

Predictors and a signature of Chronic Pain

A. Vania Apkarian, PhD

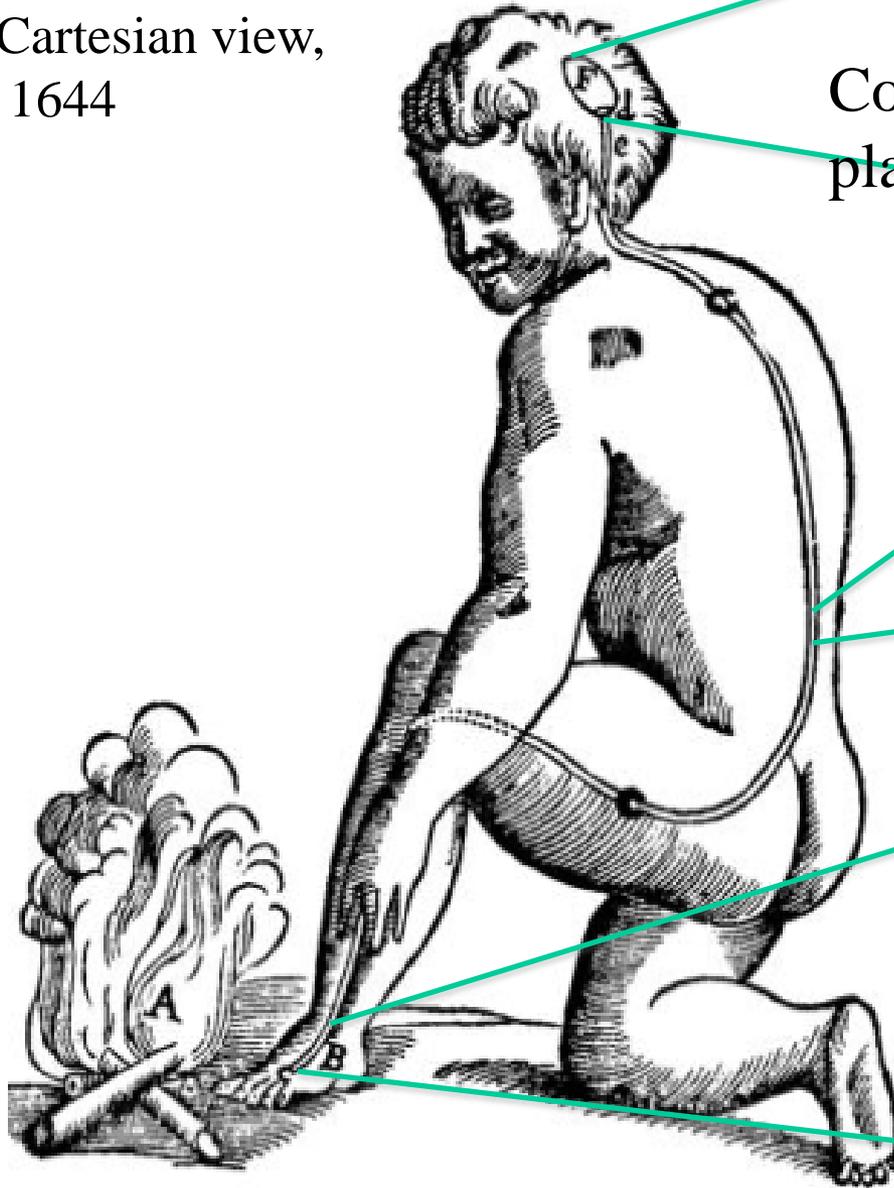
Northwestern University
Chicago, IL

May 27, 2015
PRF, NIH, DC

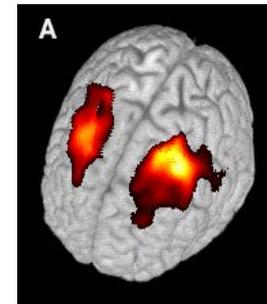


Acute to chronic pain

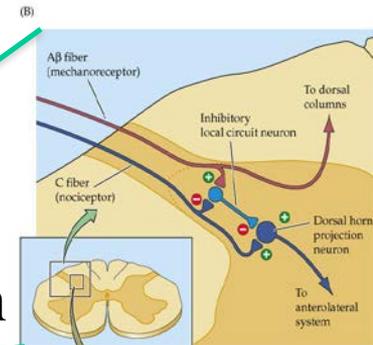
Cartesian view,
1644



Cortical
plasticity

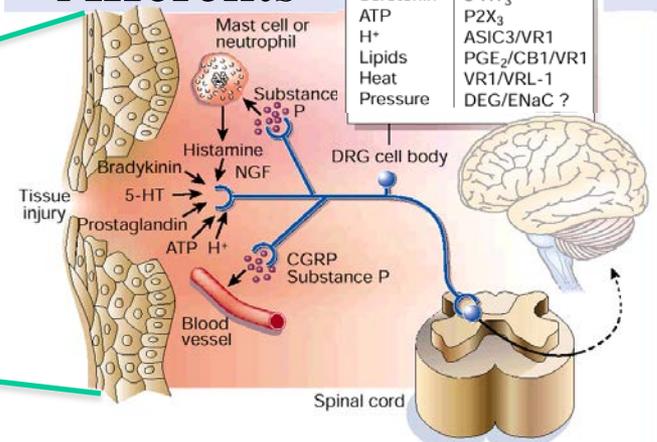


Spinal
Sensitization



End Organ
Afferents

Stimulus	Representative receptor
NGF	TrkA
Bradykinin	BK ₂
Serotonin	5-HT ₃
ATP	P2X ₃
H ⁺	ASIC3/VR1
Lipids	PGE ₂ /CB1/VR1
Heat	VR1/VR1-1
Pressure	DEG/ENaC ?



The CRITICAL question

- End organ MRI predicts only 1% of chronic back pain
- Brain imaging studies are all cross-sectional

The critical question is:

Only a small proportion of subjects with a similar injury develop chronic pain.

Why? How?

Transition from acute to chronic back pain

A longitudinal and cross-sectional, observational study.

Recruit subjects with **acute back pain of 4-12 weeks, with no history of back pain in prior one year, and with back pain >5/10 at entry.**

For one to three years monitor brain parameters.

As back pain patients transition to either recovery or to chronic pain,

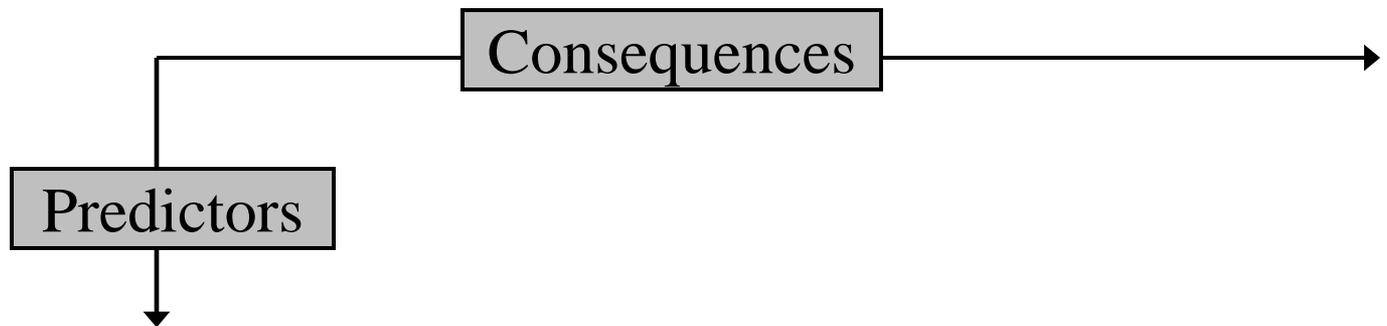
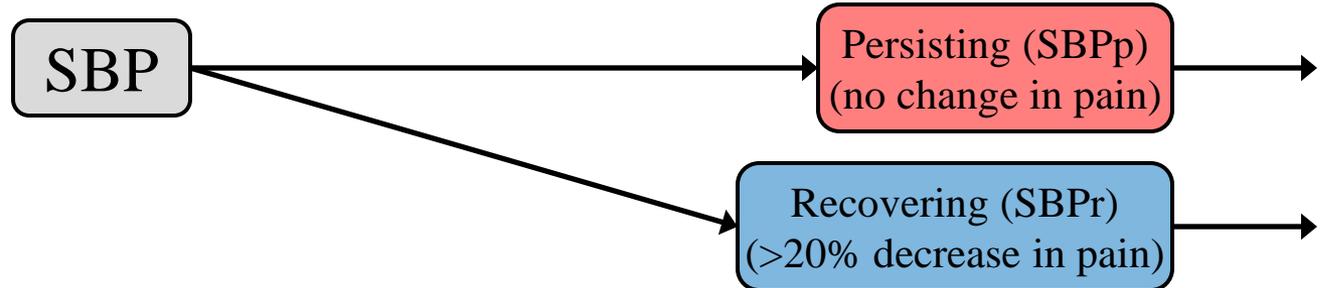
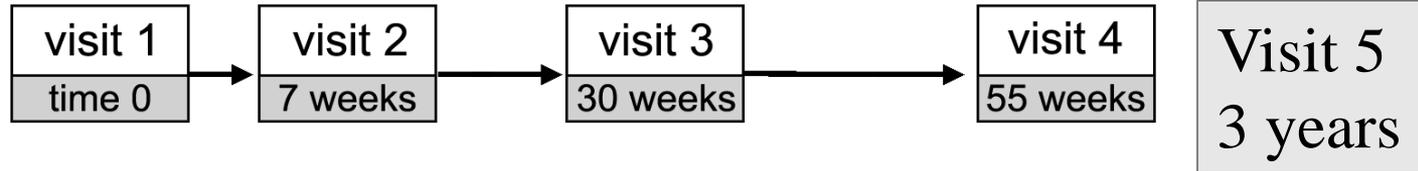
What is the role of the brain?

Baseline

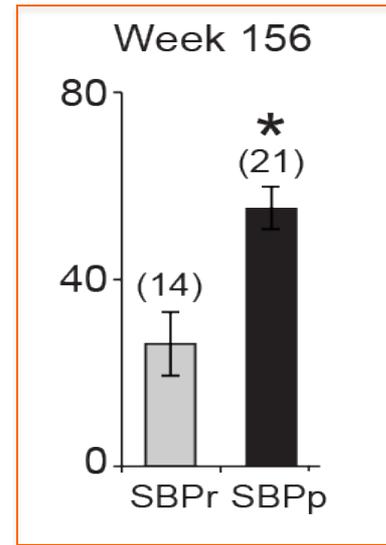
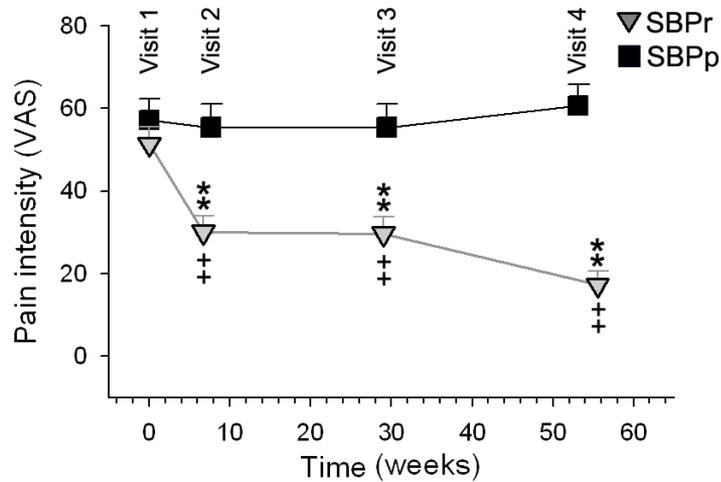
Acute

Sub-acute

Chronic



Clinical pain parameters with transition to chronic pain



	Visit 1		
	SBPp (Mean±SEM)	SBPr (Mean±SEM)	SBPp>SBPr (t-score)
VAS (0-100)	54.1±5.0	51.4±4.2	0.42
MPQ sensory	11.9±1.7	9.2±0.9	1.42
MPQ affective	3.3±0.6	1.6±0.4	2.09*
MPQ radiculopathy'	5.2±0.5	4.1±0.4	0.46
NPS	38.6±5.1	36.2±2.6	1.34
BDI	6.4±1.0	6.7±1.3	-0.83
PANAS positive	33.4±1.7	29.1±2.5	1.41
PANAS negative	22.5±2.6	22.7±3.1	-0.05

	Visit 4		
	SBPp (Mean±SEM)	SBPr (Mean±SEM)	SBPp>SBPr (t-score)
VAS (0-100)	58.9±5.1	17.2±3.4 ▼	6.73**
MPQ sensory	13.3±1.3	4.8±1.2 ▼	4.50**
MPQ affective	3.5±0.8	0.9±0.4 ▼	2.66*
MPQ radiculopathy'	5.2±0.6	3.9±0.4	2.65*
NPS	44.9±2.1 ▲	14.2±1.9 ▼	5.91**
BDI	9.3±2.1	3.8±0.8 ▼	2.02
PANAS positive	32.5±1.7	35.4±1.6	1.17
PANAS negative	20.4±1.7	14.4±1.1 ▼	2.98**

Baseline

Acute

Sub-acute

Chronic

visit 1

time 0

visit 2

7 weeks

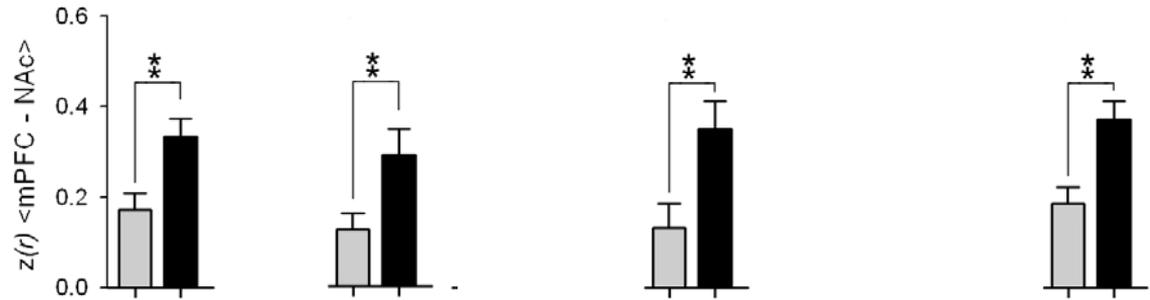
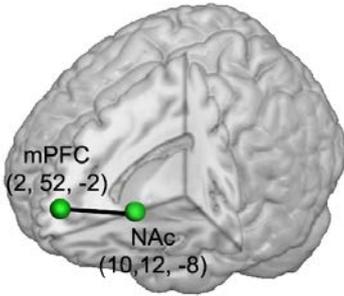
visit 3

30 weeks

visit 4

55 weeks

Functional connectivity



Post-hoc

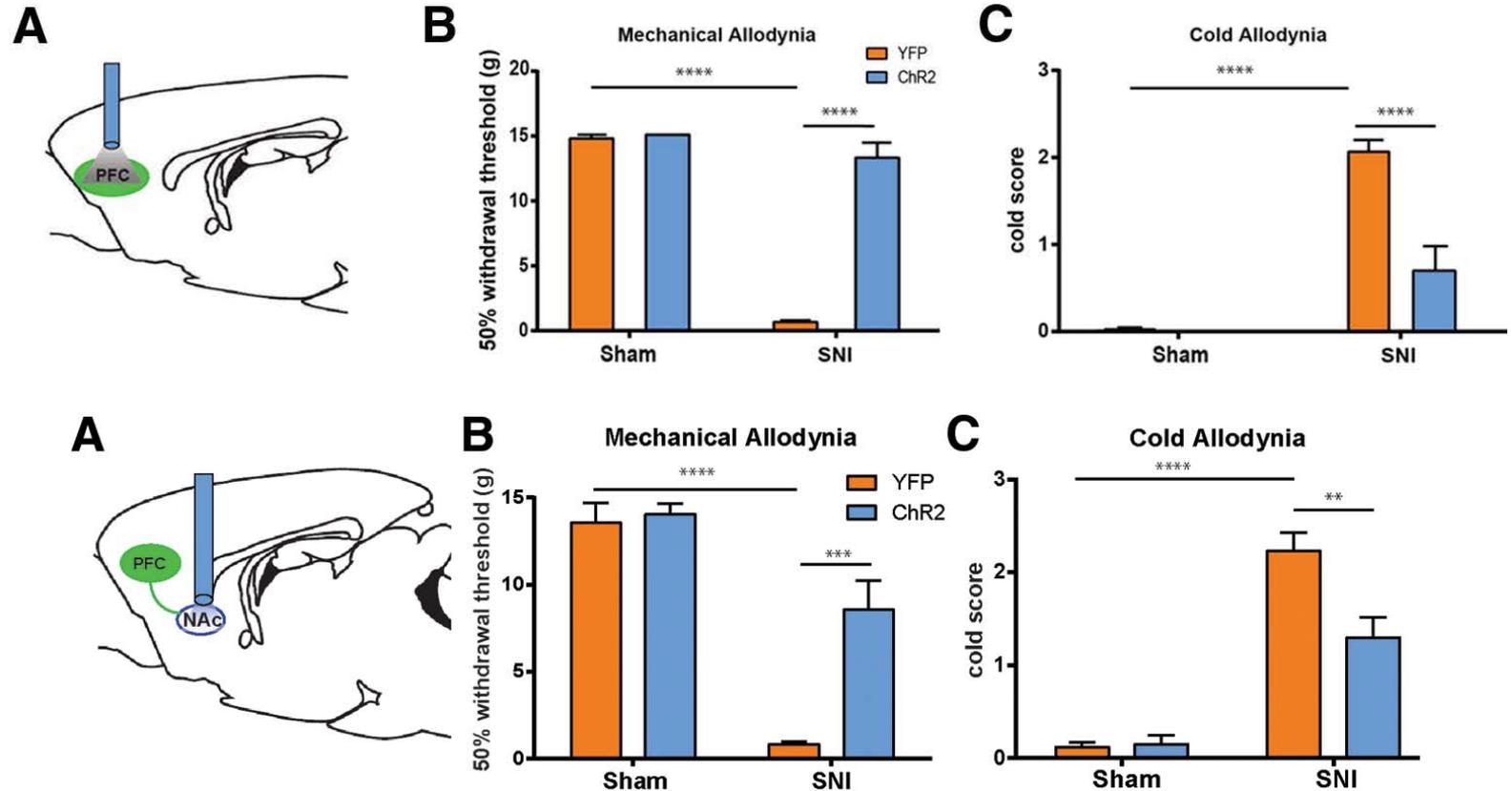
Unbiased

■ SBPr ■ SBPp

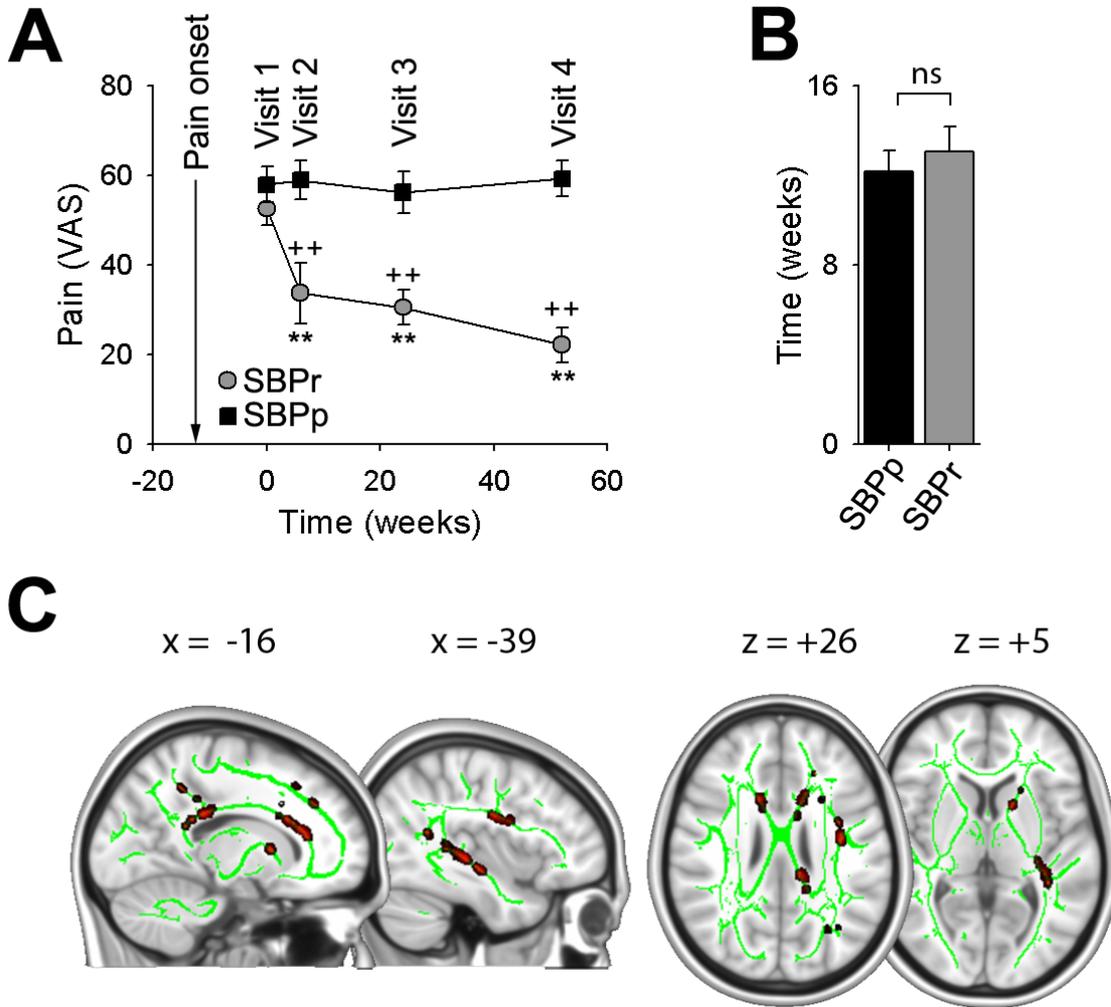
Activation of Corticostriatal Circuitry Relieves Chronic Neuropathic Pain

Lee et al.,

J Neuroscience, April 1, 2015



White matter differences at baseline distinguish SBPp from SBPr



Baseline

Acute

Sub-acute

Chronic

visit 1

time 0

visit 2

7 weeks

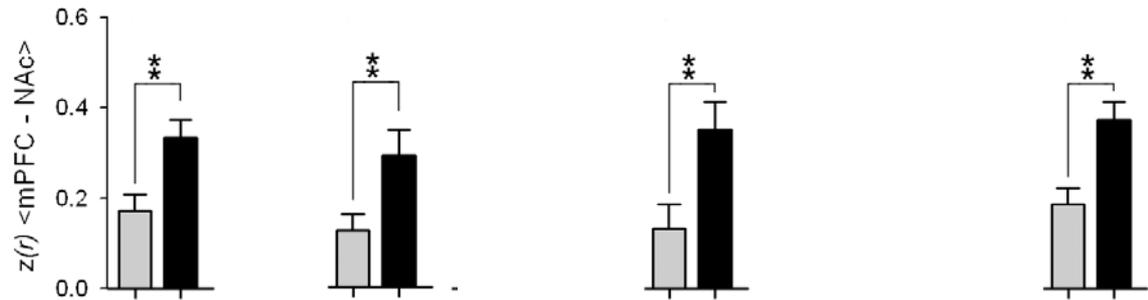
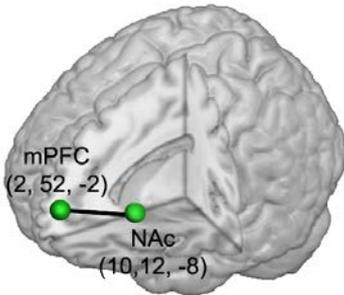
visit 3

30 weeks

visit 4

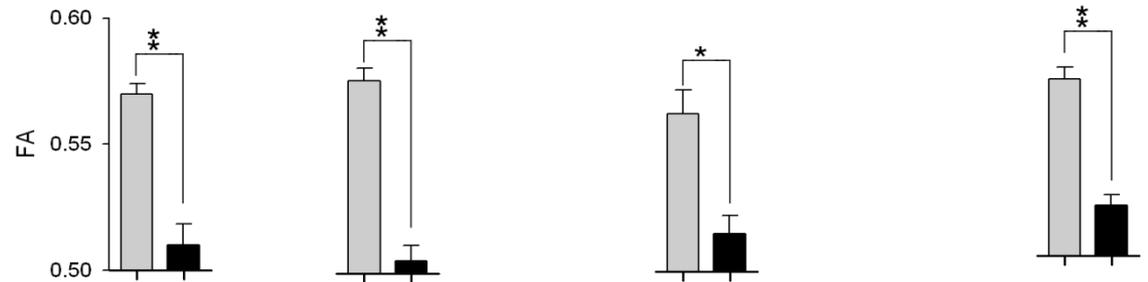
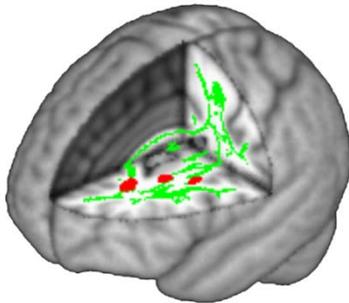
55 weeks

Functional connectivity

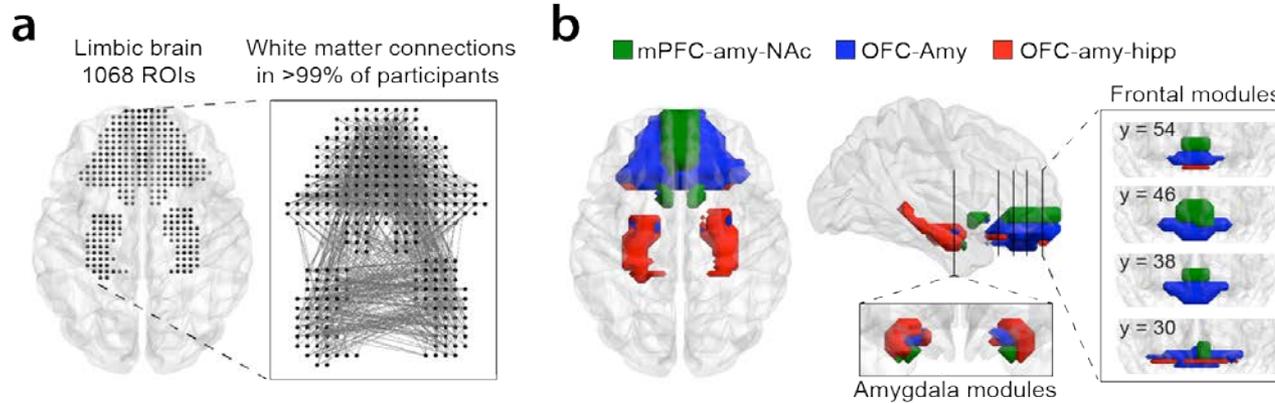


■ SBPr ■ SBPp

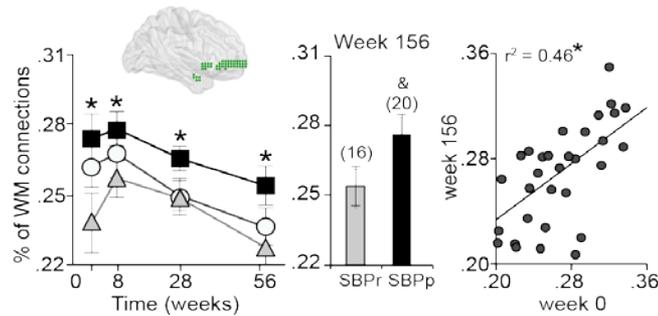
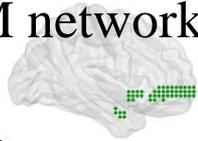
White matter diffusivity



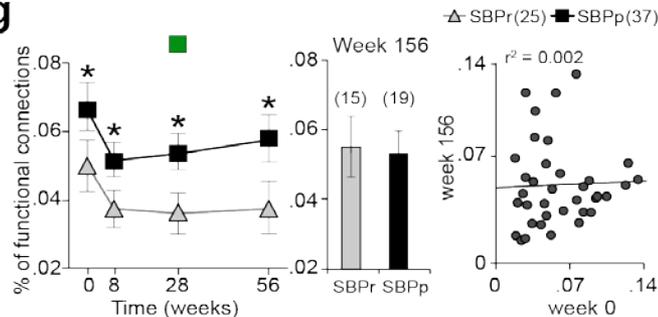
Limbic-brain white matter network clusters to 3 communities: mPFC-Nac-Amy white matter and functional connectivity distinguishes SBP groups



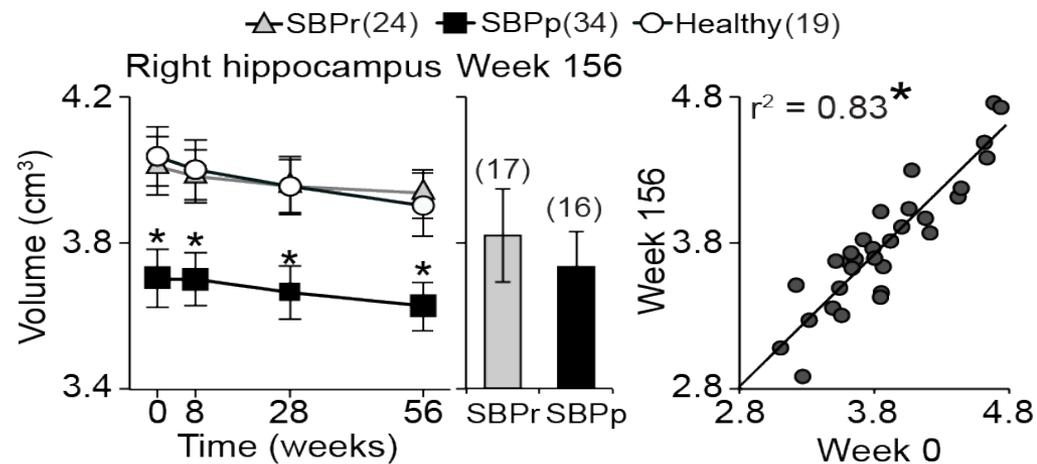
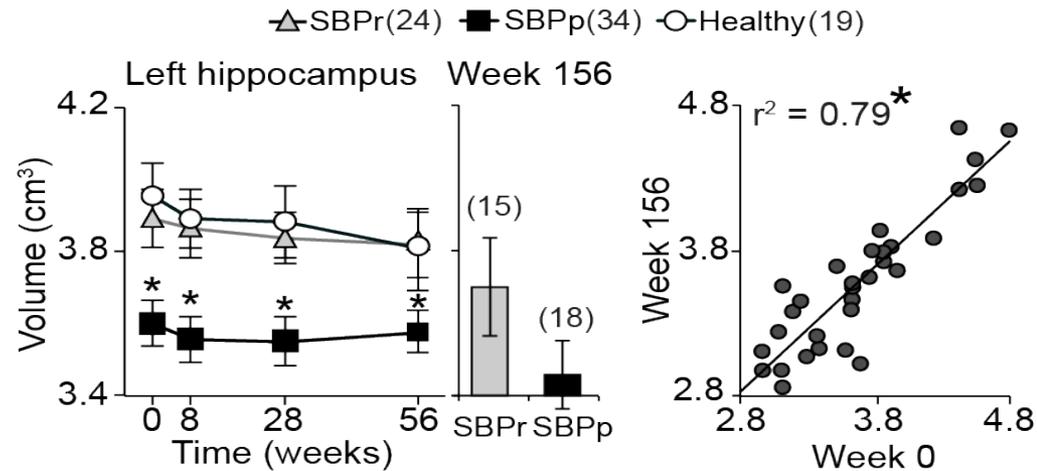
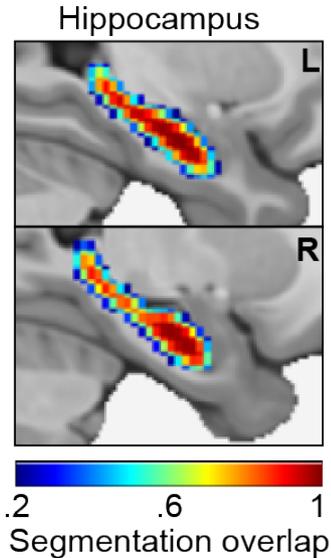
mPFC-Nac-Amy
WM network



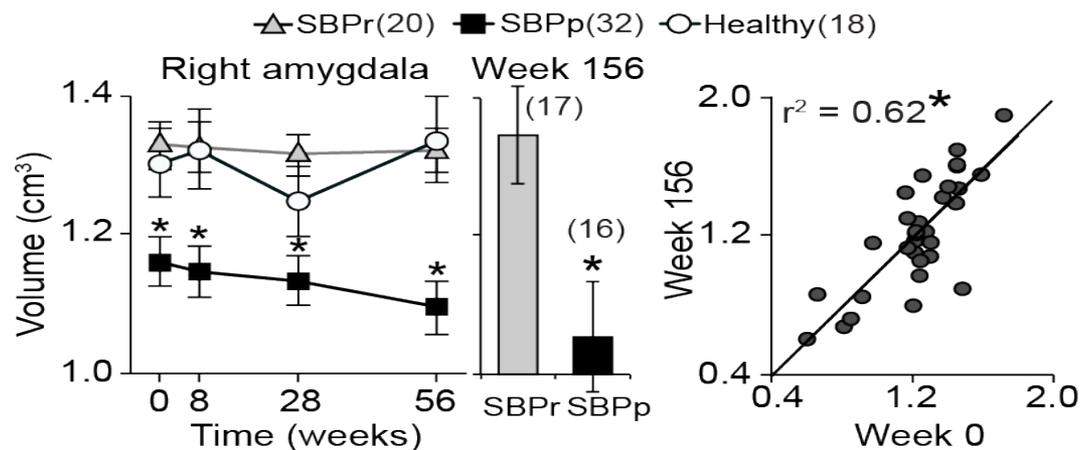
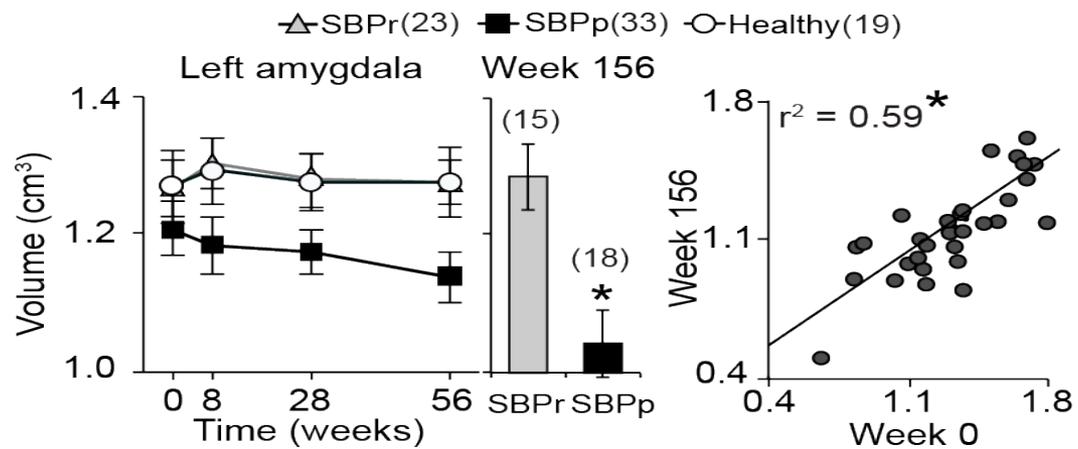
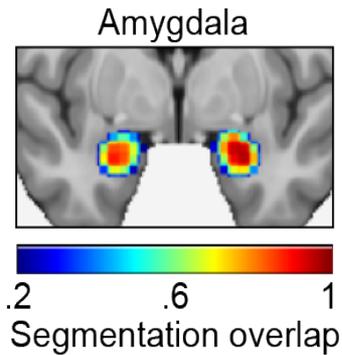
mPFC-Nac-Amy }
Func Network



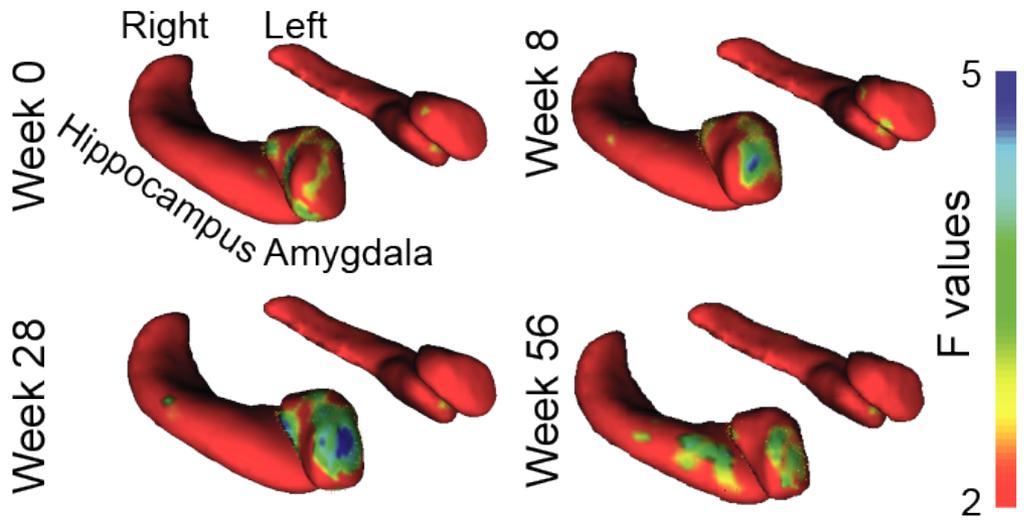
Hippocampus size is larger in subjects where back pain recovers (SBPr) and constant over 3 years



Amygdala size is larger in subjects where back pain recovers (SBPr) and constant over 3 years



Amygdala and hippocampus shape differences are seen between SBPp and SBPr, persistently





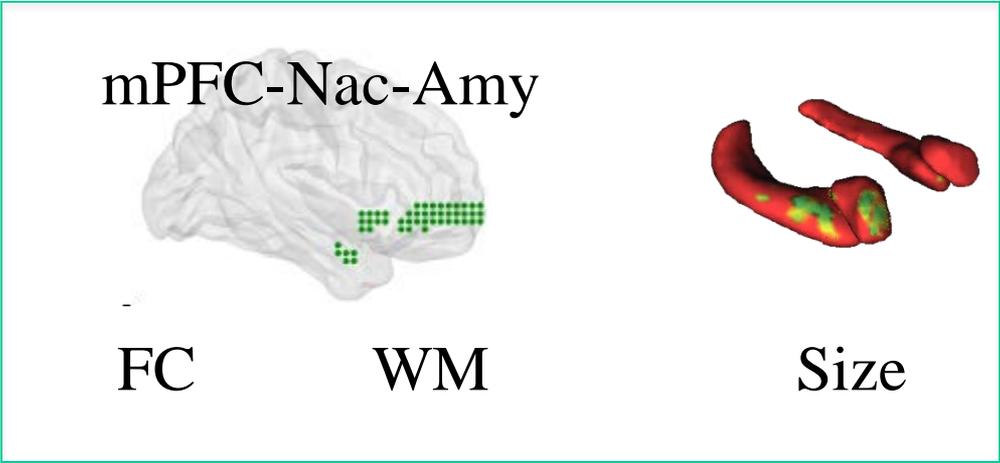
visit 1
time 0

visit 4
55 weeks

Persisting (SBPp)

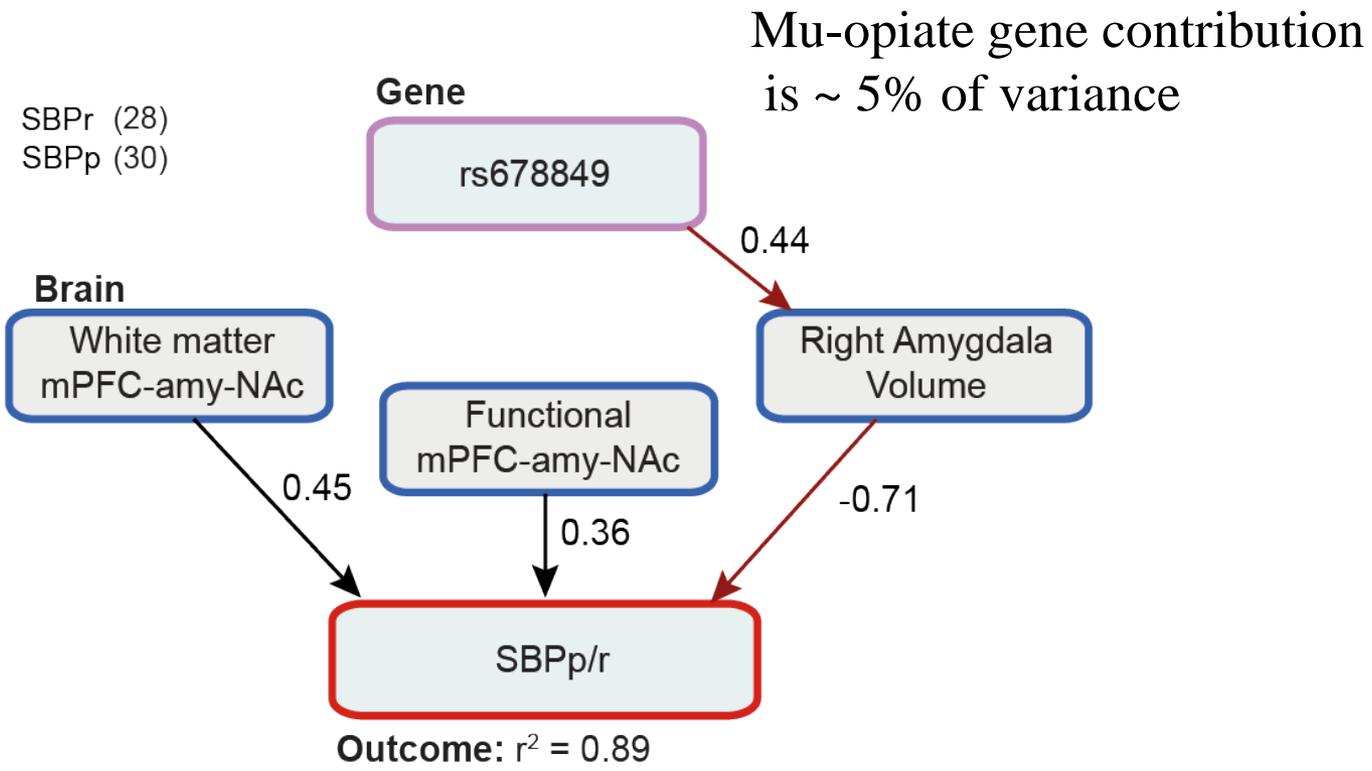
Recovering (SBPr)

Predictors



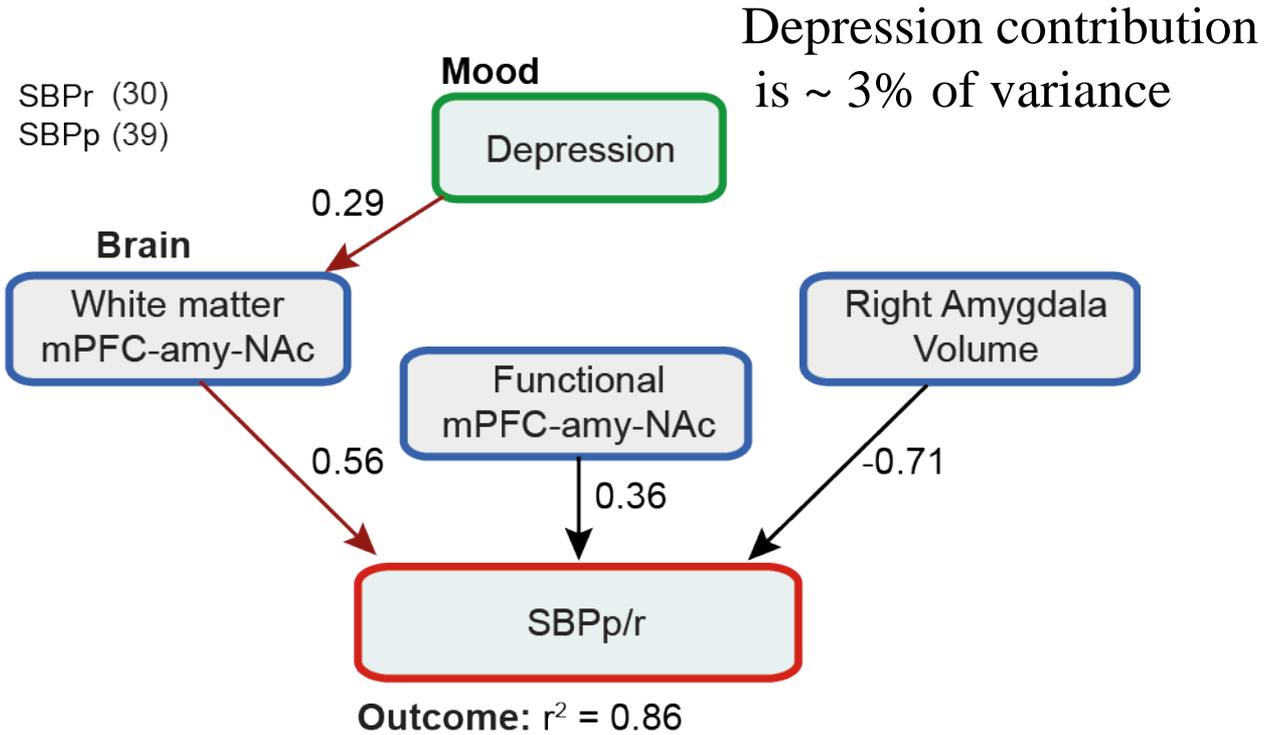
Full model for PREDICTING development of chronic pain at 1 year based on brain values observed within weeks after start of back pain

Model prediction is ~90% correct



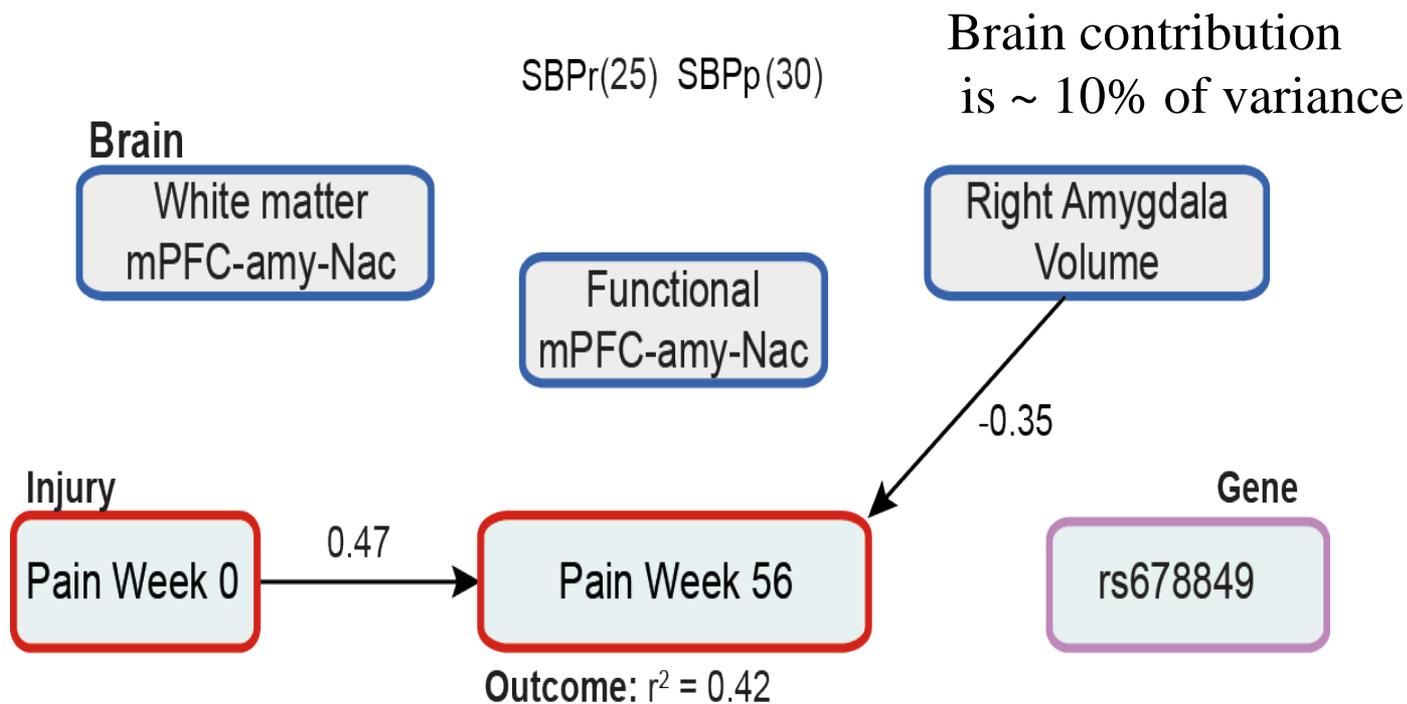
Full model for PREDICTING development of chronic pain at 1 year based on brain values observed within weeks after start of back pain

Model prediction is ~85% correct



PREDICTING intensity of back pain at 1 year based on parameters observed within weeks after start of back pain

Model prediction is now only ~40% correct



Prediction is poor and dominated by pain at entry into study

Can we identify a signature of chronic pain common across conditions and species?

Analysis of resting state fMRI regarding network graph properties:

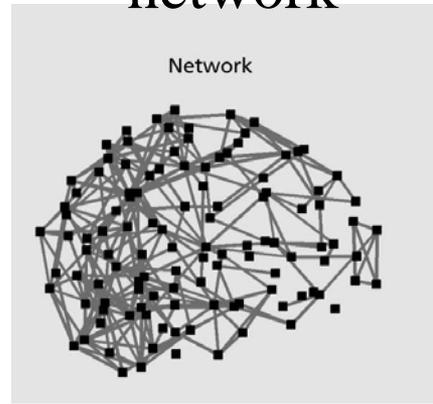
Chronic pain is characterized by a global disruption of information sharing.

Resting state brain networks: undirected functional connectivity

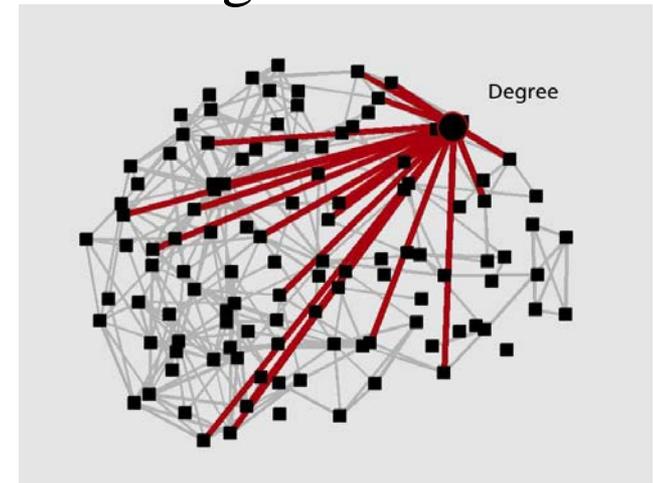
7kx7k
Correlation
matrix



Fixed density
network

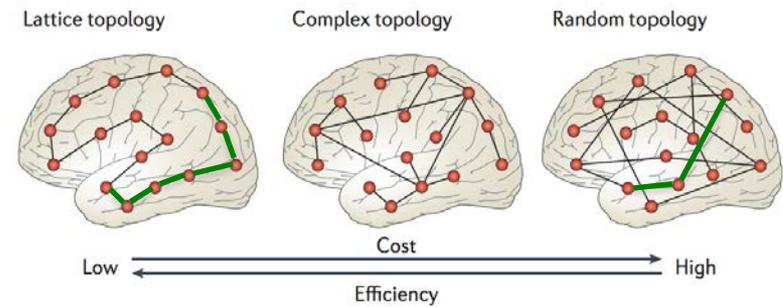
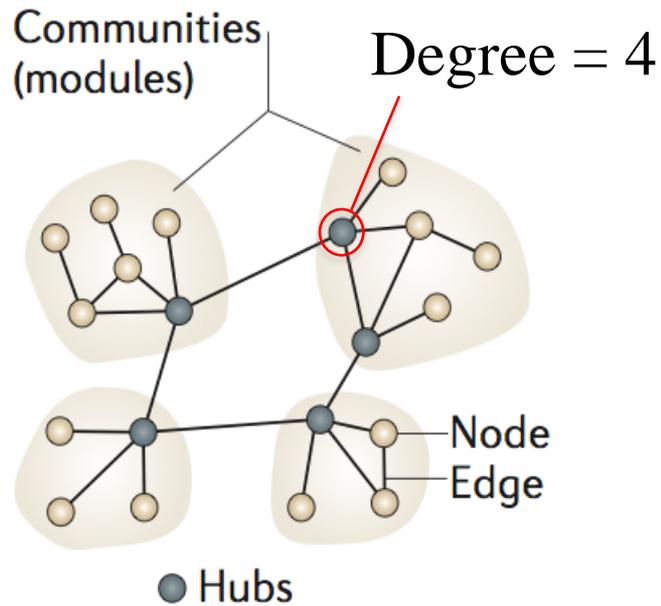


Number of links
for a given node

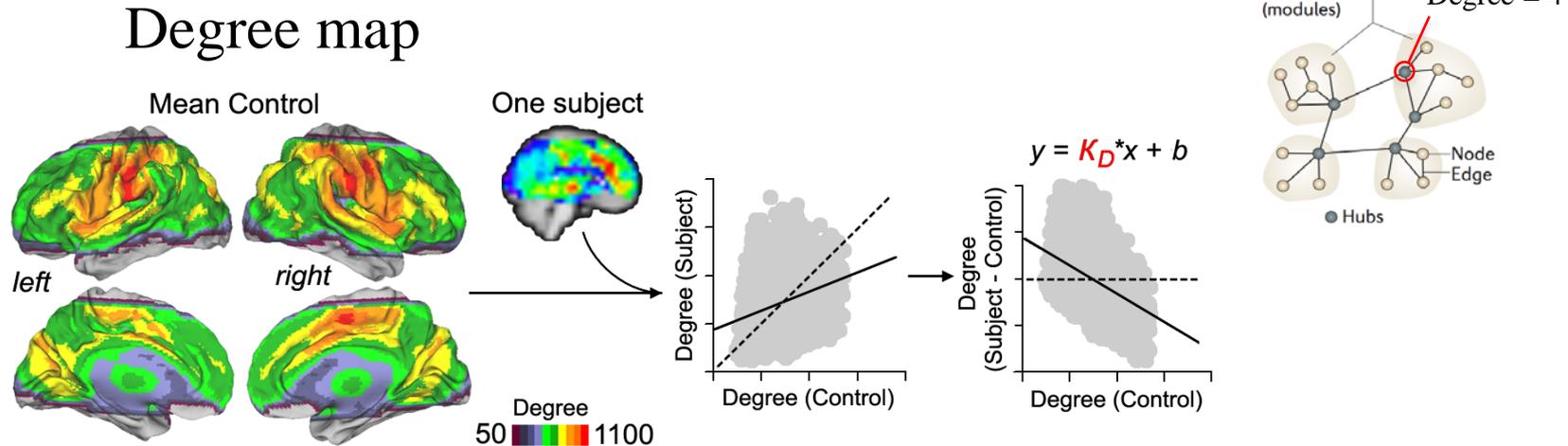


Generate link maps for patients & controls
Contrast them as a function of number of links

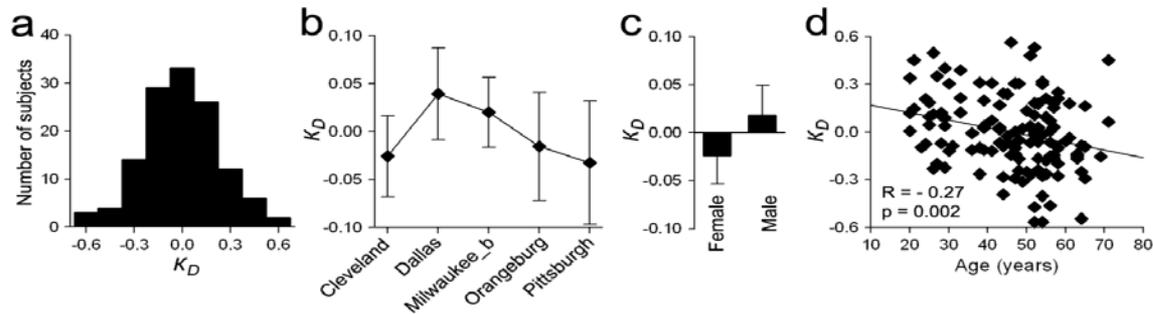
Basic elements of a graph



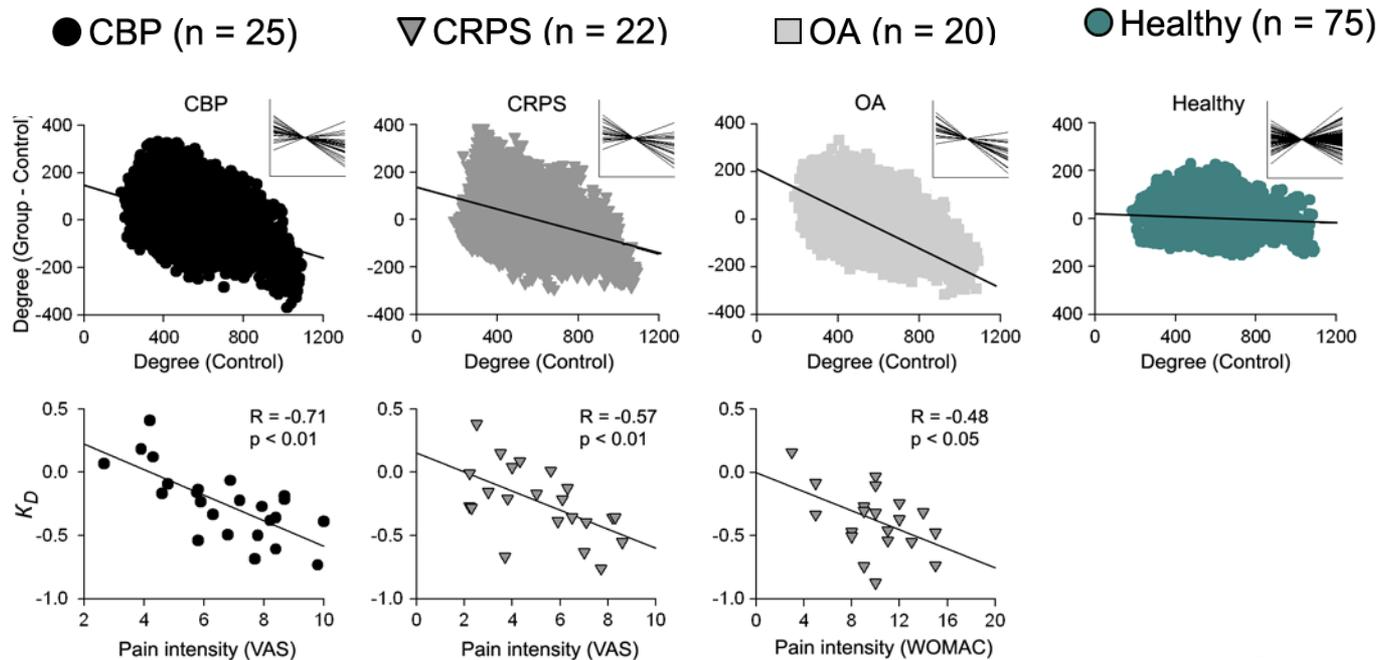
Deriving K_D : a global network measure of rank order disruption



Mean control = 150 OFF-SITE subjects from NITRC connectome1000

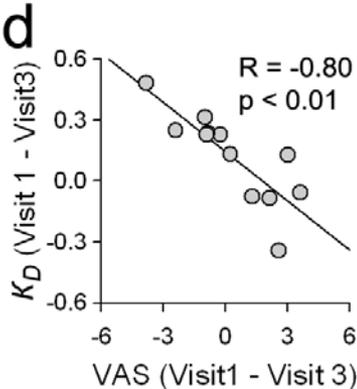
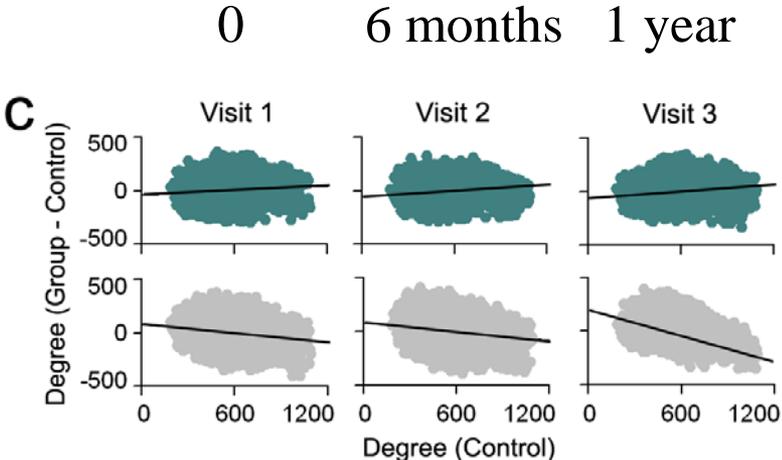
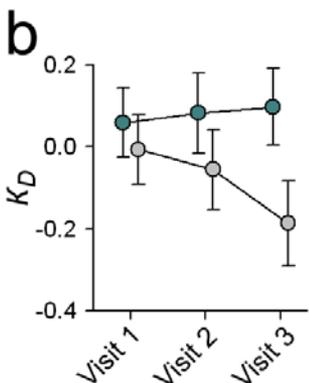
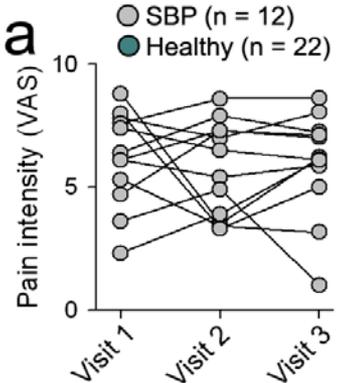


K_D is about -0.3 in chronic pain patients and related to pain intensity (at link density of 10%)

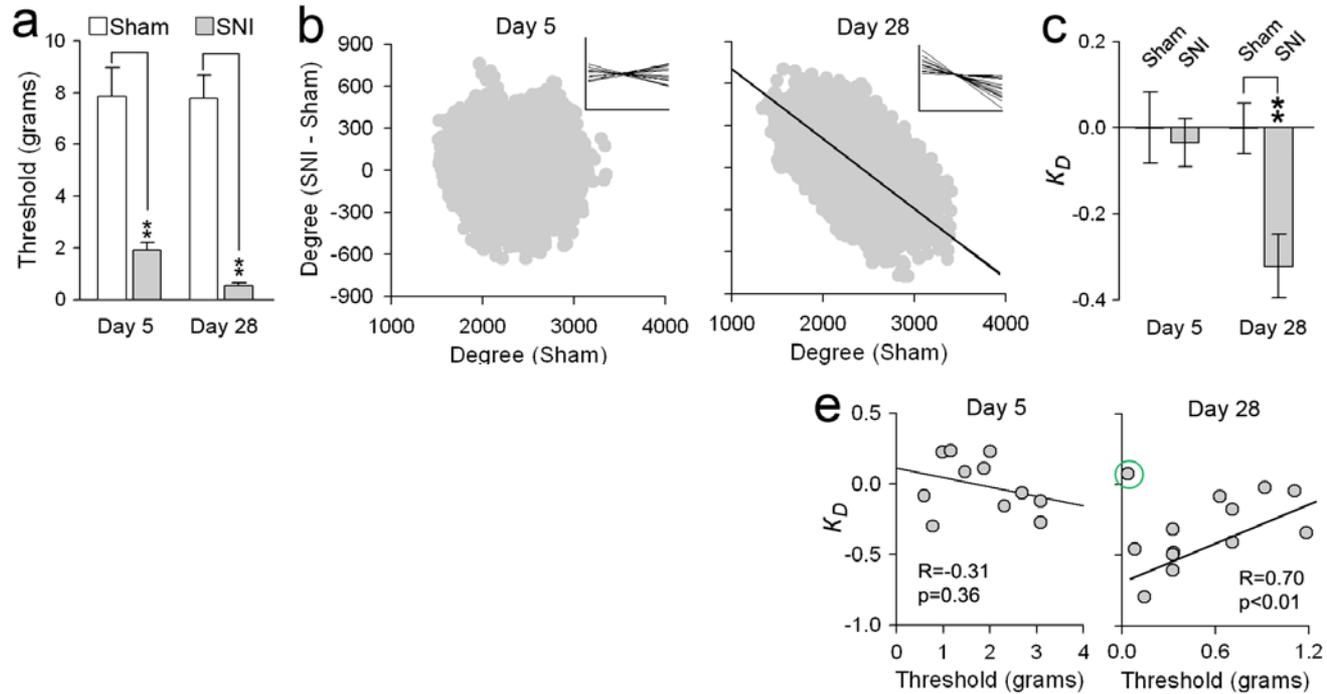


K_D emerges in time during transition to chronic pain

Acute Sub-acute Chronic



K_D emerges in time in rats after a neuropathic injury



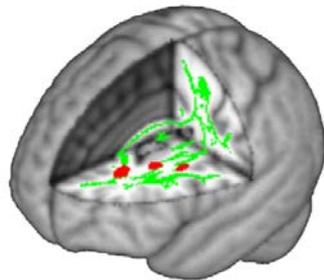
Four distinct stages for chronic pain

1. Predisposition

2. Injury

3. Transition

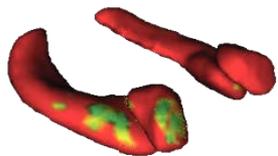
4. Maintenance ...



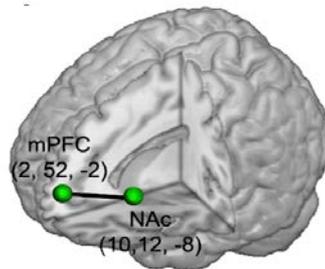
$$3 = 1 + 2$$

+ mesolimbic learning

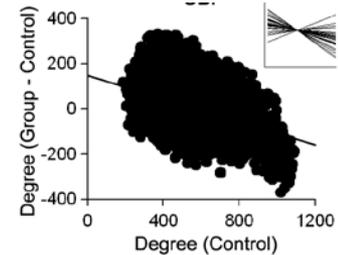
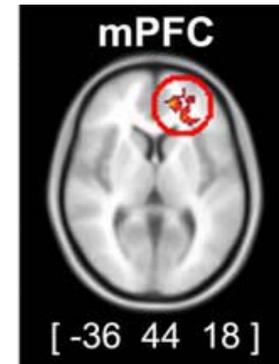
WM vulnerability



Limbic
Structures
+ Genes



mPFC-NAc



Cortical reorganization
Emotional pain state
Rank order disruption

Summary

- Brain characteristics determine propensity for chronic pain. Therefore, it is a NEUROLOGICAL vulnerability.
- Chronic pain state globally disrupts information flow/sharing in the brain
 - in proportion to the intensity of the pain,
 - commonly across types of chronic pain,
 - and even in anesthetized neuropathic rats.
- Chronic pain is a brain “network disease” state of decreased segregation and increased randomization.

Acknowledgements



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Chronic Pain

Neural Plasticity and Therapeutic Perspective

July 18 - 25, 2015

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Giandomenico Iannetti, University College, London. UK

Didier Bouhassira, INSERM, Boulogne-Billancourt, France

Newsletter

Testimonials

"I can't think of anything that would have made it better"

Milenna (NYU, USA)

"An excellent opportunity to meet with the major experts in the field and to fully interact with the Faculty"

Silvia (Swiss Fed Inst Technology, Zurich)

"The experience is one I will value professionally and treasure personally"

Elisabeth (Univ of Toronto)