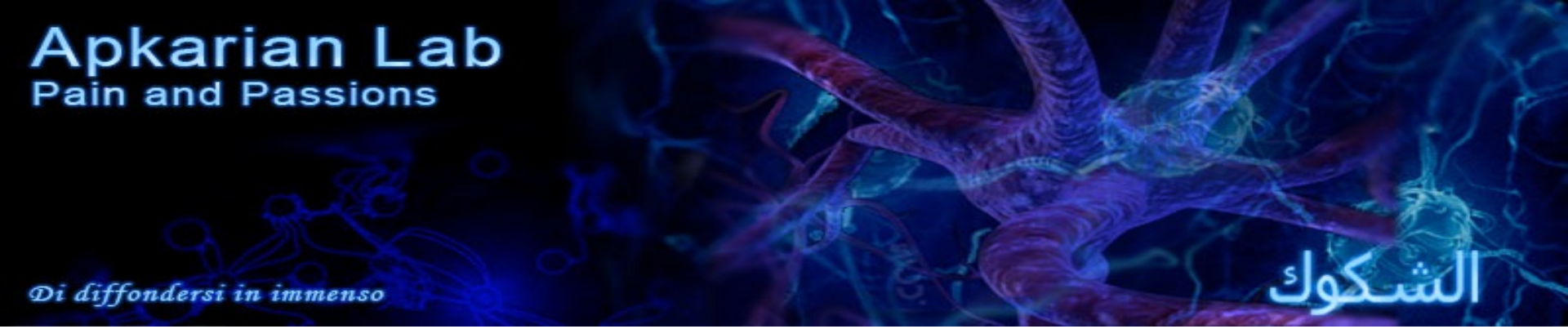


A four-phase model for chronic pain

A. Vania Apkarian, PhD

Chronic Pain Symposium January 22, 2021
Hanscom et al.

Acute vs. chronic pain?

1. Acute pain = Sensation, behavior

2. Chronic pain = ?
   = Pain that persists after healing of injury

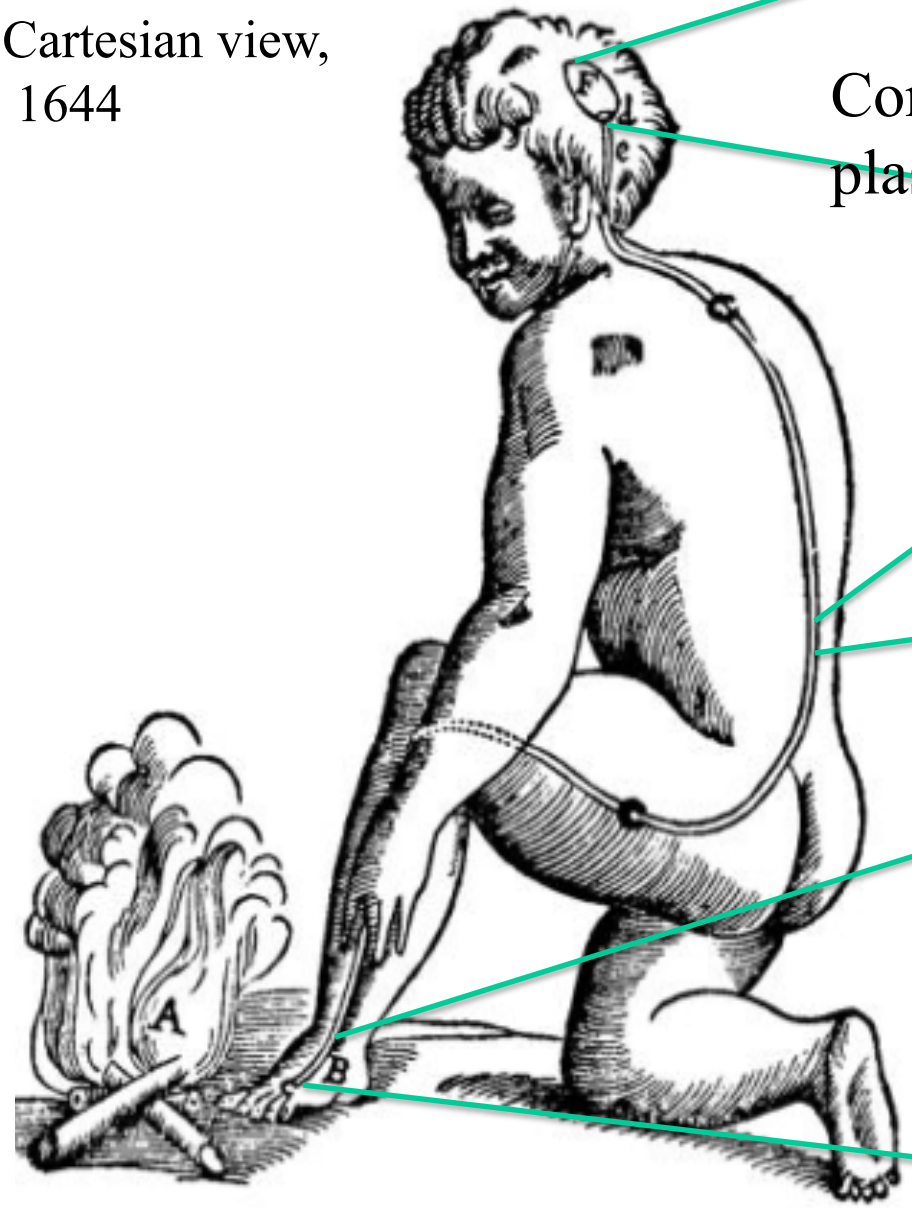
3. 20% of world population suffers from chronic pain

4. Treatments do not exist.

   It is “managed” at very high cost, major contributor to current opiate epidemic

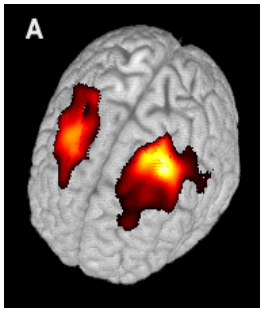
Acute to chronic pain

Cartesian view, 1644

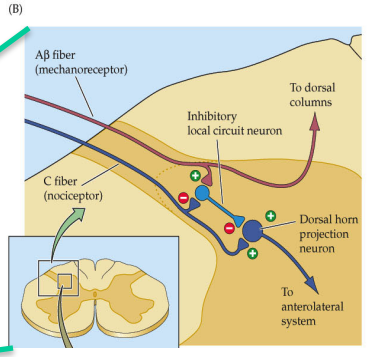


Cortical plasticity



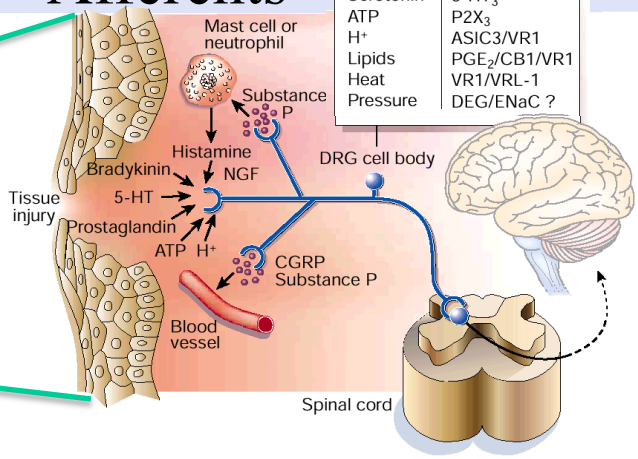


Spinal Sensitization



End Organ Afferents

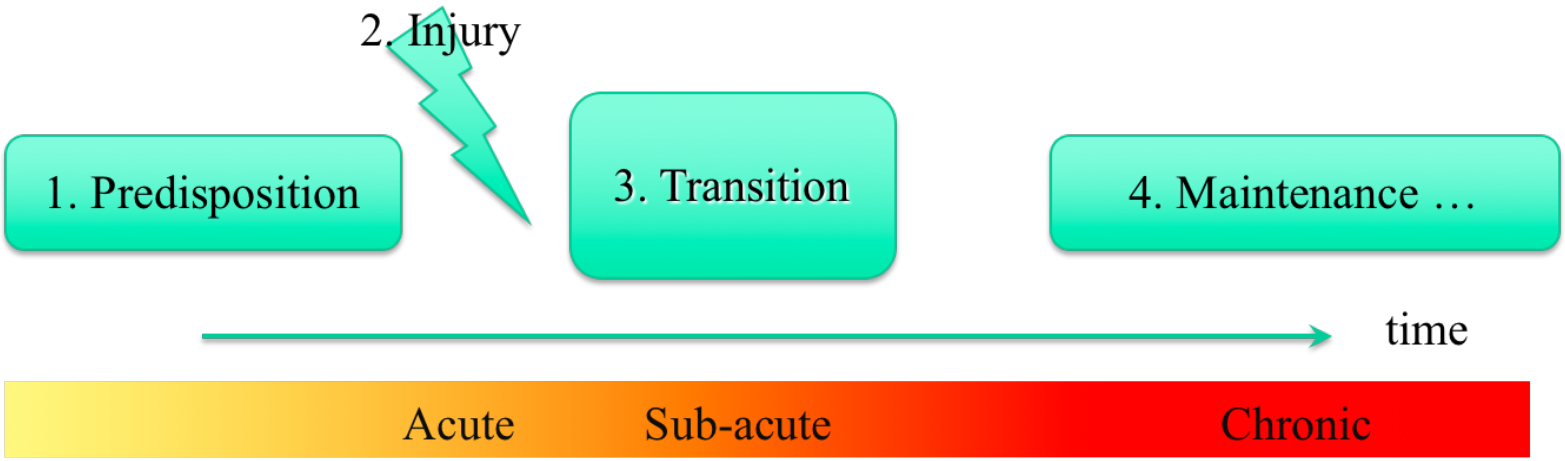
Stimulus	Representative receptor
NGF	TrkA
Bradykinin	BK_2
Serotonin	$5\text{-}HT_3$
ATP	$P2X_3$
H^+	ASIC3/VR1
Lipids	PGE_2/CB1/VR1
Heat	VR1/VRL-1
Pressure	DEG/ENaC ?



Outline:

- We can identify brain mechanisms regarding who will persist and who will recover from pain - prognostic biomarkers
- Rodent studies provide complimentary mechanistic evidence

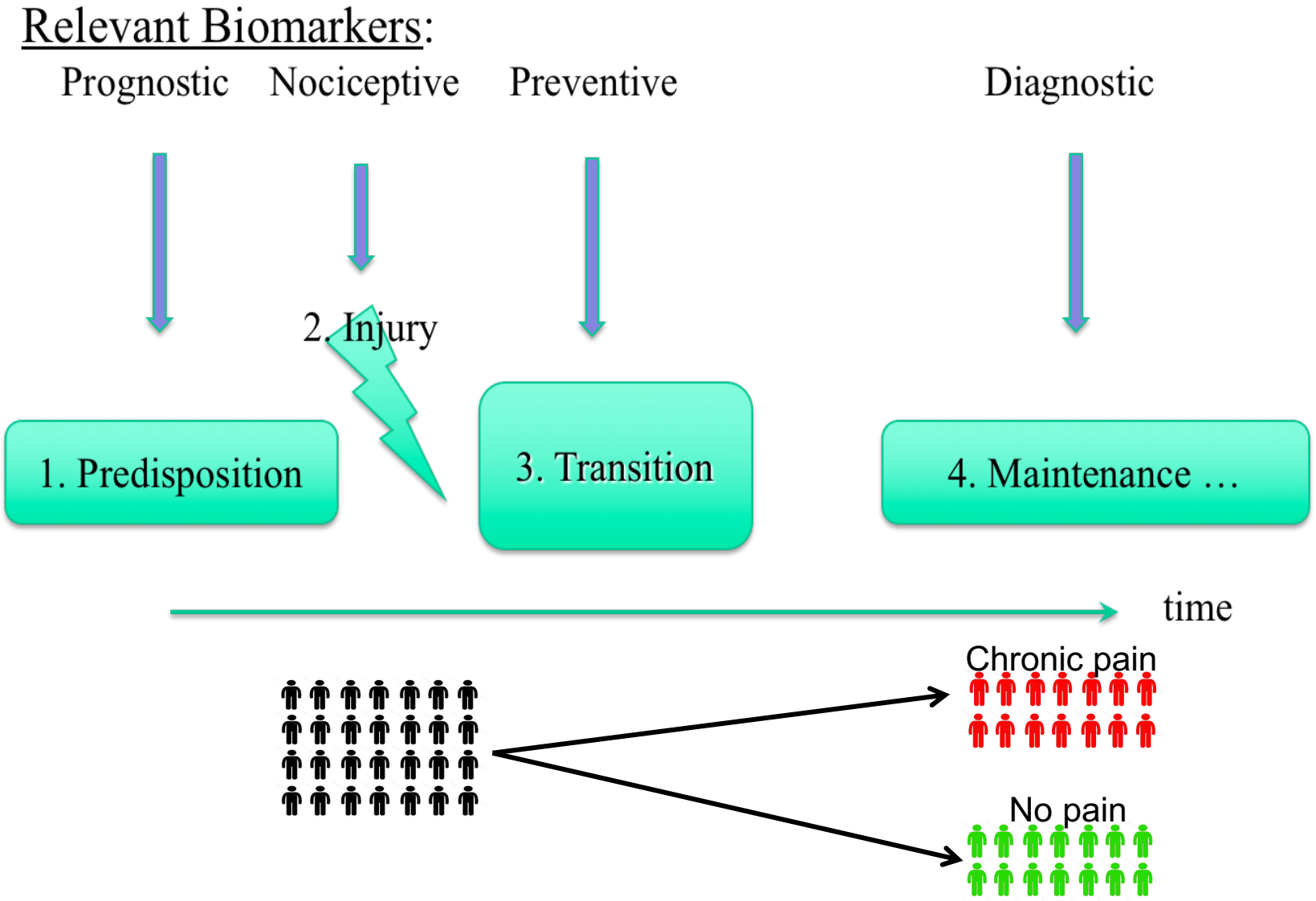
Distinct stages for chronic pain



The traditional view is that all stages are explained by nociceptive circuitry: primary afferents and spinal cord circuits

Our overall view: Limbic-emotional circuitry define risk (1), and emotional-learning underlies transition (2). Moreover, chronic pain (4) is a new brain state with distinct anatomical and functional properties.

Distinct stages for chronic pain define specific biomarker types with associated mechanisms



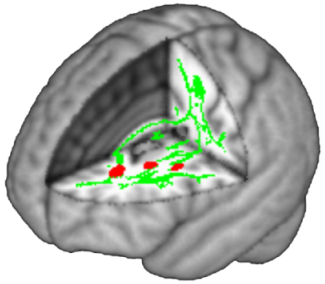
Four distinct stages for chronic pain

2. Injury

1. Predisposition

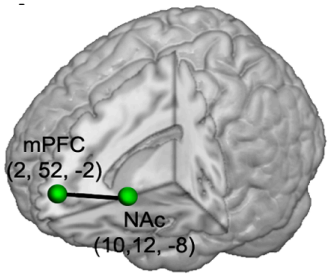
3. Transition

4. Maintenance …

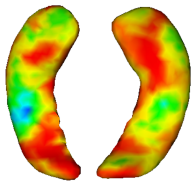


WM vulnerability

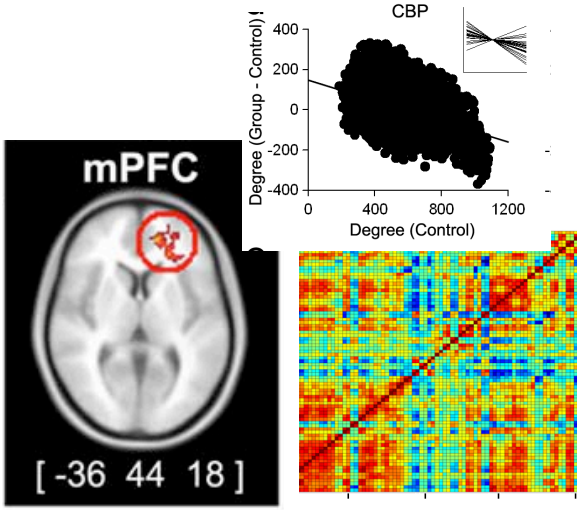
3 = 1 + 2
+ mesolimbic learning



mPFC-NAc



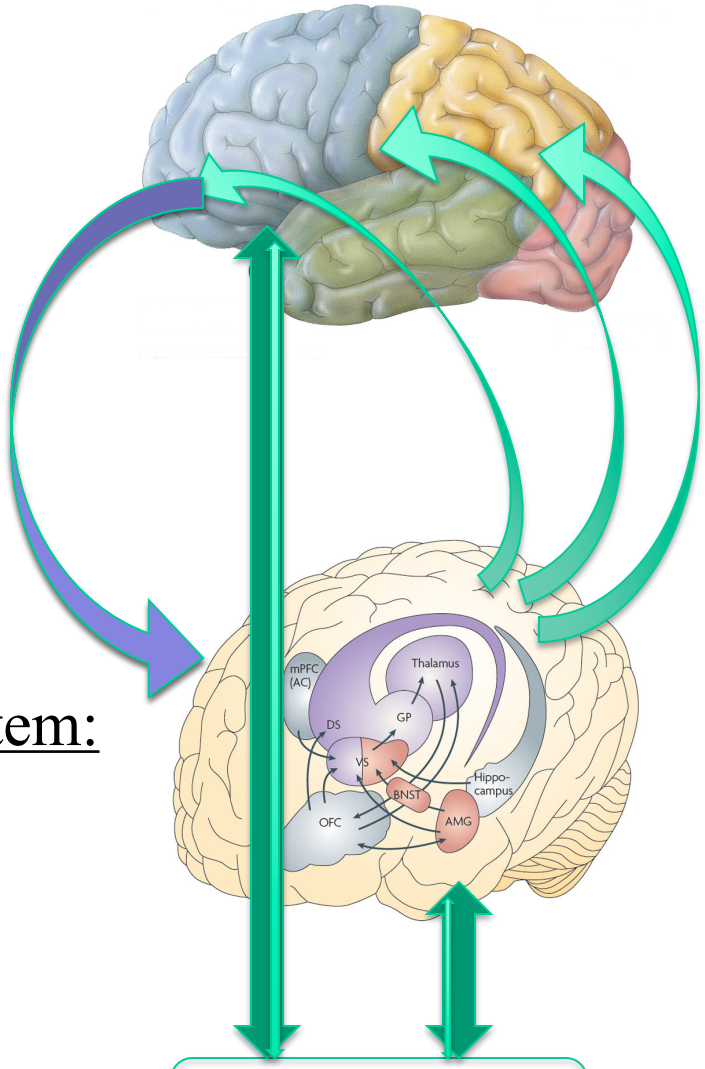
Limbic
Structures
+ Genes



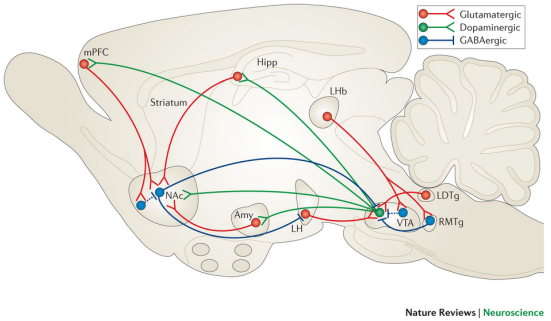
Cortical reorganization
Emotional pain state

Pain relief is shows gender by treatment interaction
Back pain is completely relieved in females with LDP+NPX

Activation
Of emotional
Learning



Emotional
learning signal
(Hipp, Amyg, Nac)

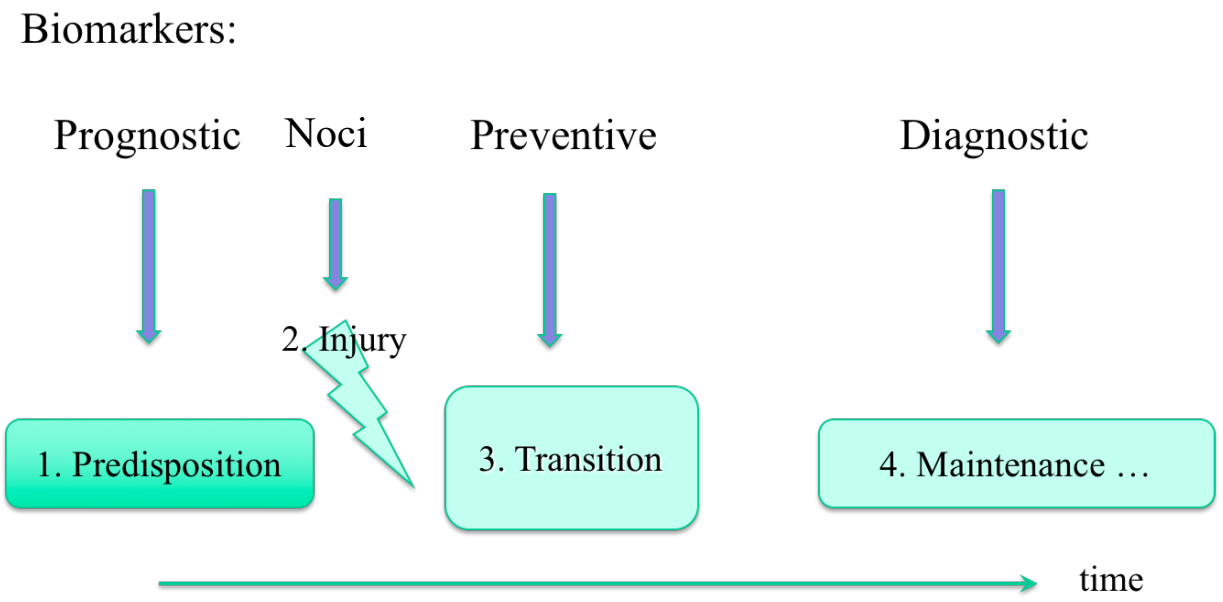


<u>Mesolimbic system:</u>
Reward,
Addiction,
Negative moods,
Chronic pain

Nociception

Injury

Prognostic biomarkers for chronic pain



- Pre-existing risk
- Predictive of transition to chronic pain, therefore, CAUSAL
- Validated
- Reveals underlying mechanisms
- Invariant while pain changes in time

2. Injury

1. Predisposition

3. Transition

4. Maintenance …

time

Acute Sub-acute Chronic

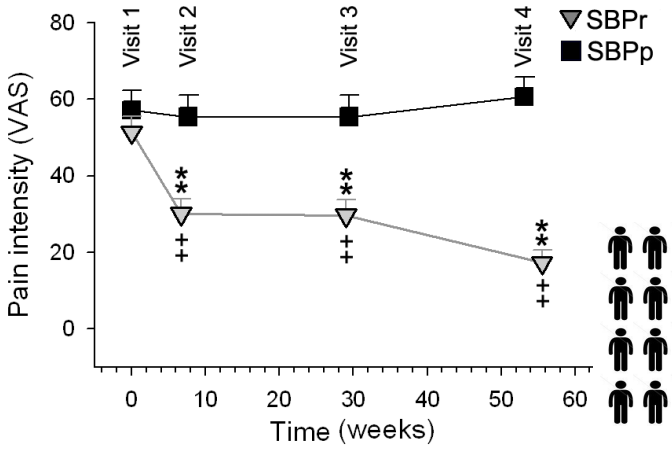
visit 1
time 0

visit 4
55 weeks

Predisposition

Persisting (SBPp)

Recovering (SBPr)



Chronic pain

No pain

2. Injury

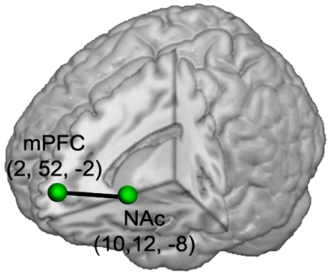
1. Predisposition

3. Transition

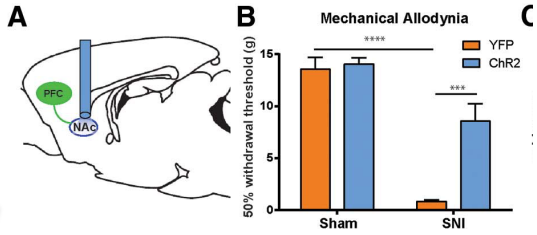
4. Maintenance …

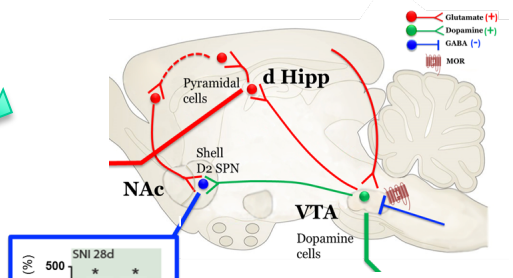
3 = 1 + 2

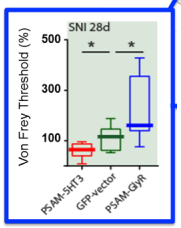
+ mesolimbic learning



mPFC-NAc







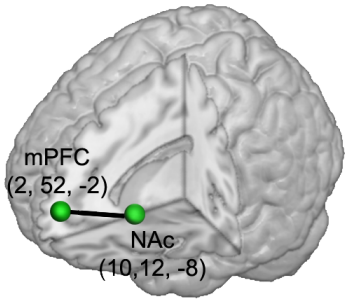
Chronic pain

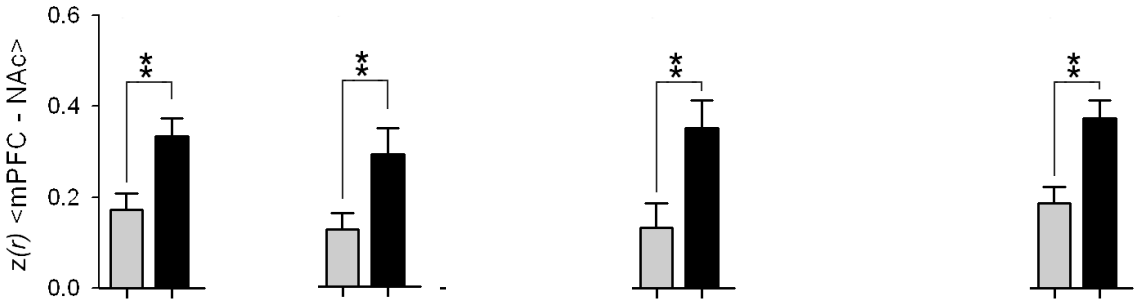
= brain becoming addicted to nociceptive inputs

Baseline | Acute | Sub-acute | Chronic

visit 1 (time 0) → visit 2 (7 weeks) → visit 3 (30 weeks) → visit 4 (55 weeks)

Functional connectivity

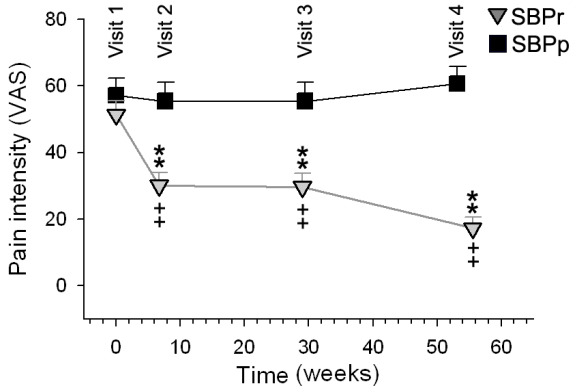




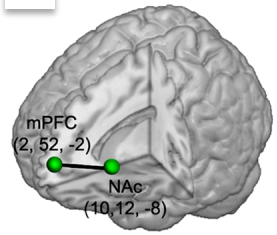
SBPr SBPp

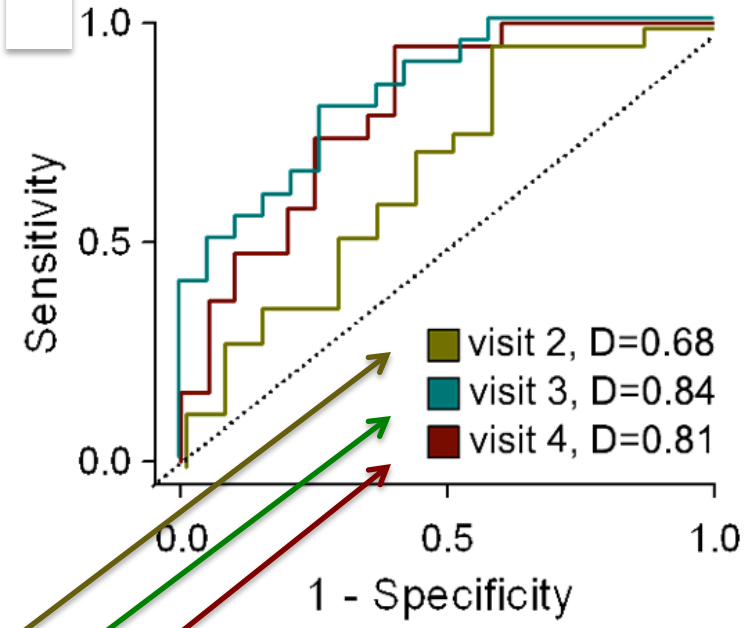
Post-hoc

Unbiased

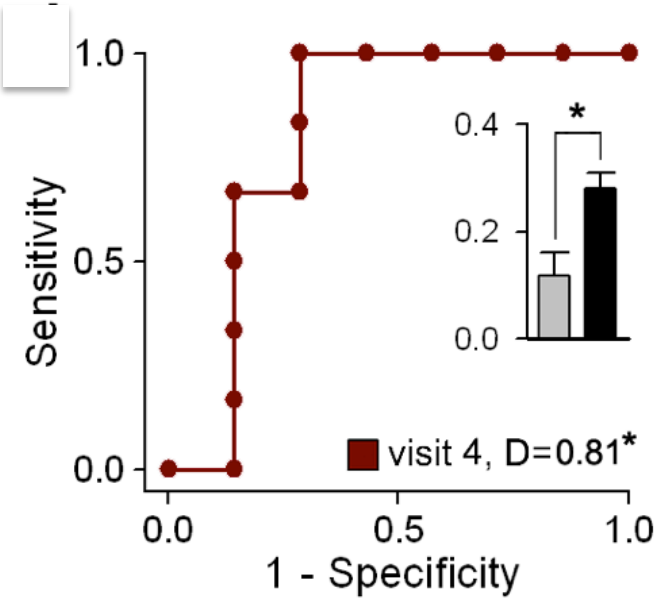


NAc-mPFC ~80% accurately PREDICTS pain chronification





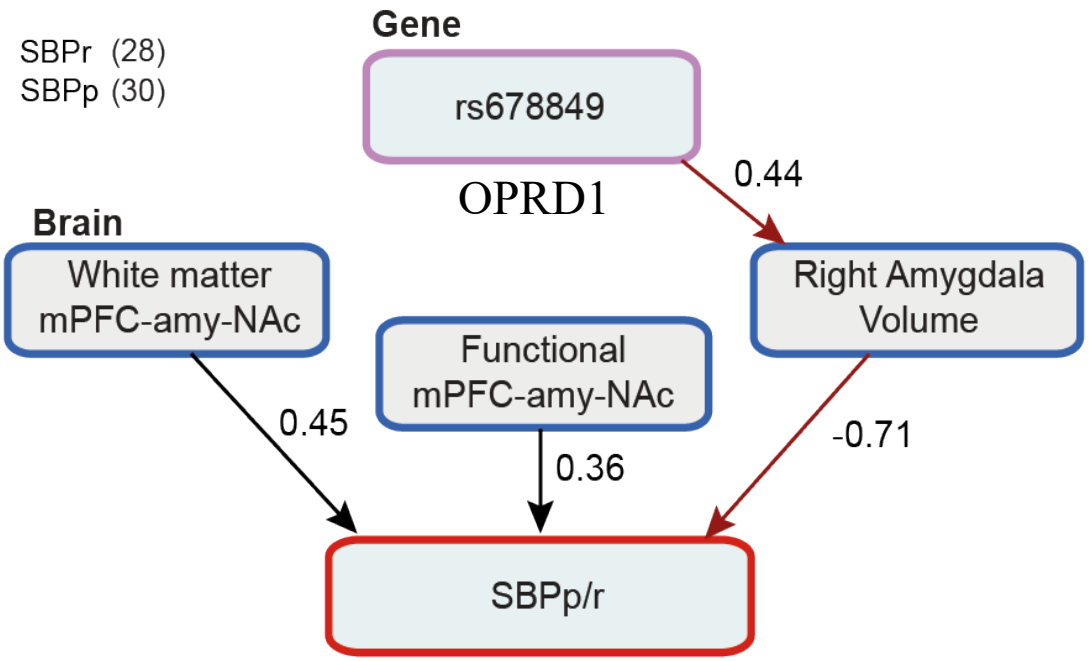
3 months
6 months
1 year



Validation cohort

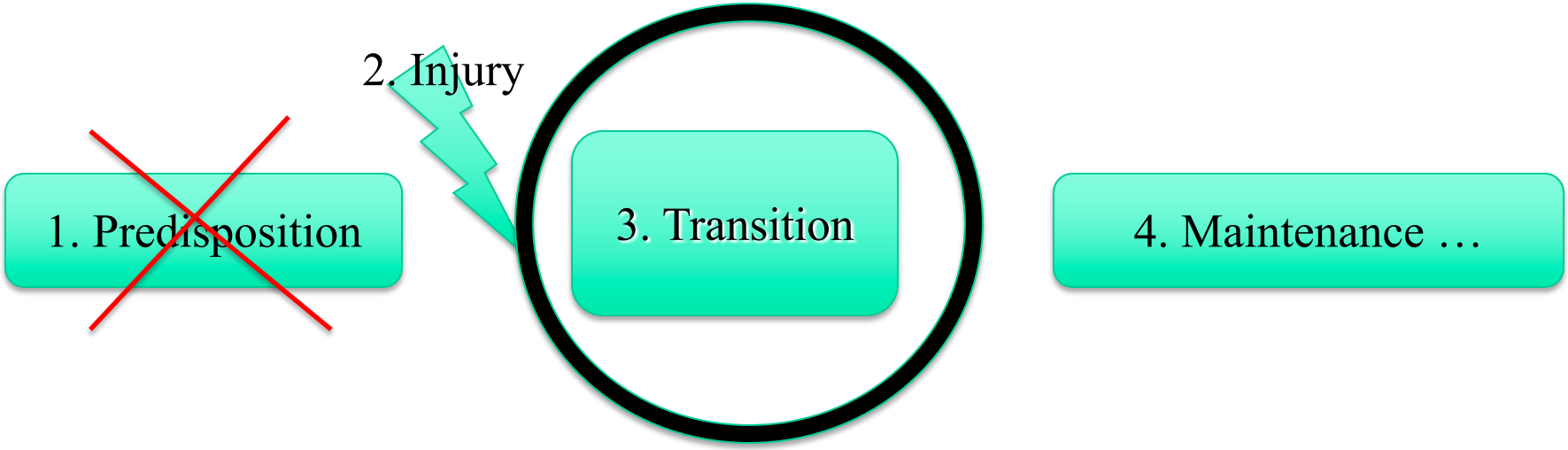
Full model for PREDICTING development of chronic pain at 1 year based on brain values observed within weeks after start of back pain

(Gene contribution ~5%)



Model predicts 60% of outcome variance

Rodent models for chronic pain



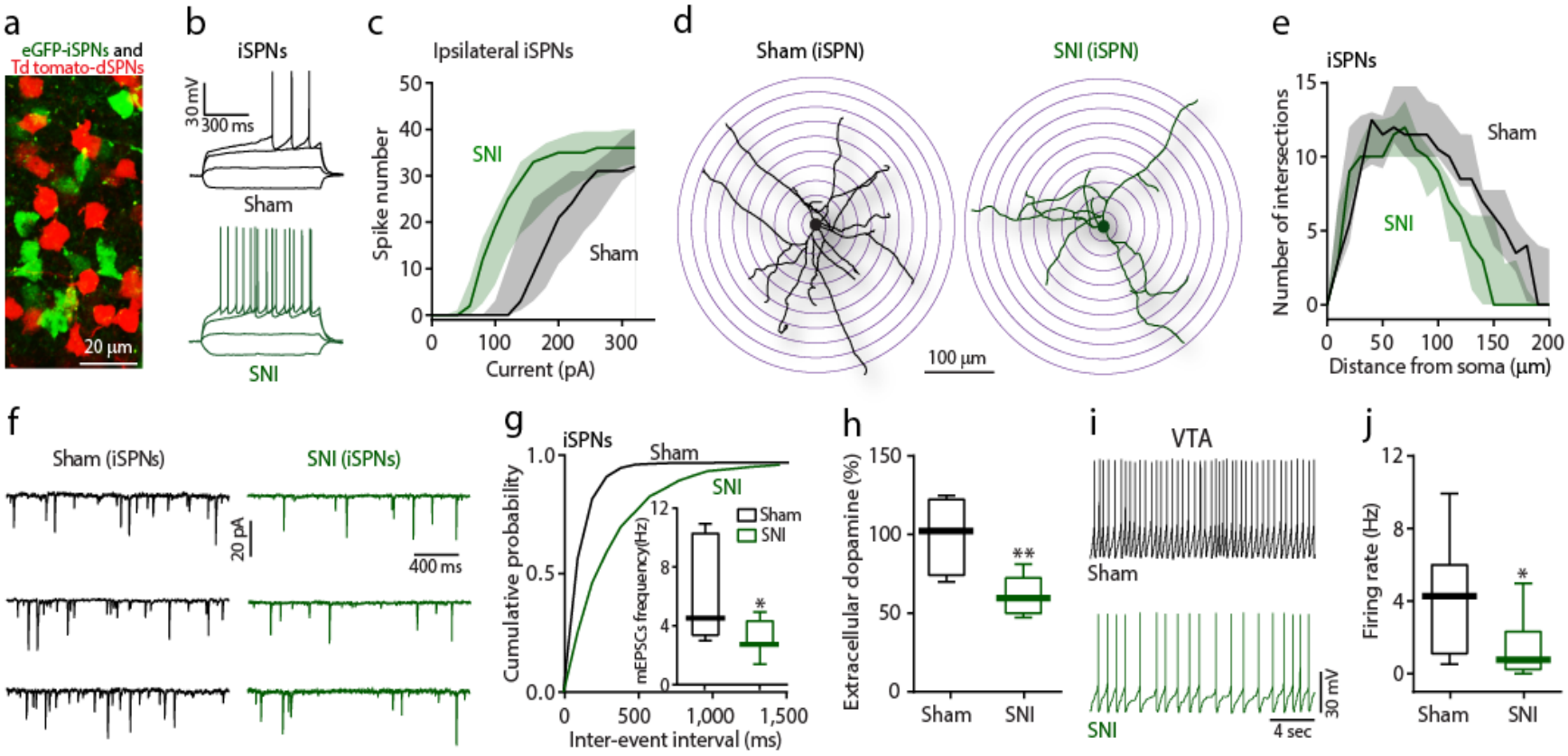
Rodent models of neuropathic pain, spared nerve injury (SNI), show strong parallels to the human chronic pain regarding limbic circuitry in transition to chronic pain:

1) Functional reorganization
2) Causal role of medial shell Nac neurons

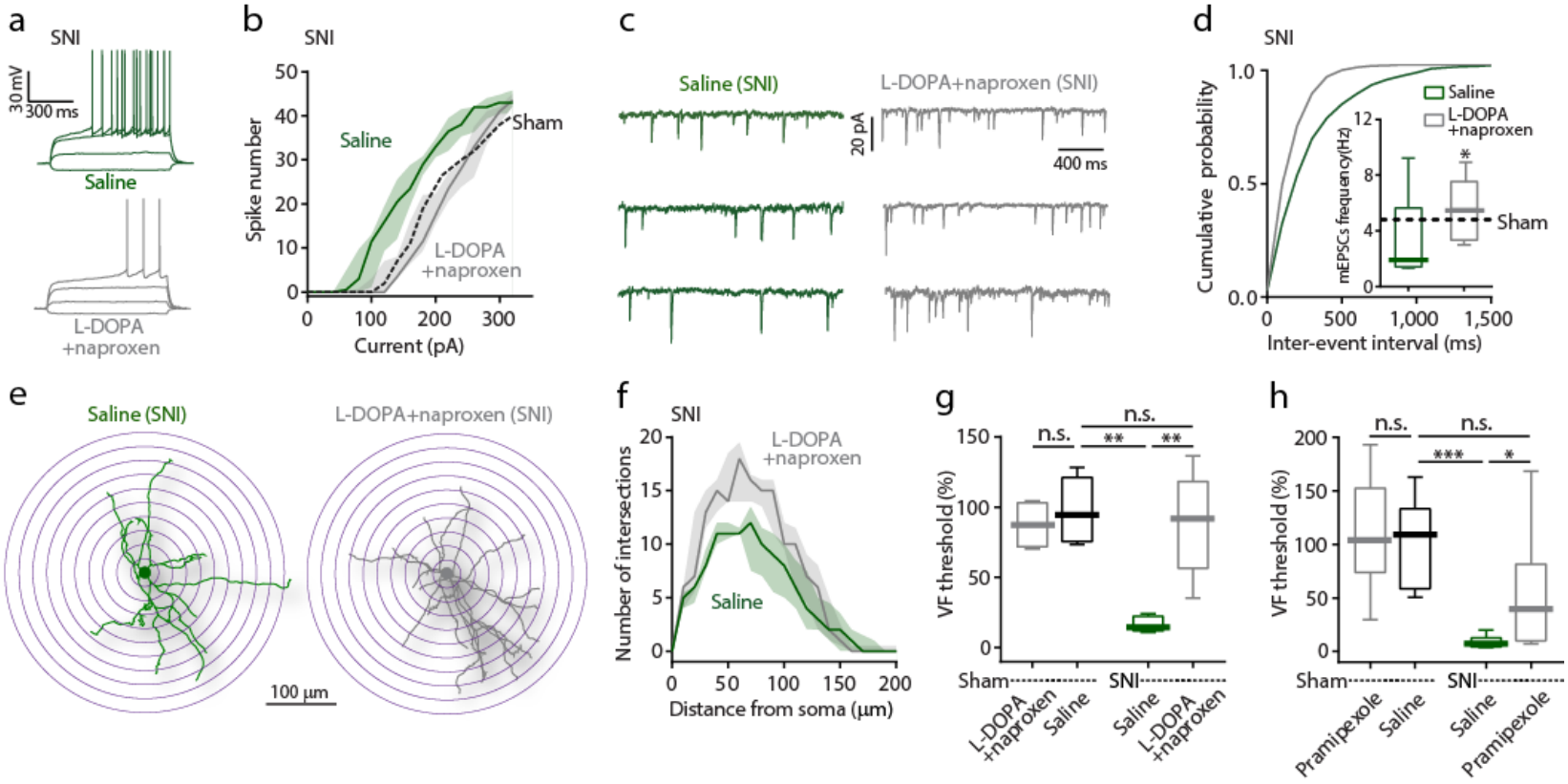
Excitability & morphology of Nac shell D2 neurons modulated within days from peripheral nerve injury (patch clamp recordings)



Wenjie Ren

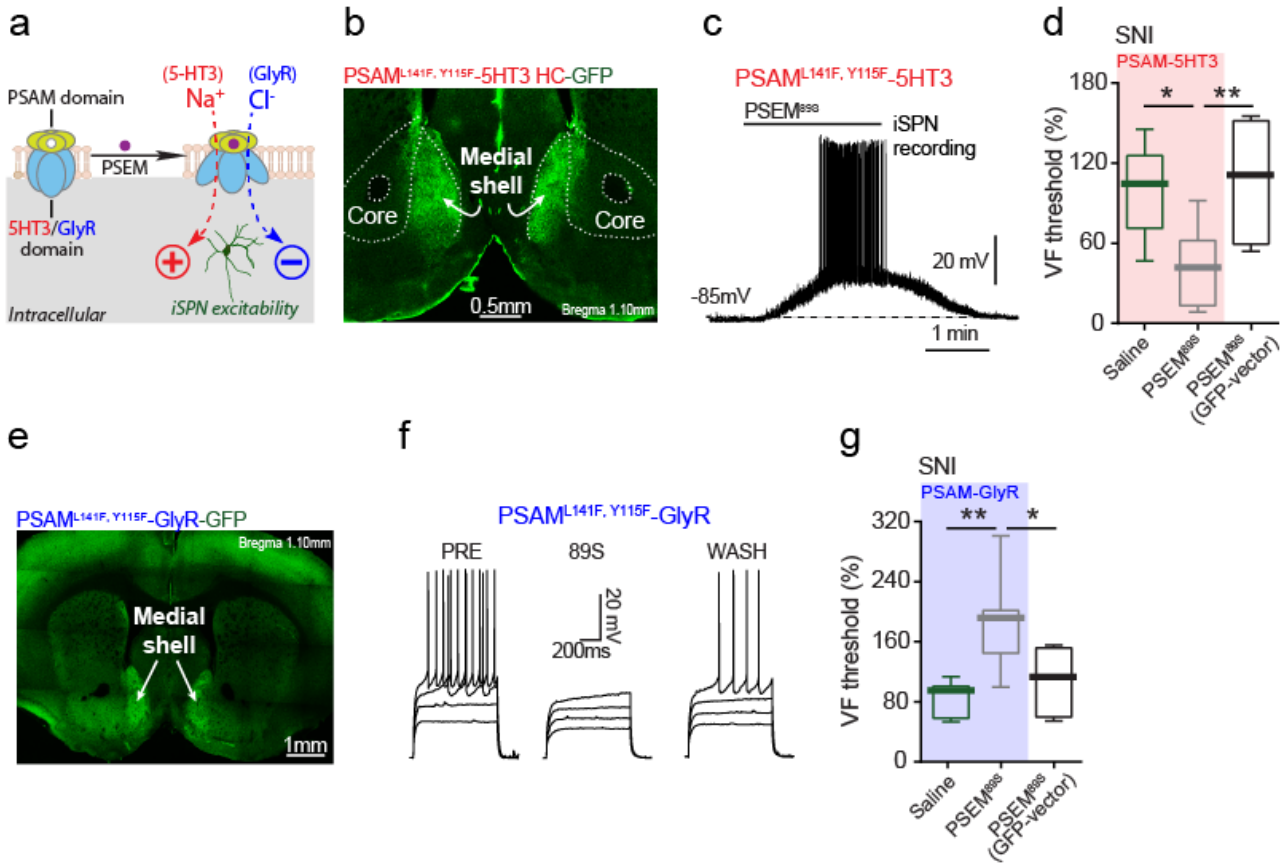


Proper treatment can reverse pain, excitability & morphology of Nac shell D2 neurons in peripheral nerve injury animals



Nac shell D2 indirect-pathway controls neuropathic pain behavior

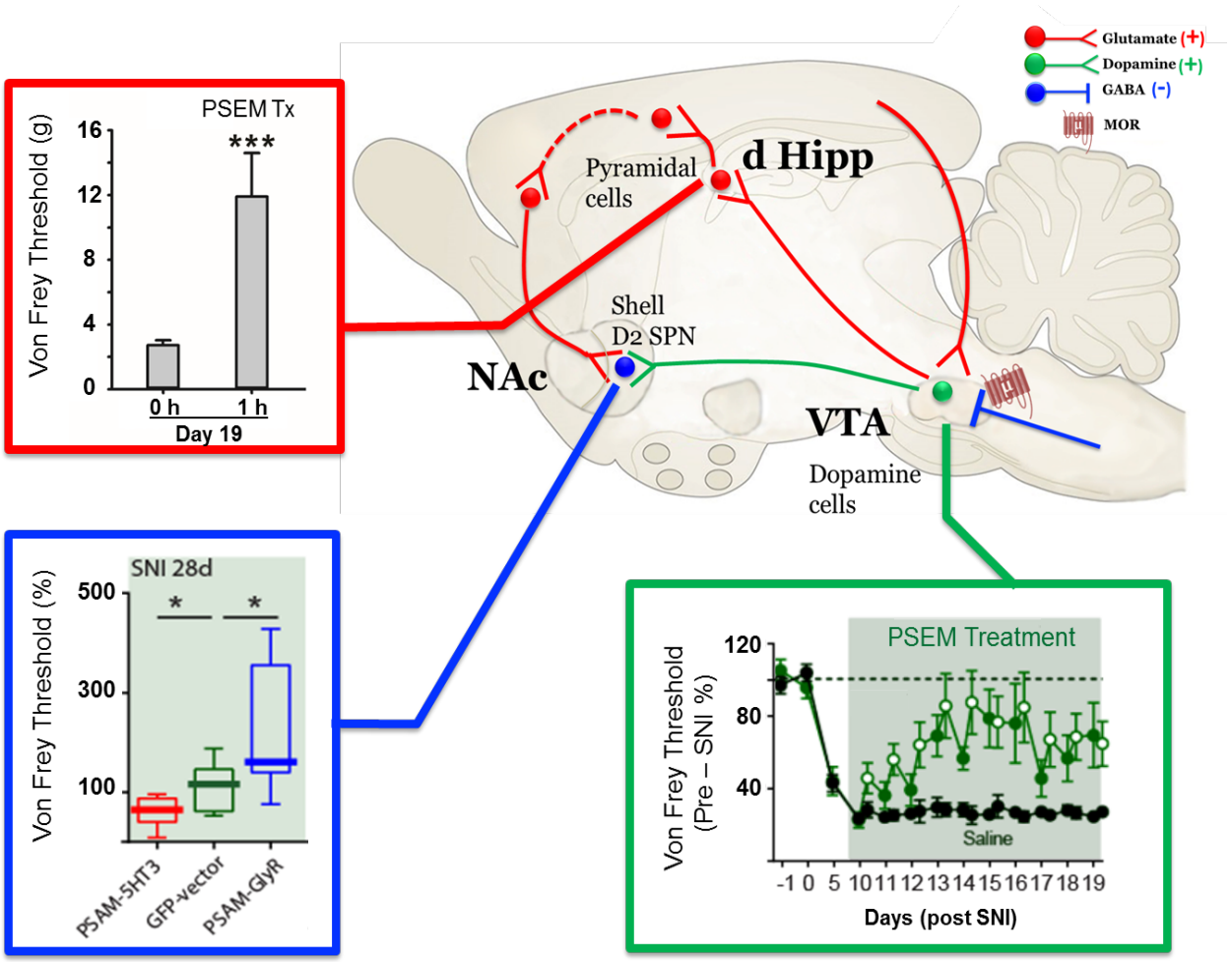
Chemogenetic modulation of shell iSPNs on von-frey thresholds in SNI animals



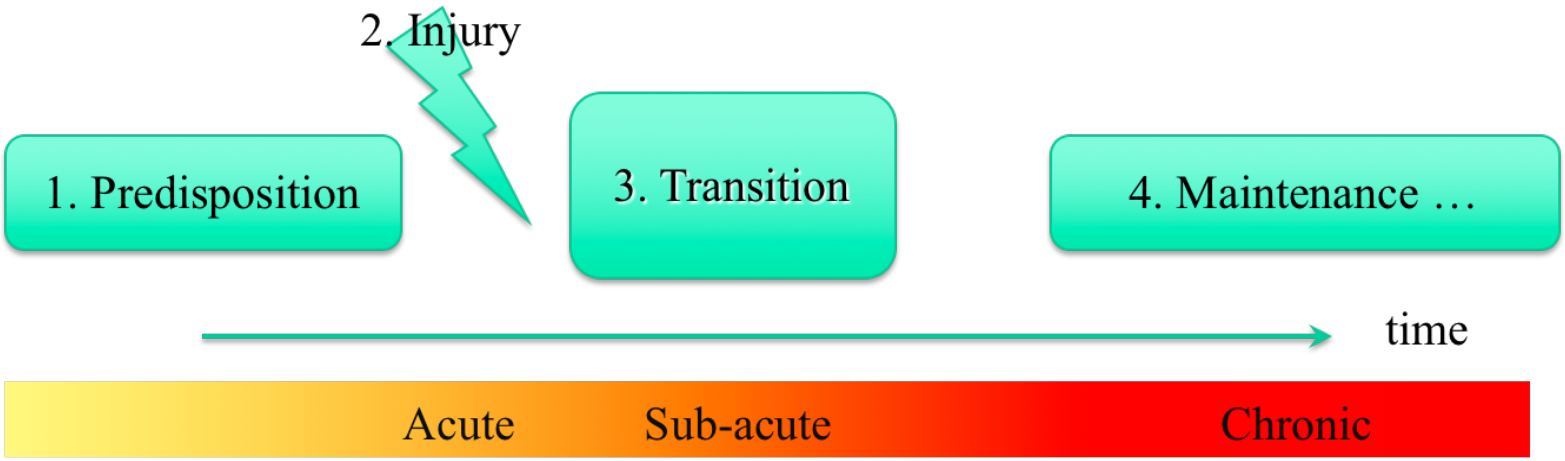


Wenjie Ren

Chronic pain can be CAUSALLY controlled from multiple limbic circuits



Distinct stages for chronic pain



Critical Qs re different types of chronic pain:

Does (1) involve distinct circuits?

(2) Is usually different.

Relative contributions in 1+2 = 3 likely different

(4) Includes both distinct and common brain consequences.

Nociceptive inputs must always be included as they define the somatic referral of the suffering (headache vs backpain).

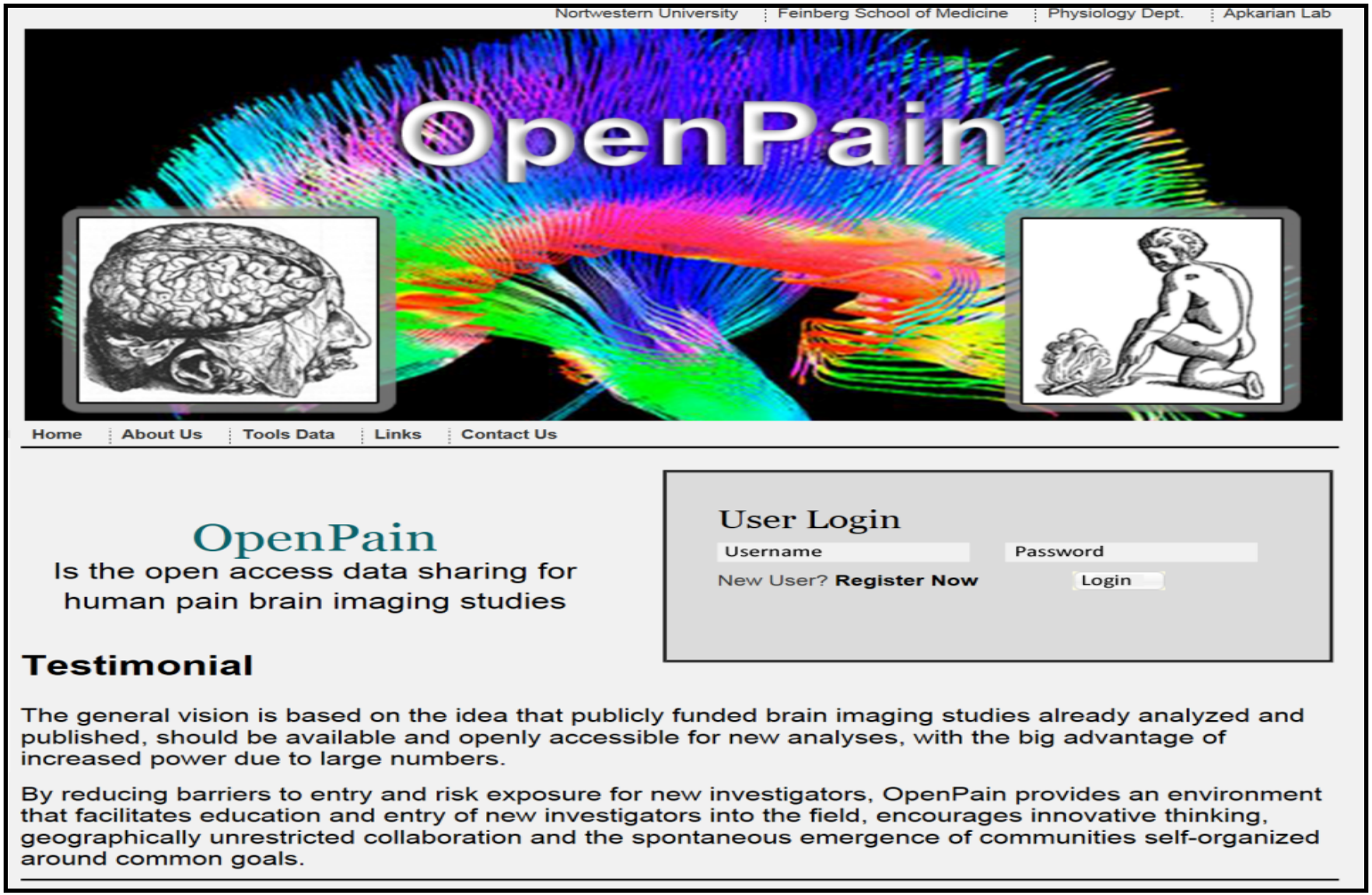
Summary

- Brain imaging has revolutionized concepts regarding pain, especially for predicting persistence of pain.

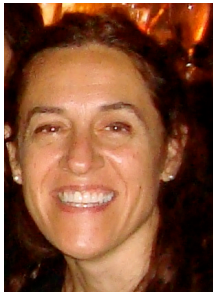
- Risk for chronic pain is a neurological property.

- Chronic pain is a new anatomical and functional state

Open access shared brain imaging resource:



Center for Pain Translation Research


Centeno

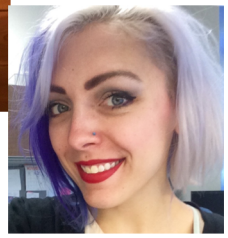

Tom Schnitzer


Marwan Baliki


Mariam Ghantous


Lejian Huang


Bogdan Petre


Sara Berger


Taha Abdullah


Pascal Tetrault


Alex Baria


Wenjie Ren


Chang P.

NIDDK, NIDCR, NCCIH, NINDS, NIDA