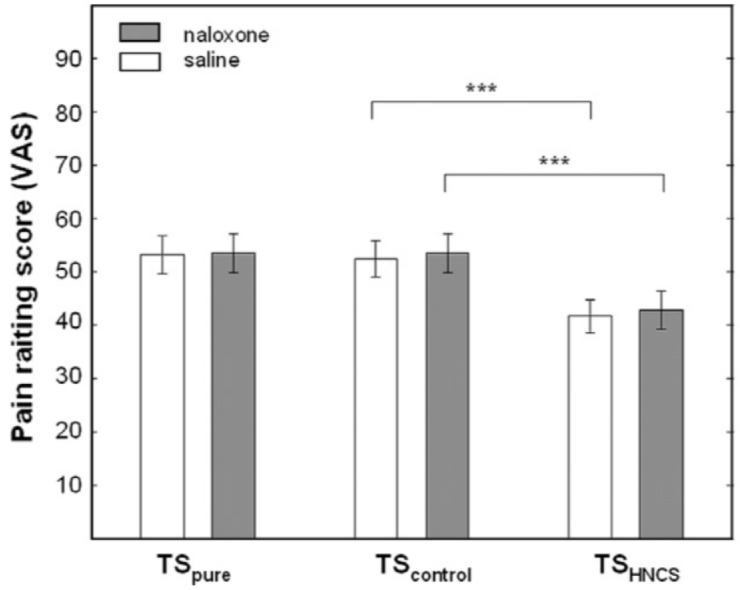


Conditioned Pain Modulation (CPM) in healthy adults

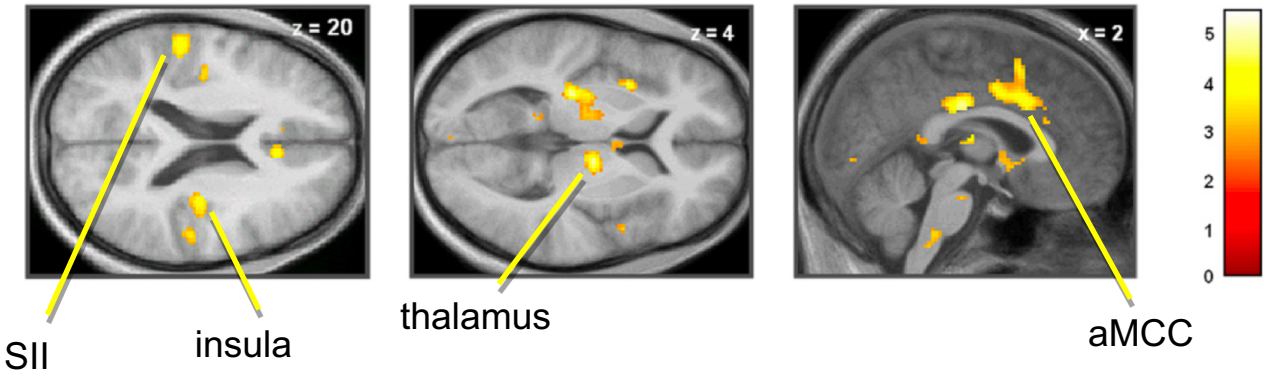
- Few studies have assessed CPM with fMRI (and found group effect for reduced pain!)
- CPM reduced pain coincides with reduced thalamus, aMCC, insula, SII activation



Sprenger et al., Pain 2010

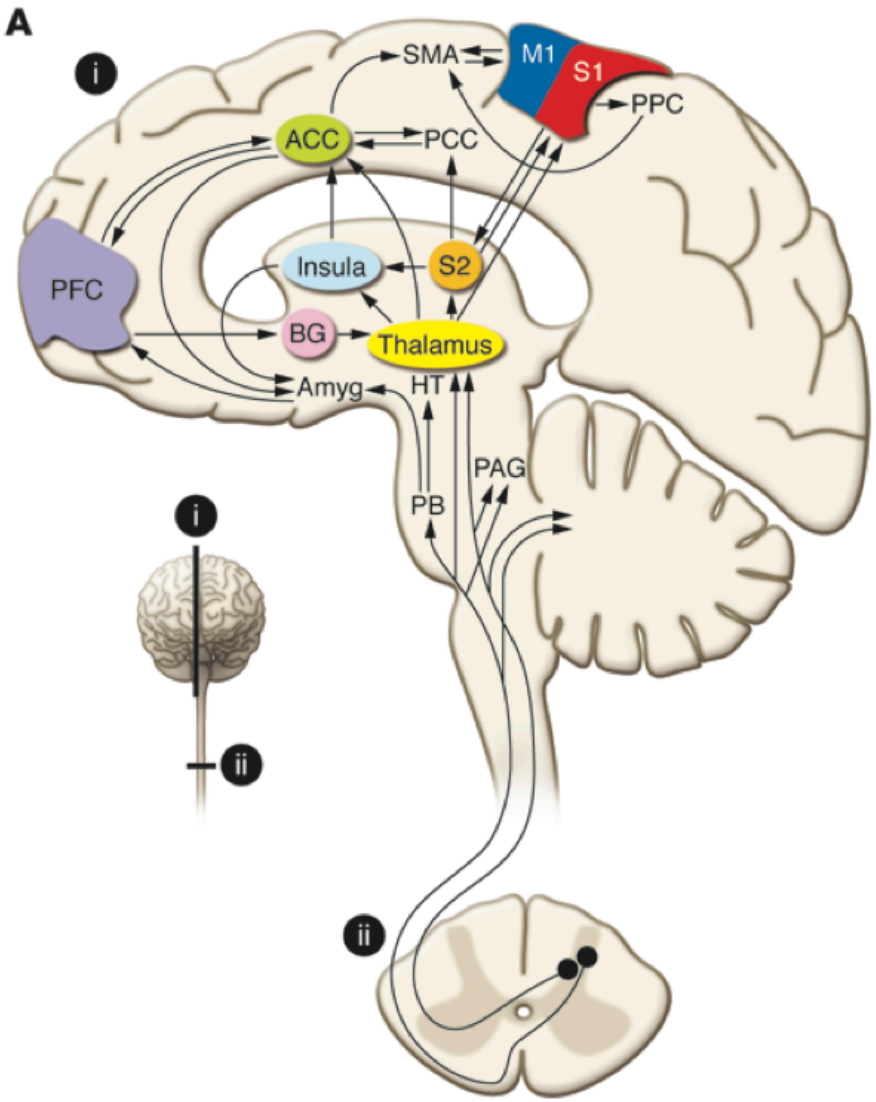


Test Stimulus$_{control}$ – Test Stimulus$_{HNCS}$



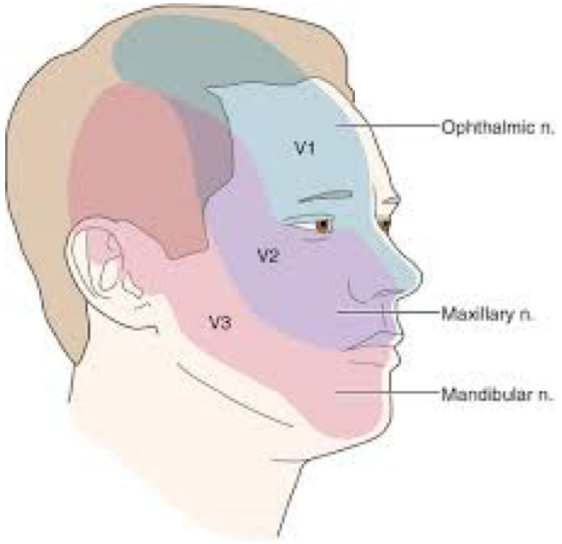
The search for more specific fMRI applications for central sensitization

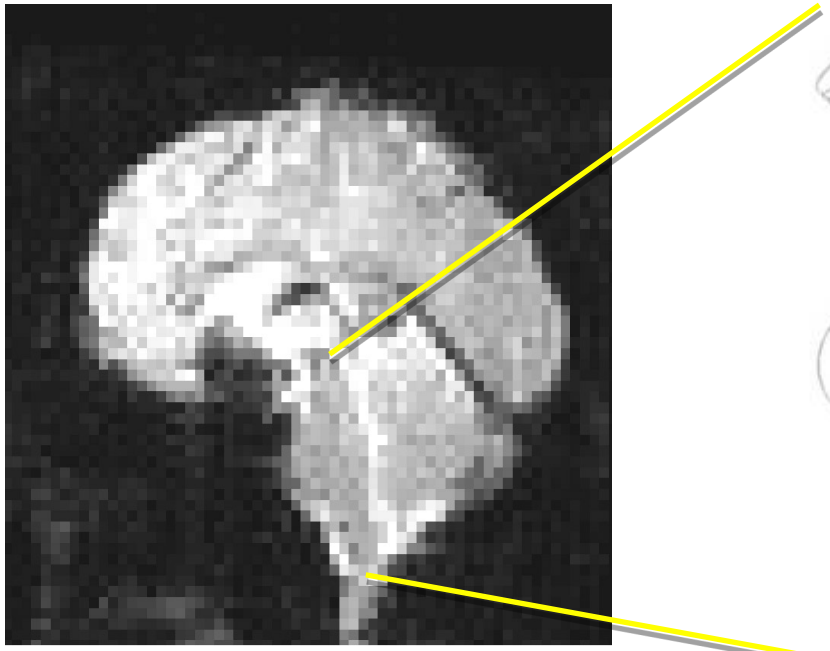
- "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" → i.e. standardized input & peripheral afference, but central amplification: ***Is it cord? is it brain?***
- *Do chronic pain patients show amplification at primary synapse (e.g. dorsal horn) or higher up? Or both?*

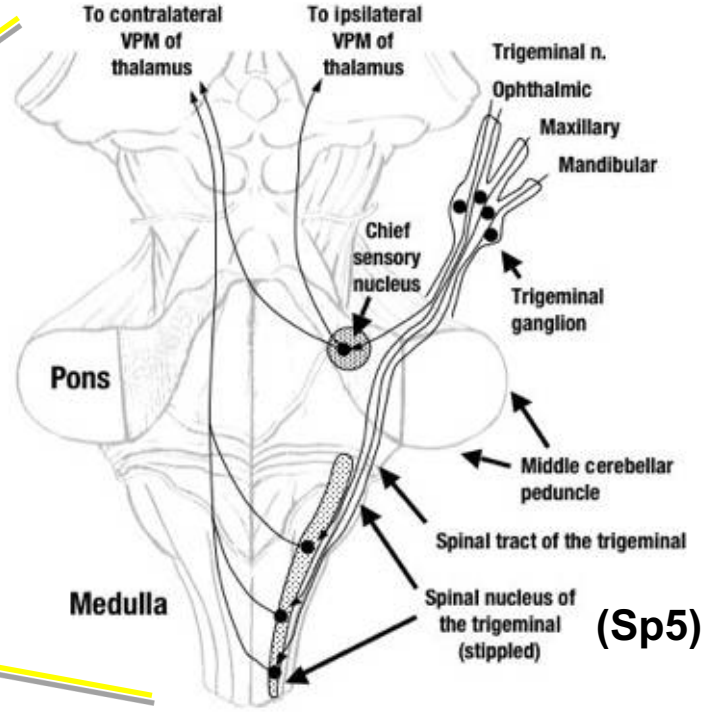


Facial stimulation to assess trigeminal pathways in migraine

- Sensory stimuli to face (trigeminal nerve) allow fMRI evaluation of ***both*** Sp5 nucleus in brainstem (analogous to dorsal horn) and brain response

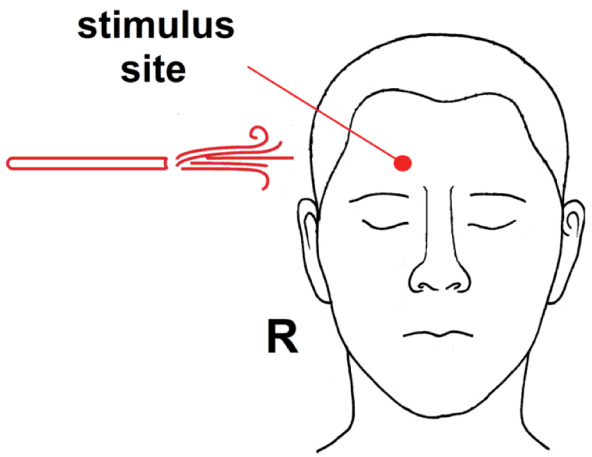


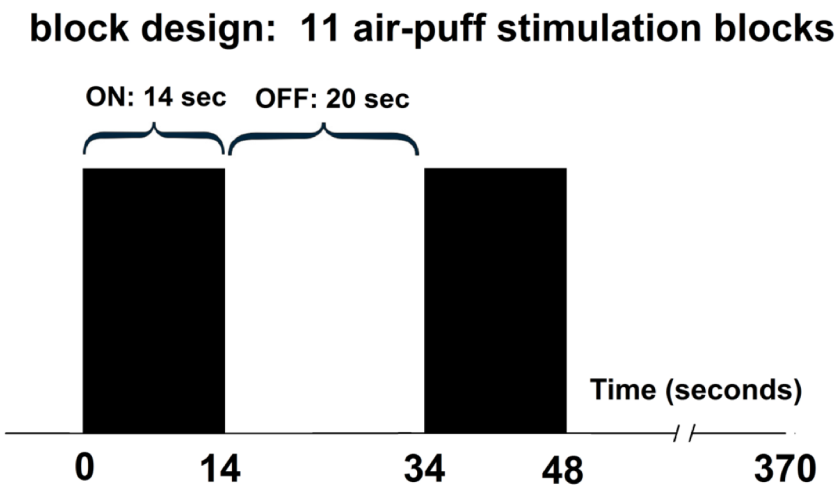




Swenson, 2006

Facial stimulation to assess trigeminal pathways in migraine





- 16 interictal migraine patients (15 F, 35.8 ± 13.4 yo), 2-15 attacks / mo.
- 16 sex/age-matched healthy controls (15 F, 36.0 ± 13.7 yo)
- Airpuff stimuli (stimulus-matched): 5 Hz, 12mm tubing, 80 PSI

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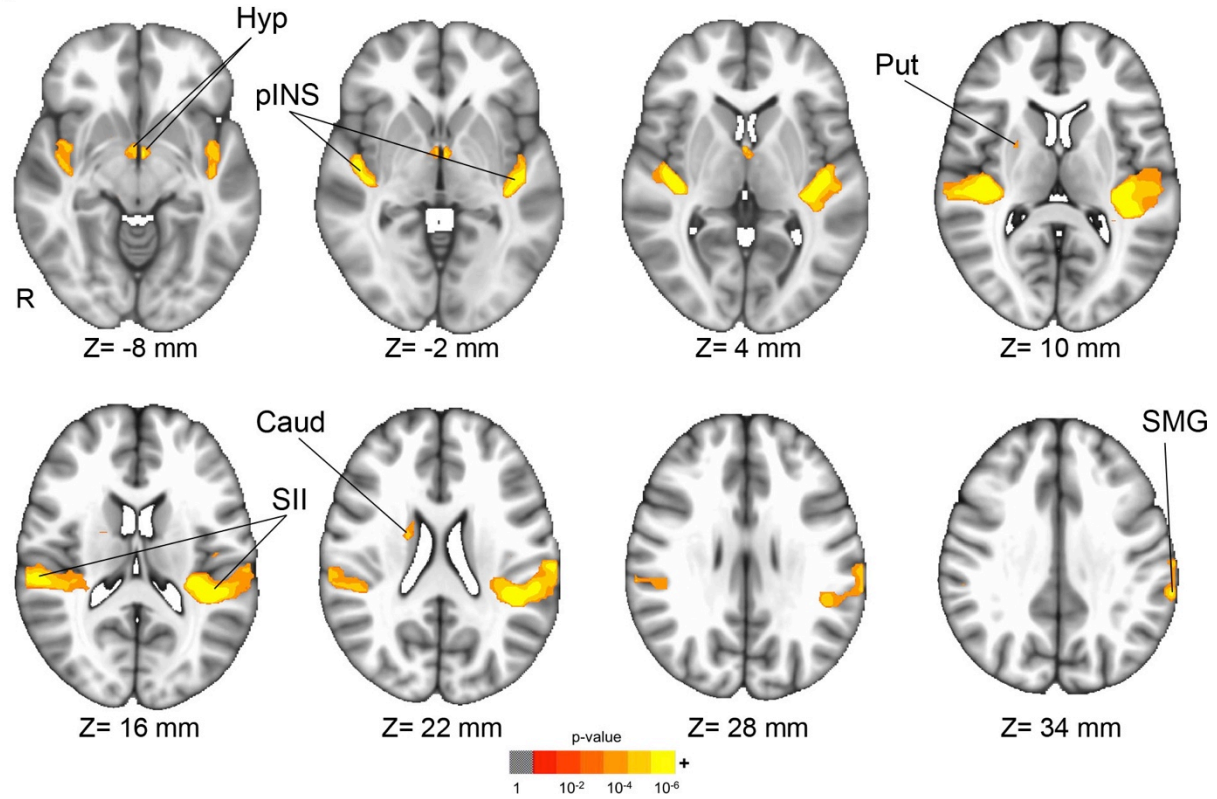
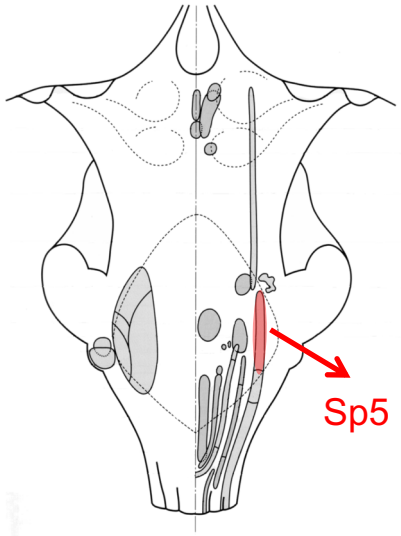
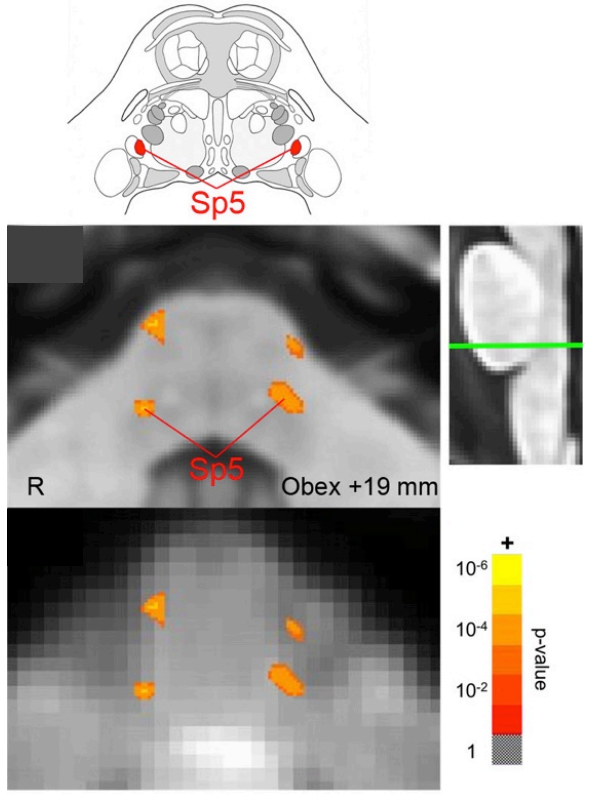
Brain / brainstem response to (stimulus-matched) forehead stimulation

- Combined group (MIG+HC) fMRI response evident in Sp5, as well as hypothalamus, posterior insula, SII
- Combined group response was then used to determine *unbiased* ROIs for calculating central sensitization metrics







Lee et al., Cephalalgia, 2016

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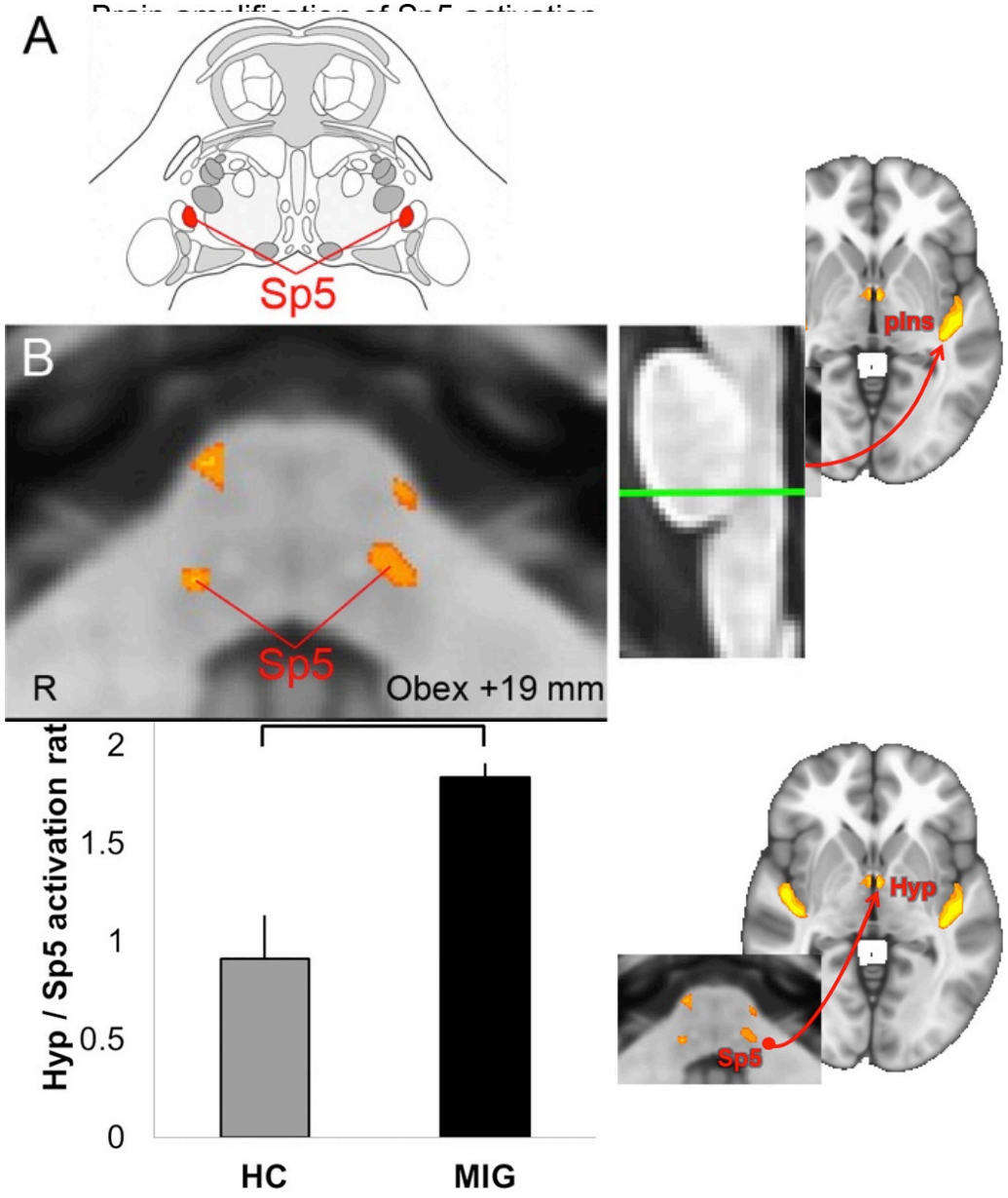
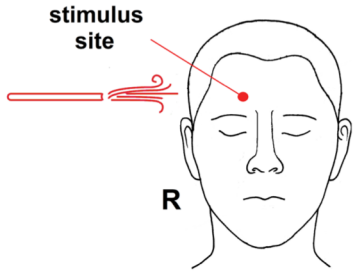
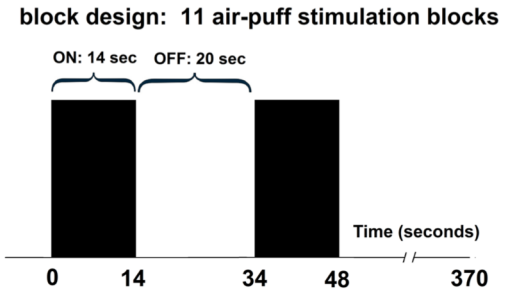
Central Sensitization: Amplification ratio (Sp5-to-brain) increased in Mig

- Sp5 response was *not* different between migraine and HC
- *<u>Amplification ratio ("gain"):</u>* Cortical / subcortical fMRI activation relative to Sp5 activation – i.e. amplification of afference from Sp5 to higher levels
- Amplification ratio: MIG > HC for ***<u>posterior Insula</u>*** *and* ***<u>hypothalamus</u>*** (*sensitization can occur above* the *spinal cord / Sp5*)

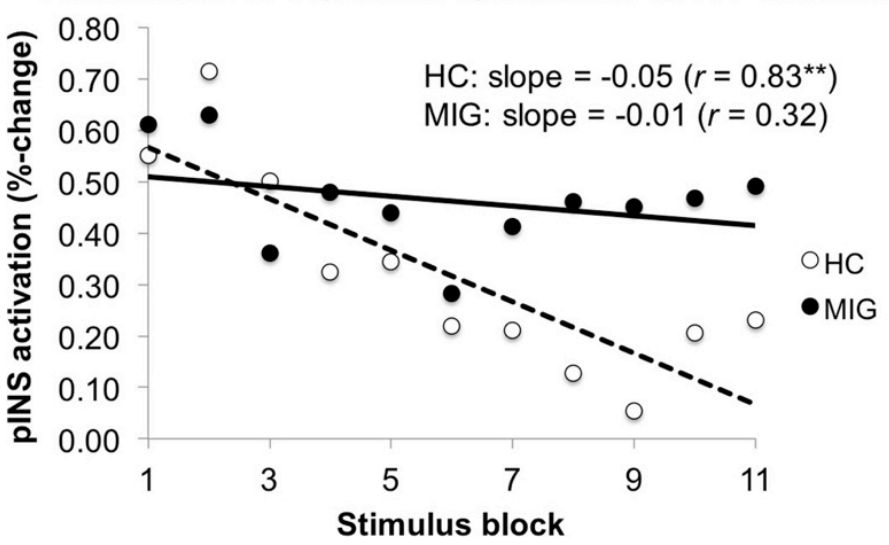


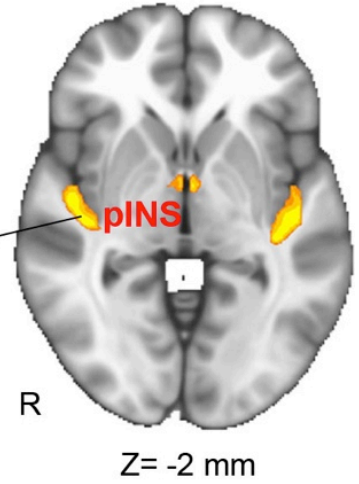
Central Sensitization: Habituation is reduced in migraine

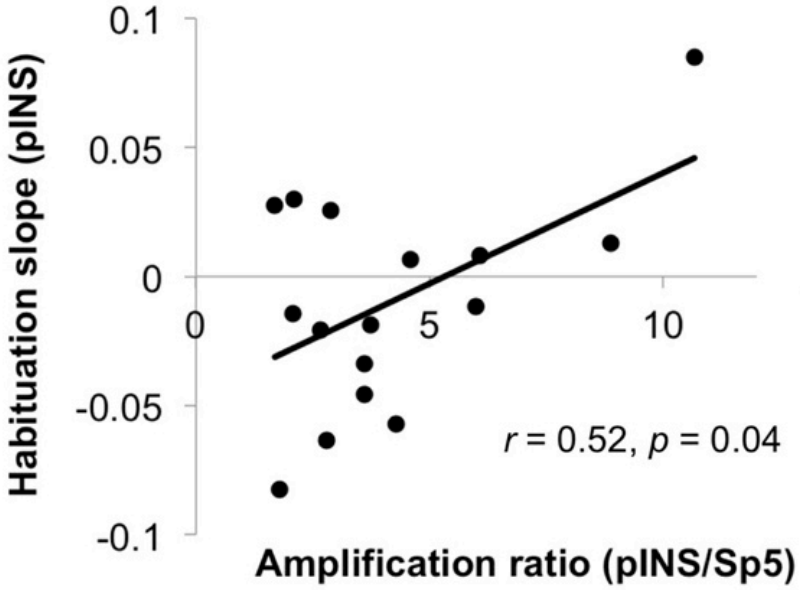




- Each of the 11 stimulation blocks modeled as separate regressors in GLM → assess activation for each individual stimulus block
- Fit linear regression line and contrast slope between MIG and HC
- → *MIG shows reduced habituation in **pIns***
- *Habituation and amplification are linked in pIns and SII*







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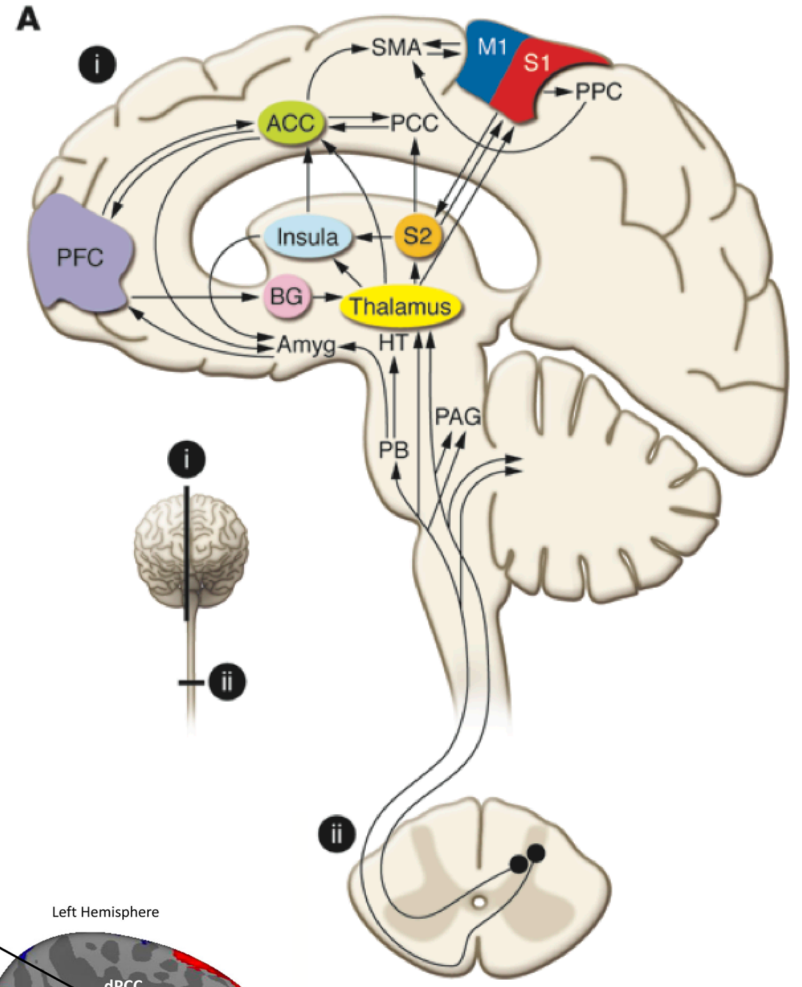
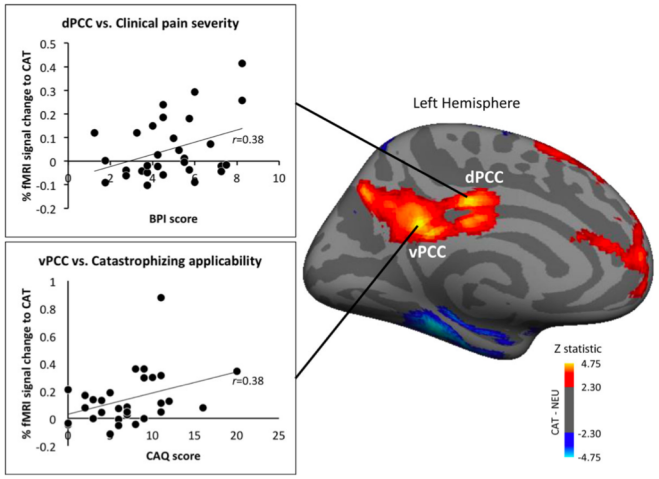
Differentiating central sensitization metrics in the brain with fMRI

- Elevated/altered fMRI response in chronic pain patients to *stimulus-matched* sensory stimuli:
  - *thalamus, S1, S2, anterior insula* (visual too!), *posterior insula, ACC*
- Temporal summation
  - *S1 / anterior insula connectivity*
- Brain amplification from primary synapse (e.g. Sp5)
  - *posterior insula, hypothalamus*
- Reduced habituation
  - *posterior insula*
- *These responses may be mediated by other pain processing regions: e.g. mPFC, PCC ← linked to pain catastrophizing*





Lee et al., A&R, 2018

Conclusions

- Central sensitization, once considered purely a spinal cord phenomenon, is clearly noted in multiple brain responses, including primary somatosensory cortex, S1
- Different aspects of central sensitization (i.e. *CPM, temporal summation, gain, habituation, receptive fields*) can be assessed via different fMRI methods and supported by differential brain circuitries
- Future directions: Novel experimental designs and analysis methods needed to better assess the brain circuitry associated with central sensitization in chronic pain

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