Inaugural Joseph W. Howe Oration in Diagnostic Imaging

Inaugural
Oration in Diagnostic Imaging
William D. Purser Center, DC Center
Logan College of Chiropractic
St. Louis Missouri
April 3, 2008

Presented by:
James M. Cox, DC, DACBR, FICC
Norman W. Kettner, DC, DACBR, FICC
Terry R Yochum, DC, DACBR,
Fellow, ACCR, FICC

Pain in the Brain: The Role of Functional Neuroimaging

- Biology of Nociception, Pain and Placebo
  - Biopsychosocial model
  - Neuroanatomy of nociception
  - Perception of pain
  - Placebo response
- Functional Neuroimaging Techniques
  - Positron Emission Tomography (PET)
  - Functional Magnetic Resonance Imaging (fMRI)
- Functional Neuroimaging of the Human Brain
  - Imaging the placebo response
  - Imaging chronic pain (CTS)
  - Imaging resting state networks

Terry R. Yochum
DC, DACBR, Fellow, ACCR, FICC

- Graduate (Honors)
  National College of Chiropractic 1972
- Assistant Professor of Radiology
  National College of Chiropractic
- Professor, Chair Department of Radiology Logan College of Chiropractic
- Head, Department of Radiology 1978
  School of Chiropractic, Phillip Institute Melbourne Australia

Terry R. Yochum
DC, DACBR, Fellow, ACCR, FICC

- Adjunct Professor of Radiology
  Los Angeles College of Chiropractic
- Instructor, Skeletal Radiology
  Department of Radiology
  University of Colorado School of Medicine, Denver, CO
- Director,
  Rocky Mountain Chiropractic Radiological Center, Denver, CO

The heights of great men reached and kept

Were not attained by sudden flight,

But they, while their companions slept,

Were toiling upward through the night,

Henry Wadsworth Longfellow

“The Ladder of St. Augustine”

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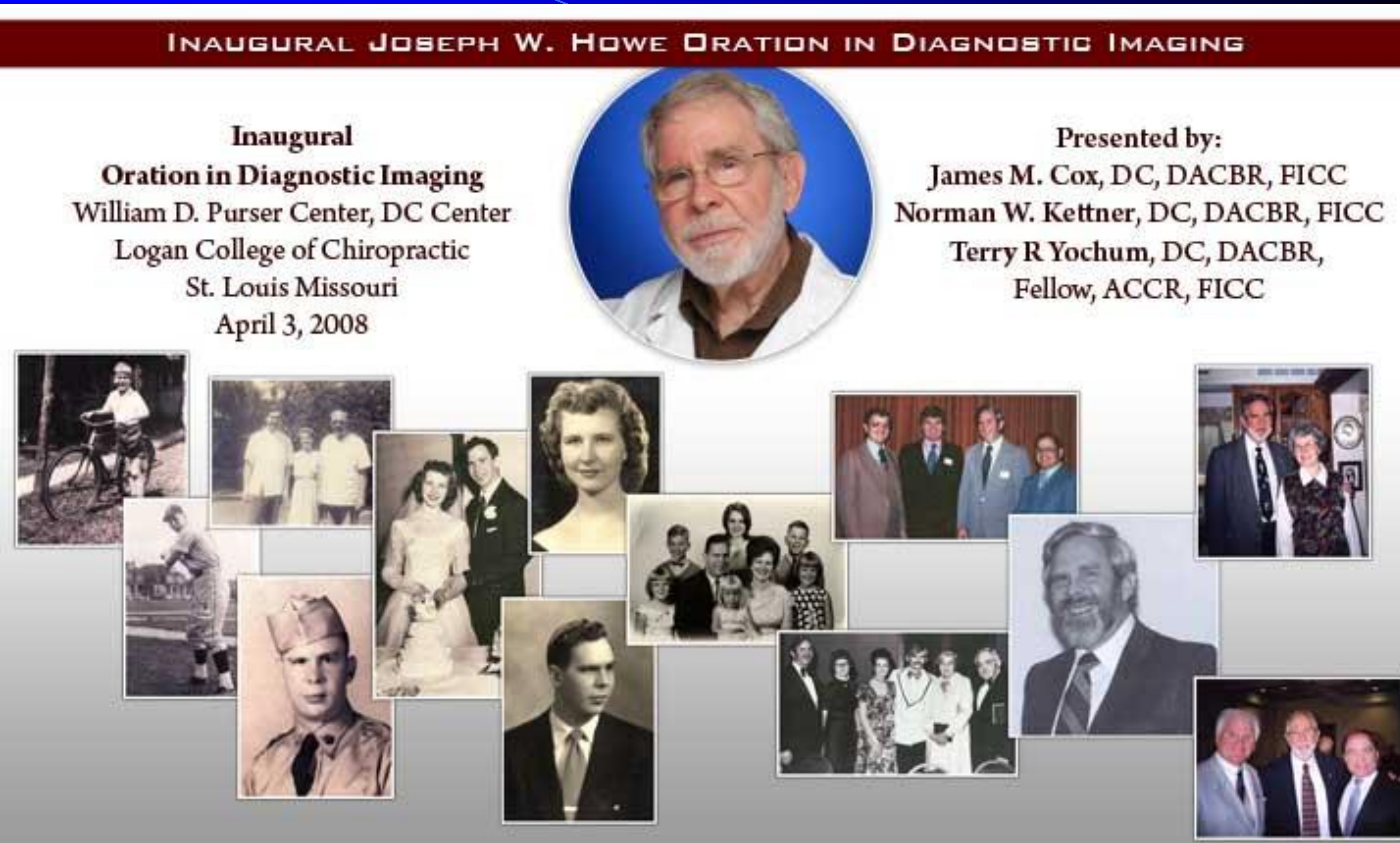
James M. Cox, I, DC, DACBR, FICC

- Purdue University
- National College of Chiropractic, 1963
- Radiology Residency, Lincoln & National College of Chiropractic 1967-1970
- Diplomate, American Chiropractic Board of Radiology, 1970
- Director, Chiropractic Associates, Inc. Fort Wayne, IN, 1970

James M. Cox, I, DC, DACBR, FICC

- Fellow, International College of Chiropractic, 1978
- Inventor of COX® Distraction Manipulation Instrument
- Chief Radiologist, Fort Wayne Chiropractic Center, 1993
- Past-President, Indiana State Chiropractic Association
- Editorial Board, JMPT


INAUGURAL JOSEPH W. HOWE ORATION IN DIAGNOSTIC IMAGING
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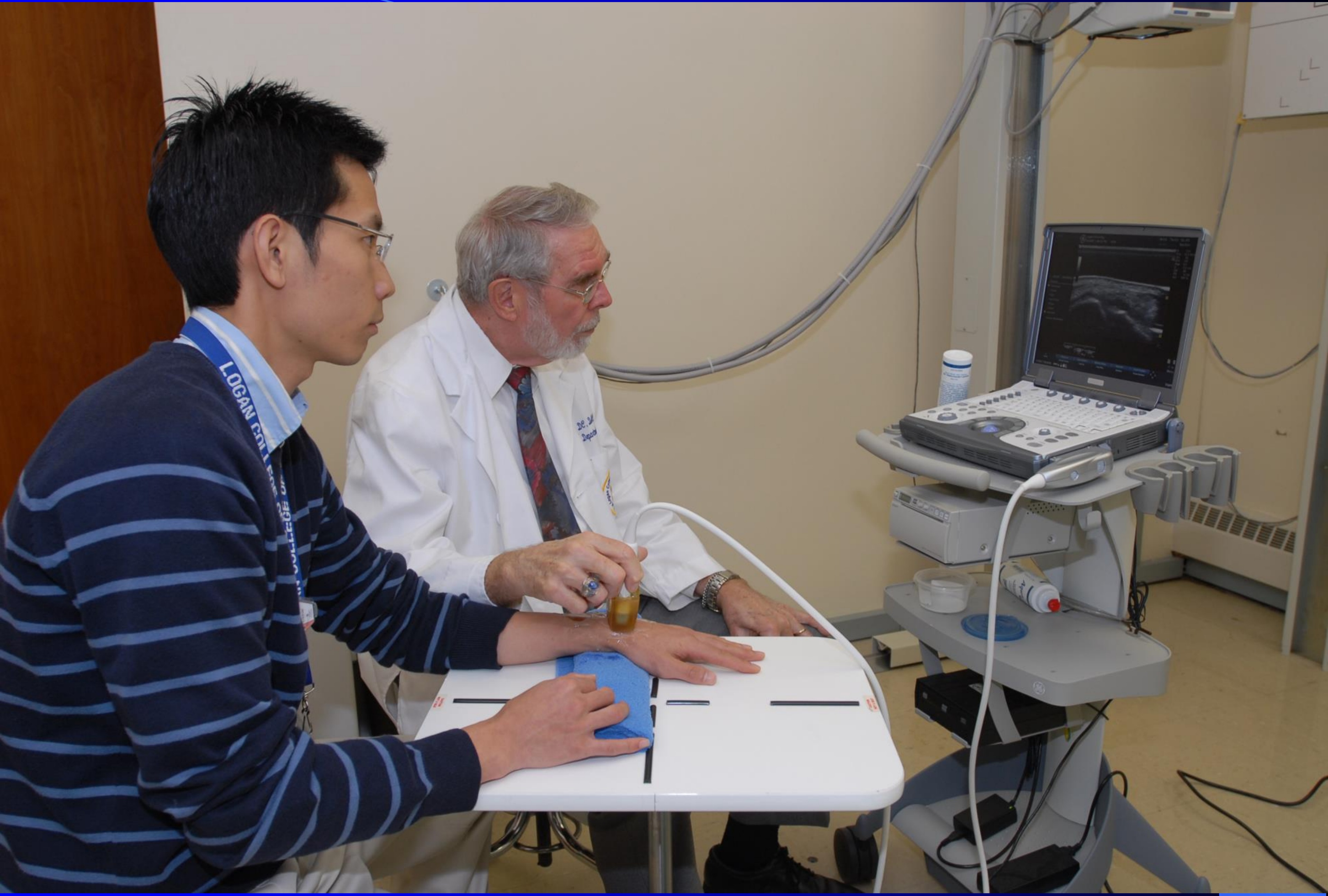
Imaging the Brain in Pain: The Role of Functional Neuroimaging

Norman W. Kettner, DC, DACBR, FICC
Chair, Department of Radiology
Logan College of Chiropractic
Chesterfield, Missouri


LOGAN COLLEGE

The Pain Revolution

Melzack R, Wall PD.

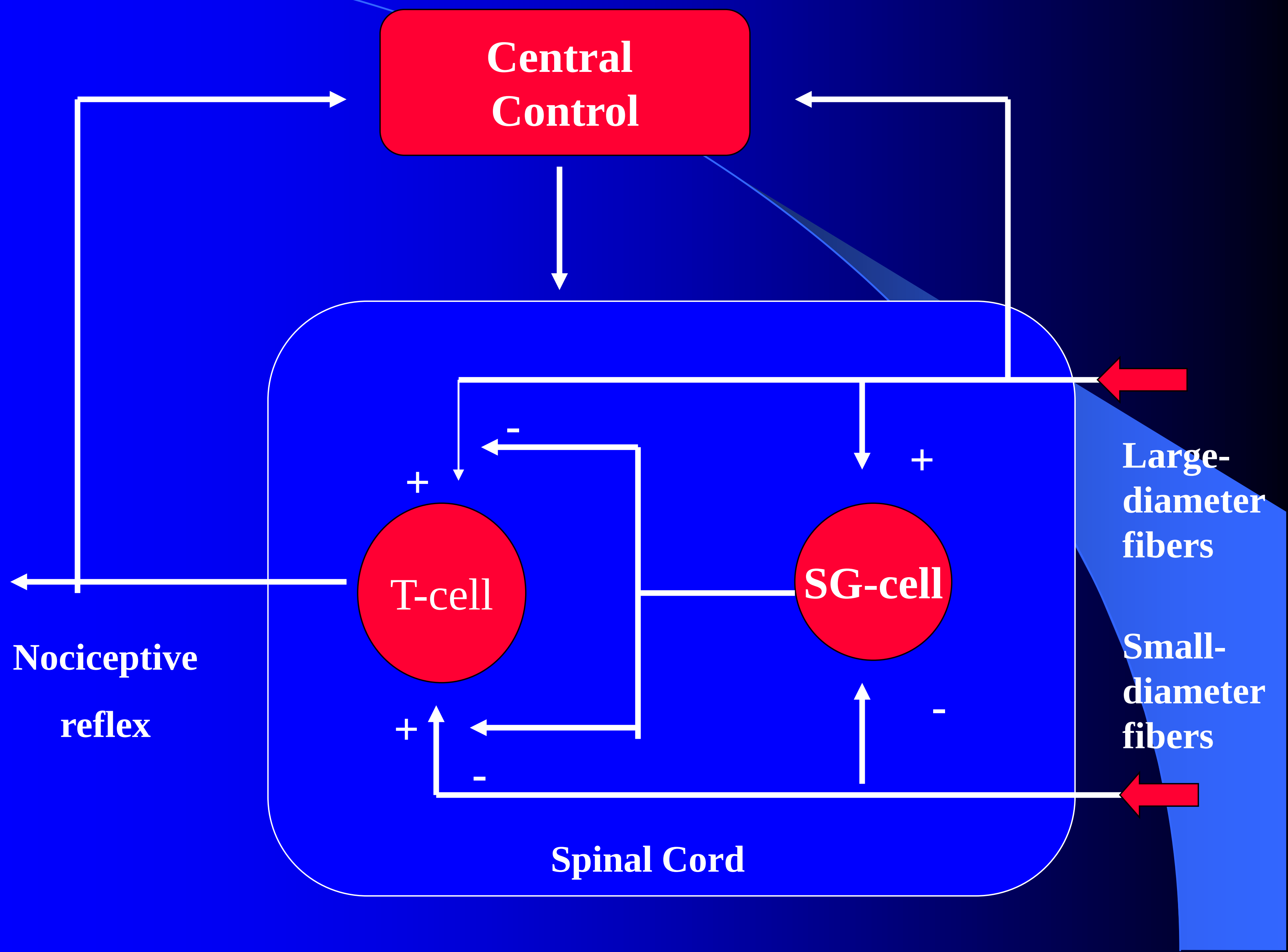
Pain mechanisms: a new theory.

Science. 1965 Nov 19;150(699):971-9

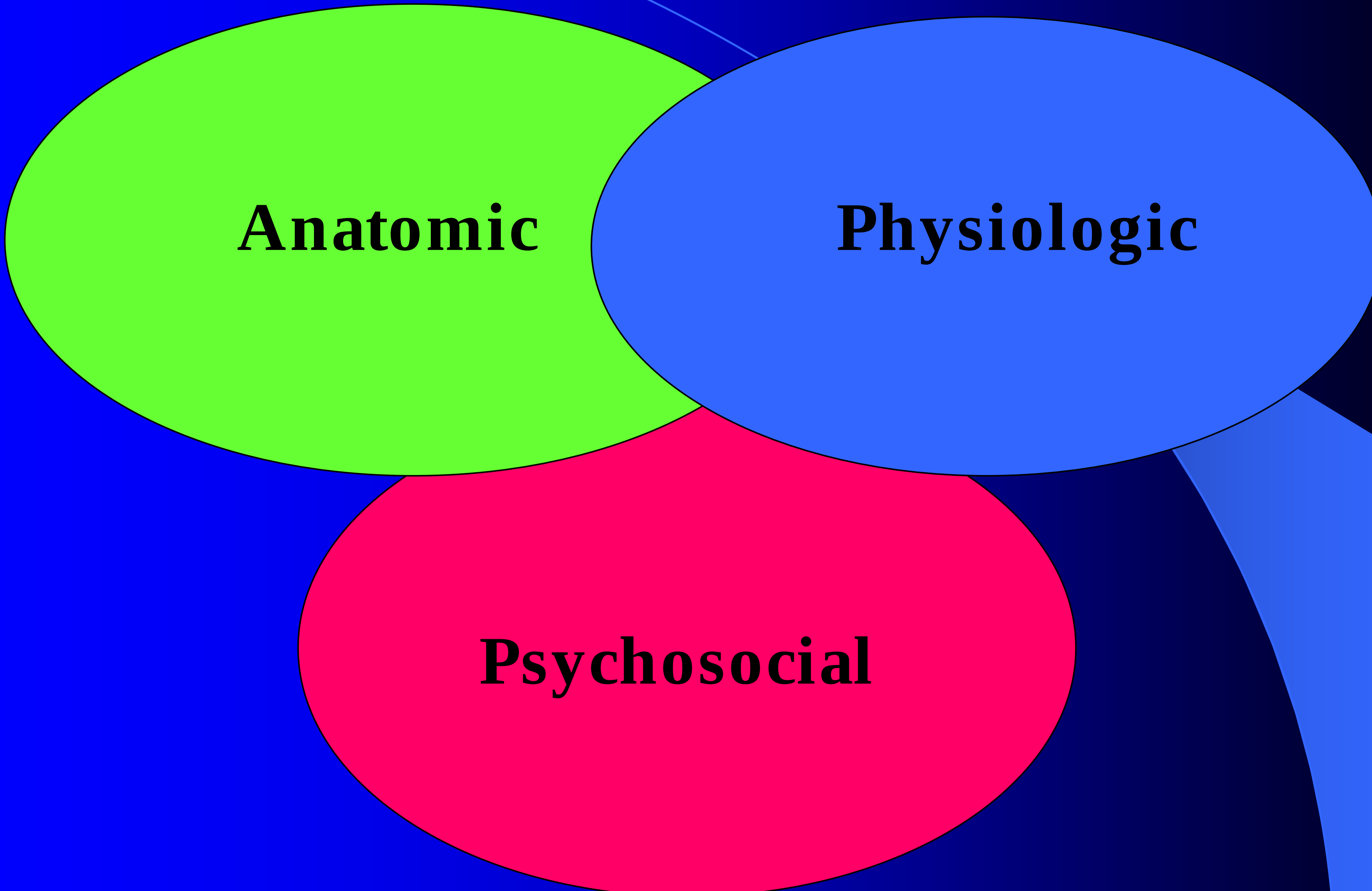
Engel GL.

The need for a new medical model: a challenge for biomedicine.

Science. 1977 Apr 8;196(4286):129-36

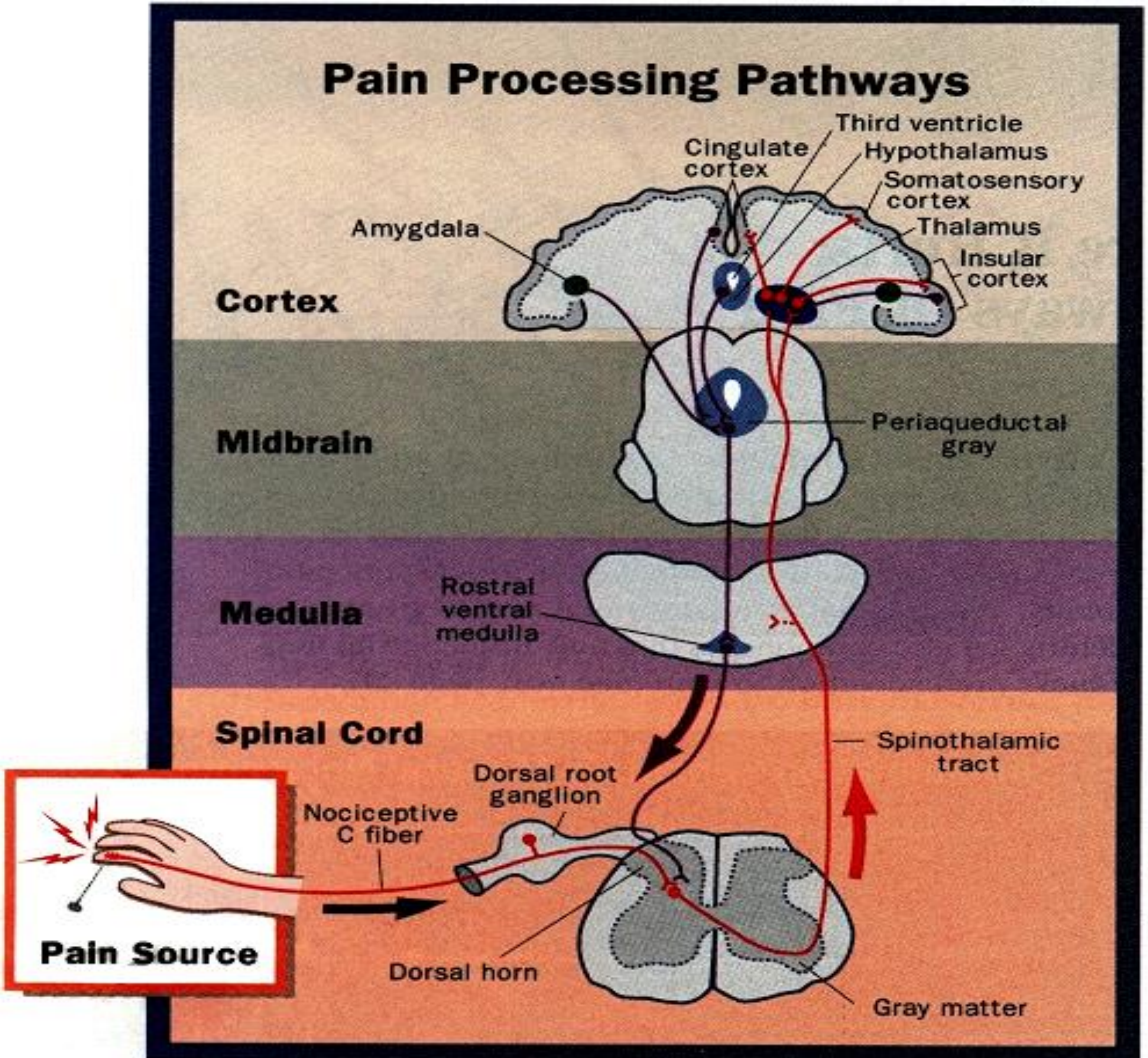


Central Control
T-cell
SG-cell
+
-
+
+
-
-
Nociceptive reflex
Large-diameter fibers
Small-diameter fibers
Spinal Cord

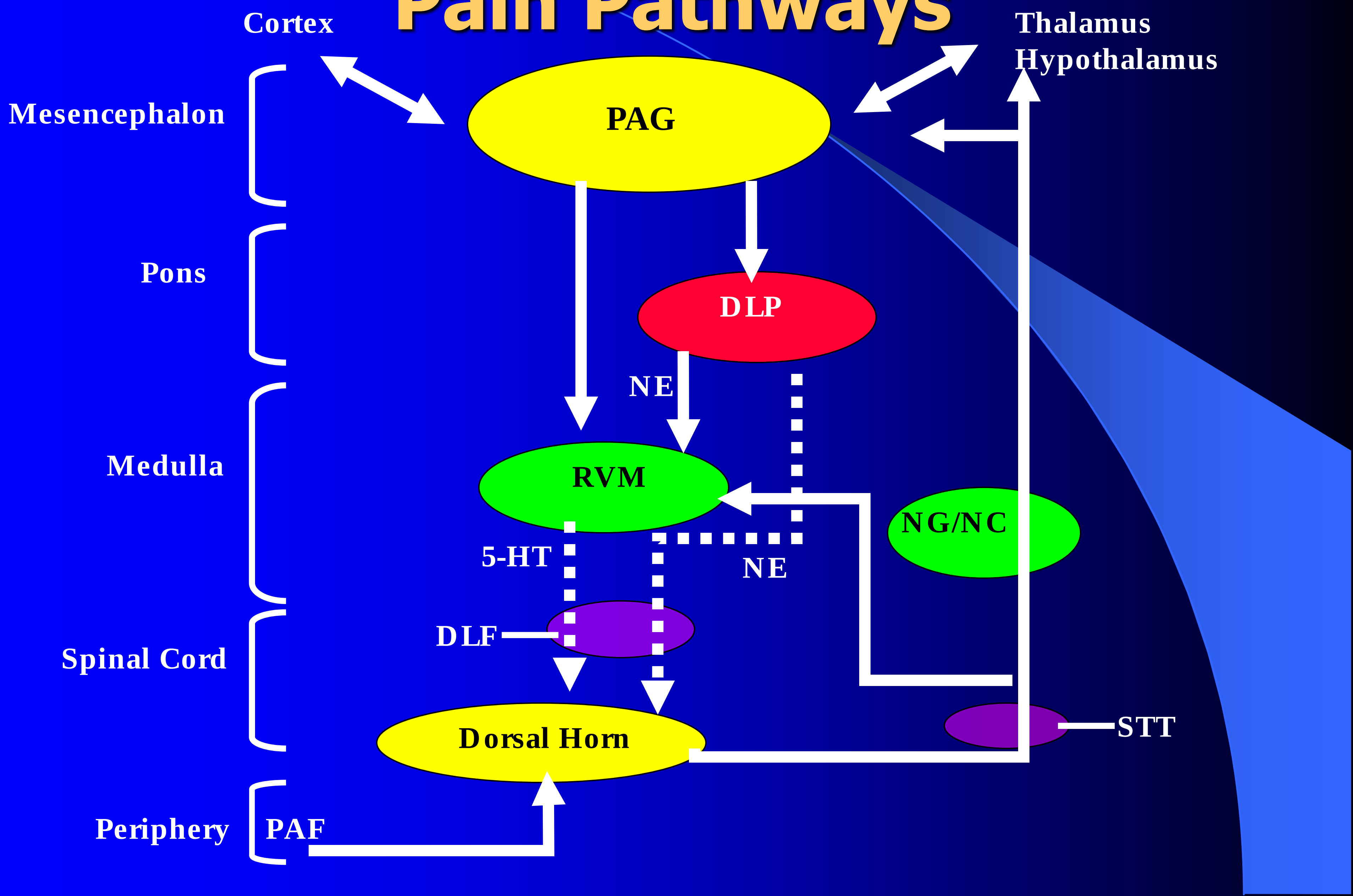

Anatomic
Physiologic
Psychosocial

Classification of Fibers in Peripheral Nerves

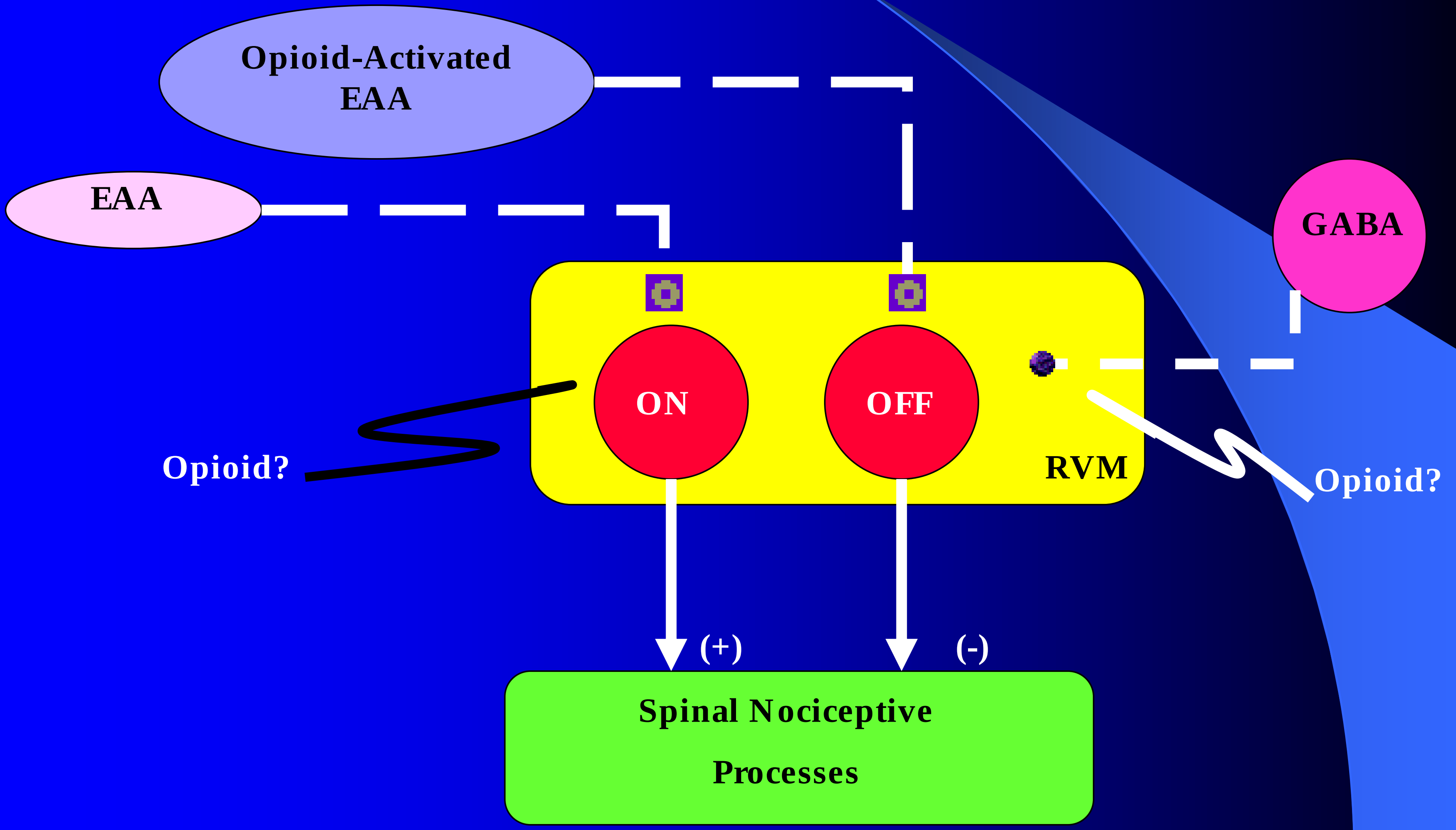
Lloyd/Hunt System	Diameter (μm)	Letter System	Conduction Velocity (m/sec)	Myelin	Receptor/ending types
I-a[a]	12-20	___	70-120	+	Muscle spindle primary endings
I-b[a]	12-20	___	70-120	+	Golgi tendon organs
___	12-20	A-α	70-120	+	Muscle efferents (extrafusal)
II	6-12+	A-β[b]	30-70	+	Encapsulated endings (Meissner, Ruffini, Pacinian); Merkel intraepithelial; muscle spindle secondary endings
___	2-10	A-γ	10-50	+	Muscle efferents (intrafusal)
III	1-6	A-δ	5-30	+	A-δ specific nociceptors; A-δ polymodal receptors; cold receptors; most hair receptors; some visceral receptors
__	<3	B	3-15	+	Preganglionic autonomic
IV	<1.5	C	0.5-2.0	No	C-nociceptors; C-polymodal receptors; some visceral receptors; warmth receptors; some mechanoreceptors; postganglionic autonomic; enteric nerve fibers

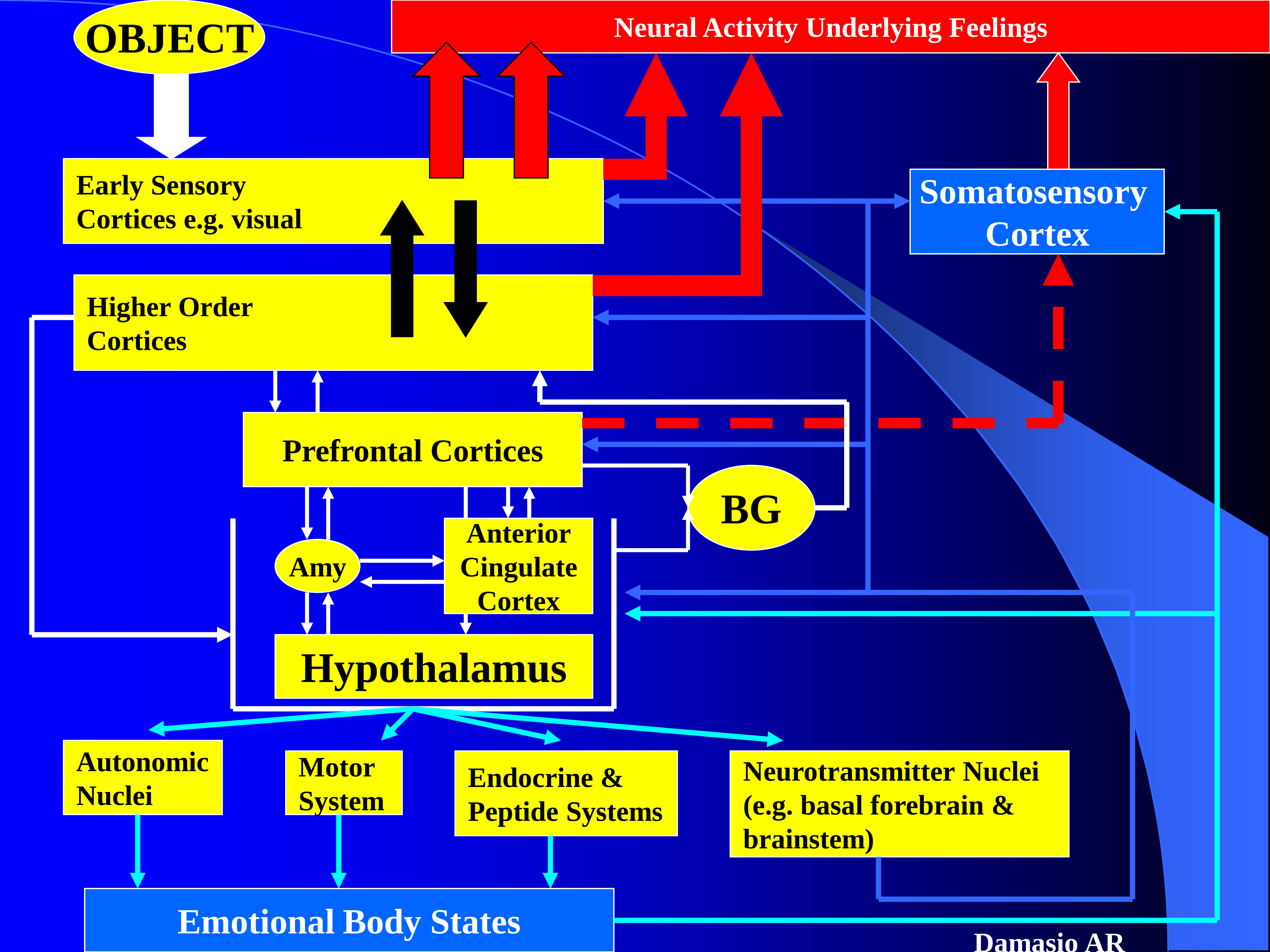

Pain Processing Pathways
Third ventricle
Cingulate cortex
Hypothalamus
Somatosensory cortex
Amygdala
Thalamus
Insular cortex
Cortex
Midbrain
Periaqueductal gray
Medulla
Rostral ventral medulla
Spinal Cord
Spinothalamic tract
Dorsal root ganglion
Nociceptive C fiber
Pain Source
Dorsal horn
Gray matter

The Ascending and Descending Pain Pathways



Circuitry Diagram of the Rostral Ventromedial Medulla




OBJECT
Neural Activity Underlying Feelings
Early Sensory Cortices e.g. visual
Somatosensory Cortex
Higher Order Cortices
Prefrontal Cortices
BG
Amy
Anterior Cingulate Cortex
Hypothalamus
Autonomic Nuclei
Motor System
Endocrine & Peptide Systems
Neurotransmitter Nuclei (e.g. basal forebrain & brainstem)
Emotional Body States
Damasio AR

Putative Functional Roles of Cortical Areas that are Activated by Noxious Stimuli

Functional Correlation	Cortical Area	Possible Functions
Pain intensity Temperature sensation	Primary somatosensory cortex Secondary somatosensory cortex and its vicinity Insula	Sensory discriminative in general,alternatively stimulus localization. Sensory integrative (touch, pain, visual) Spatially directed attention Sensory integrative (touch, pain, taste, vestibular), visceral sensory, visceral motor, limbic integration
Pain threshold	Right frontal inferior cortex Left thalamus Right	Response selection, motor suppression, attention, affect
Pain unpleasantness	Anterior cingulate cortex Left	
Pain Intensity	Right posterior cingulate cortex Brainstem/periventricular gray Prefrontal cortex	Affect, emotion, memory

Cognitive Factors Influencing Pain

PERCEPTION

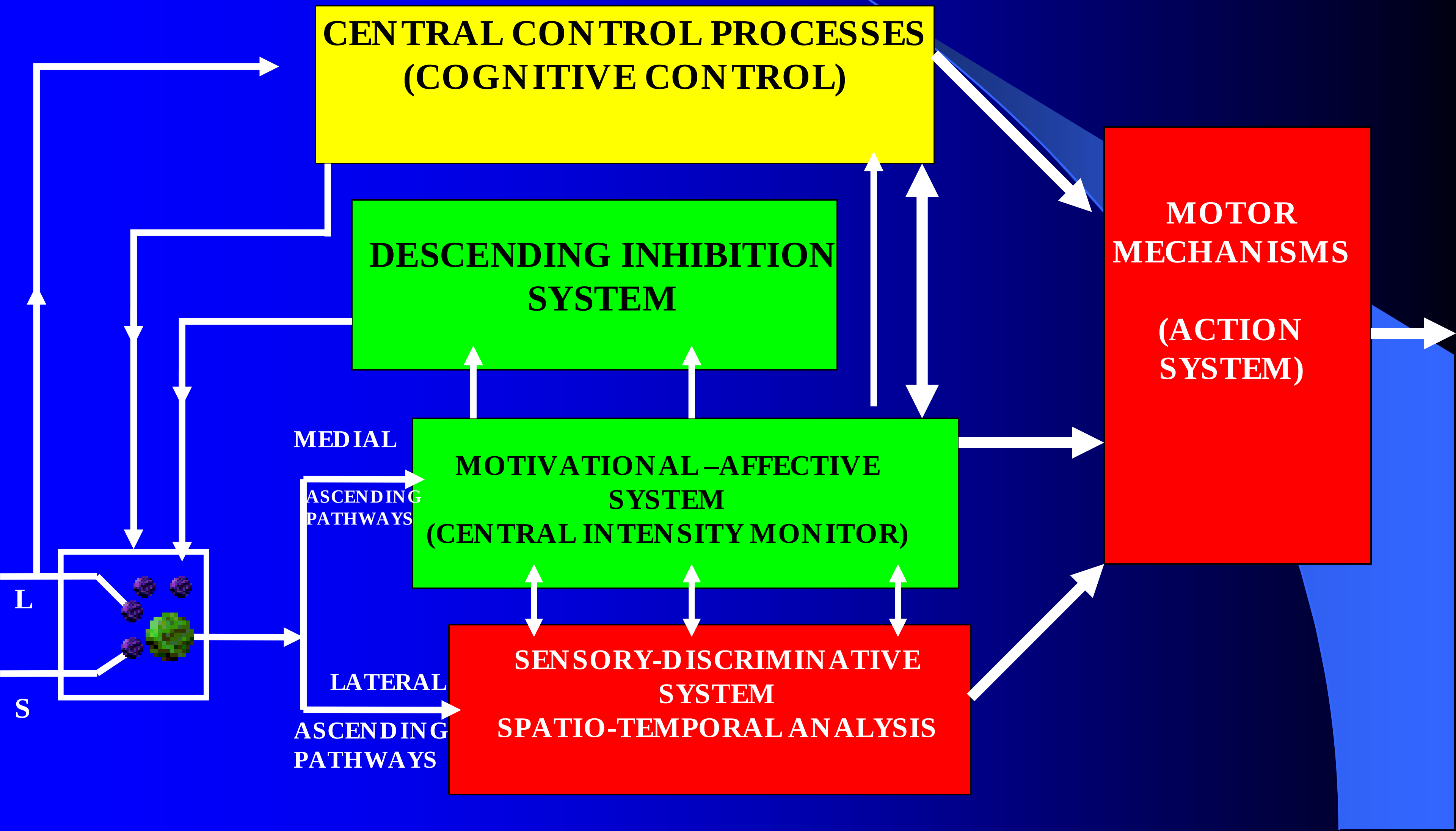
- attention
- imagery and schemata
- expectancy
- memory
- meaning making

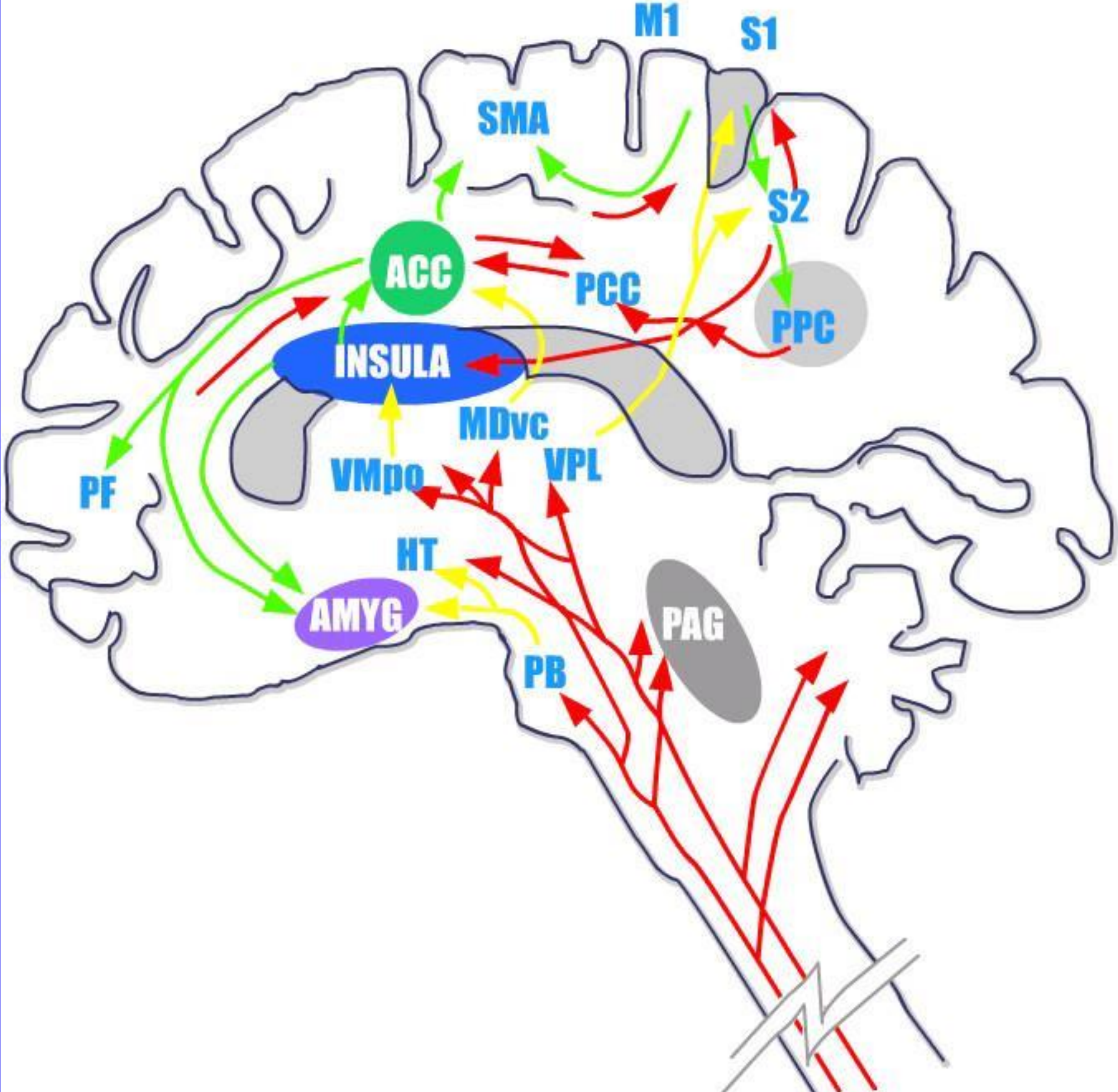
Pain

THINKING

- planning and forecasting
- decision making & classification
- mental computation
- Language and self-talk
- knowledge building

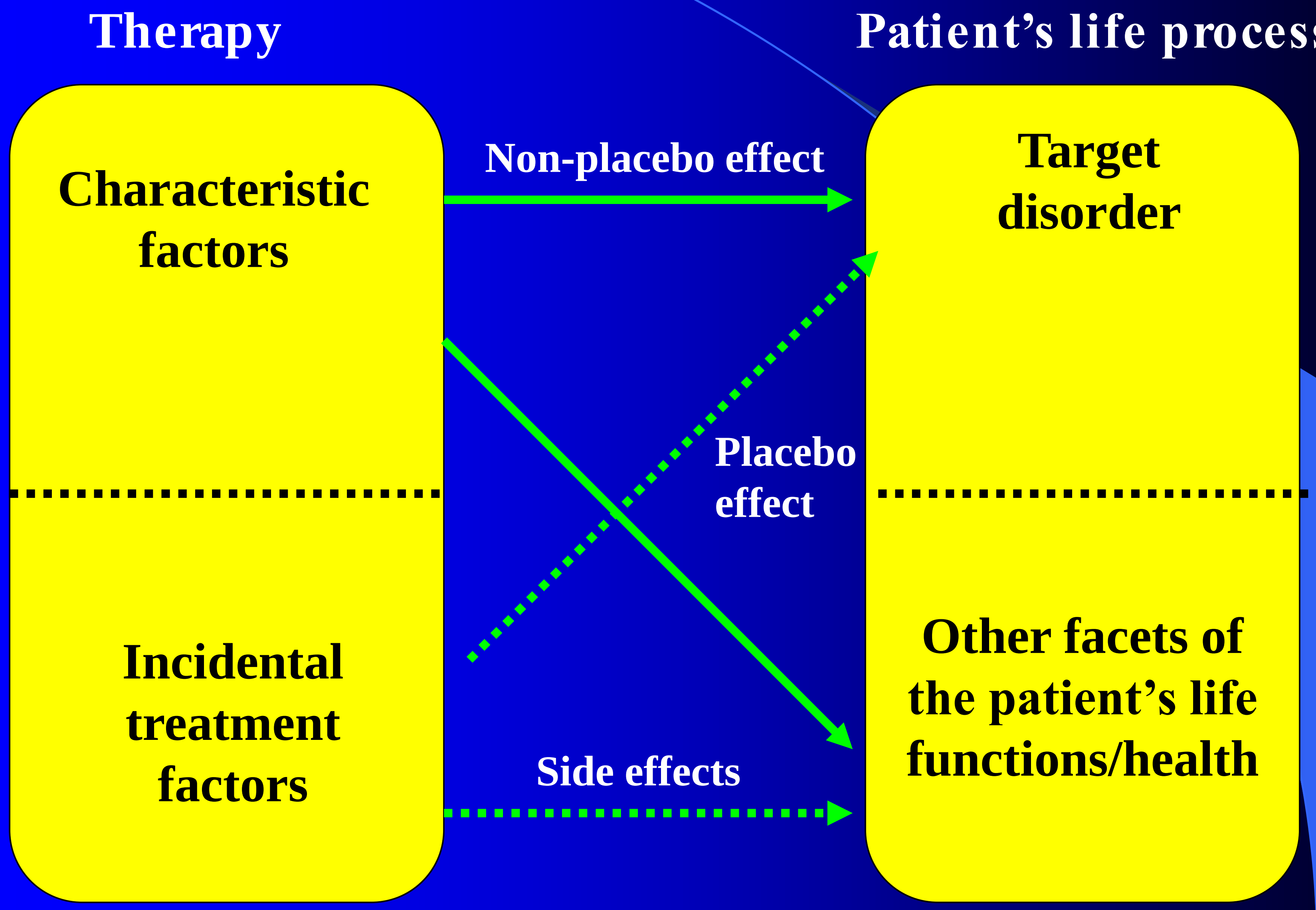
Model of the Sensory, Motivational, and Central Control of Pain



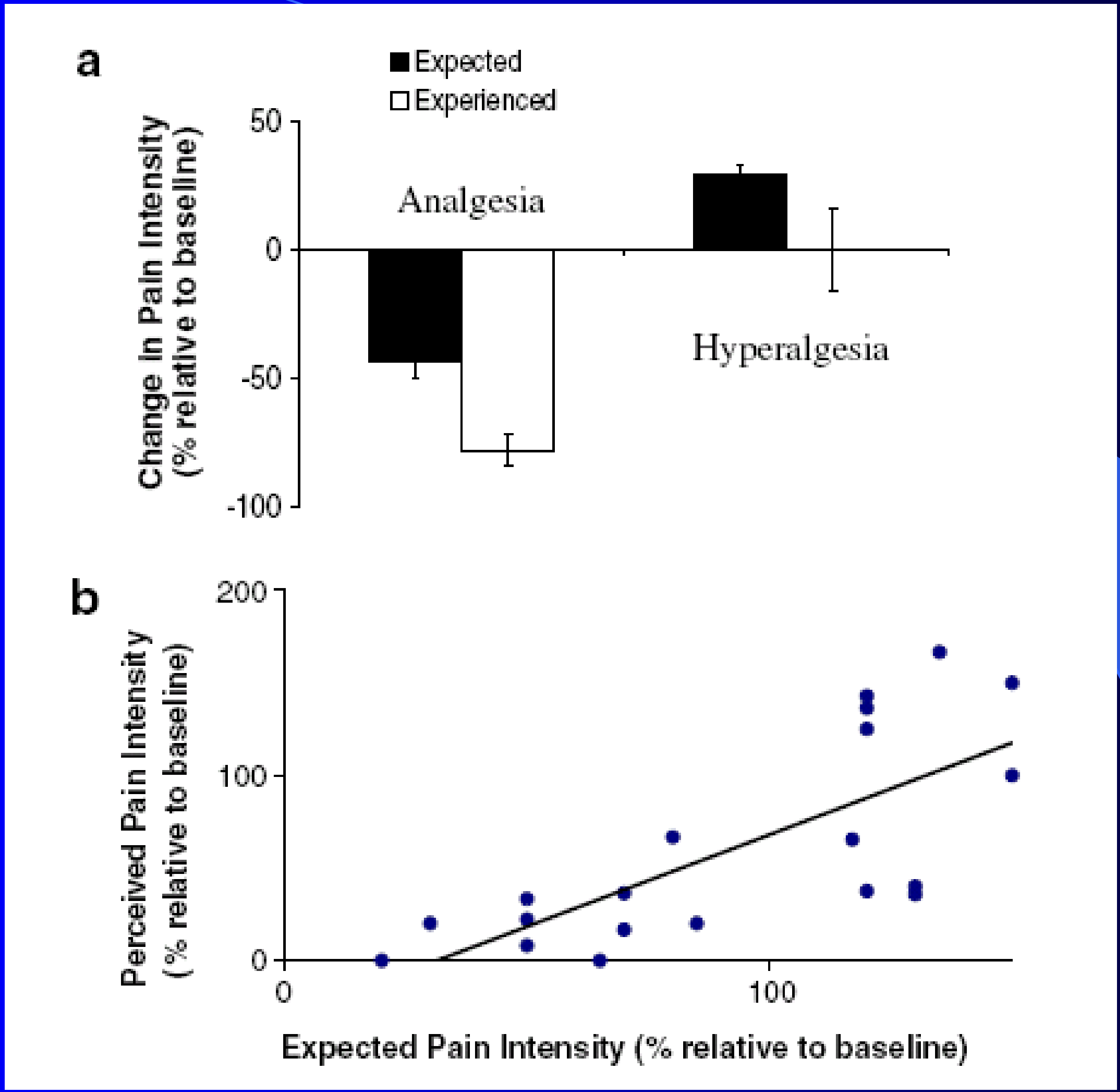


Donald D. Price
Science 9 June 2000 288: 1769-1772

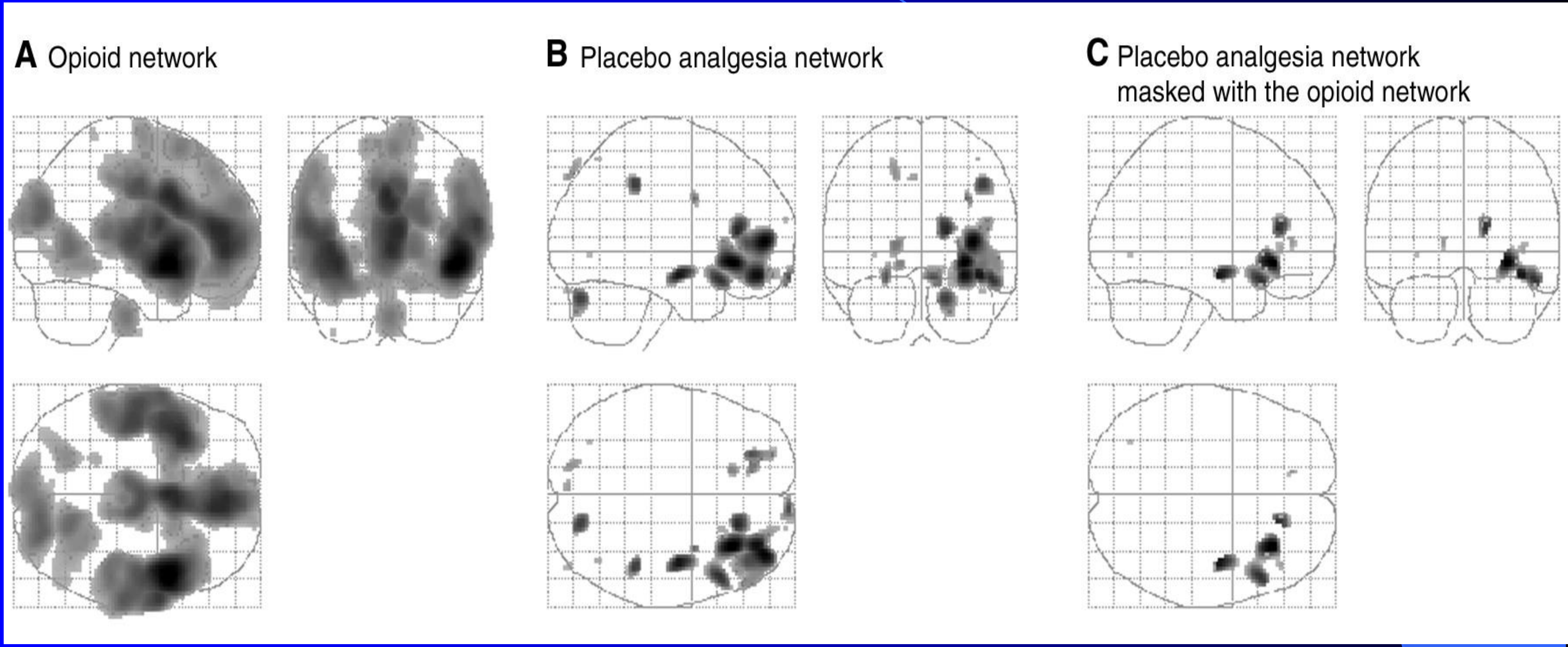
OPTIMIZING NON-SPECIFIC EFFECTS



Grunbaum, 1989

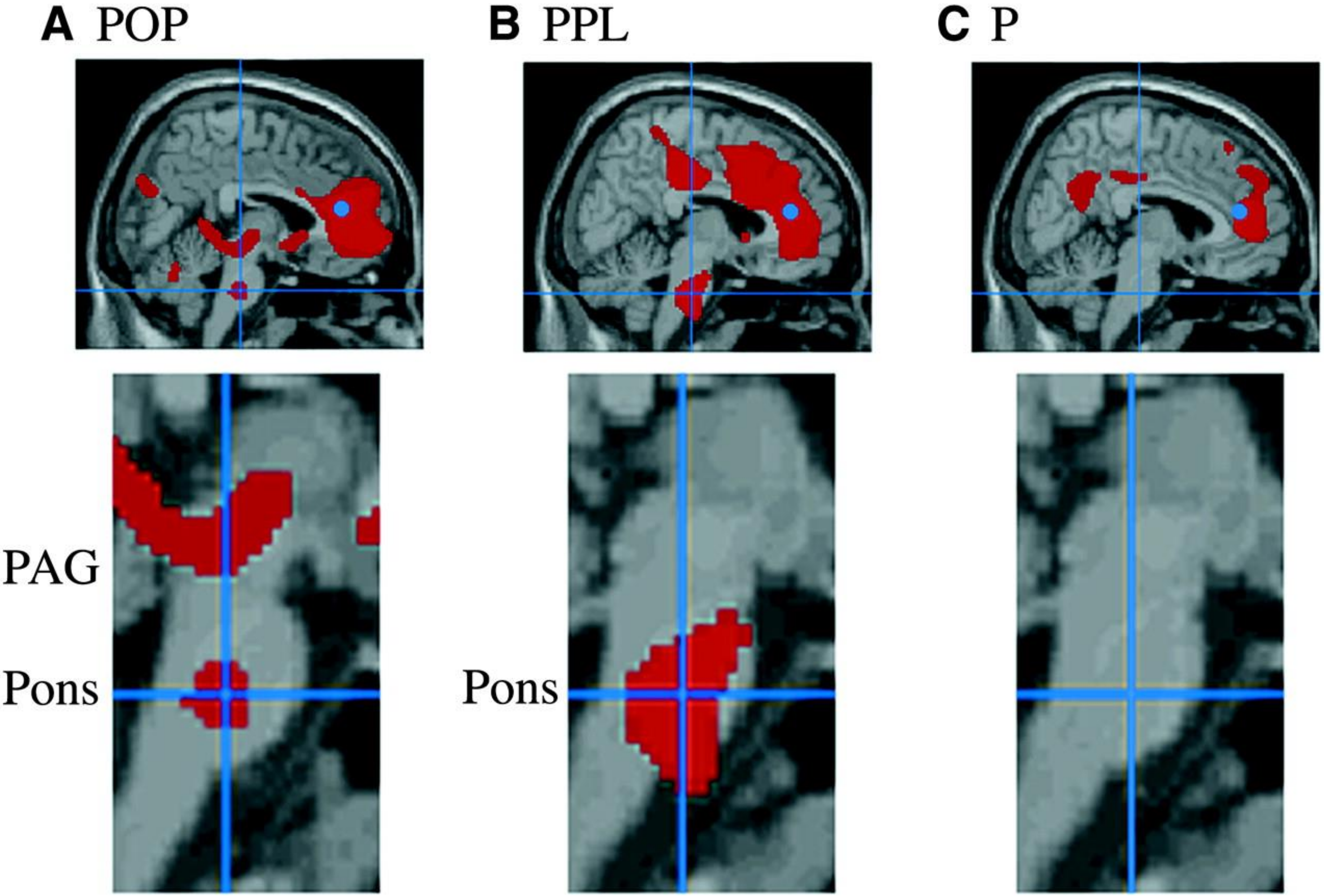


a
Expected
Experienced
Change in Pain Intensity
(% relative to baseline)
50
0
-50
-100
Analgesia
Hyperalgesia
b
Perceived Pain Intensity
(% relative to baseline)
200
100
0
0
100
Expected Pain Intensity (% relative to baseline)



Petrovic, P. et al,

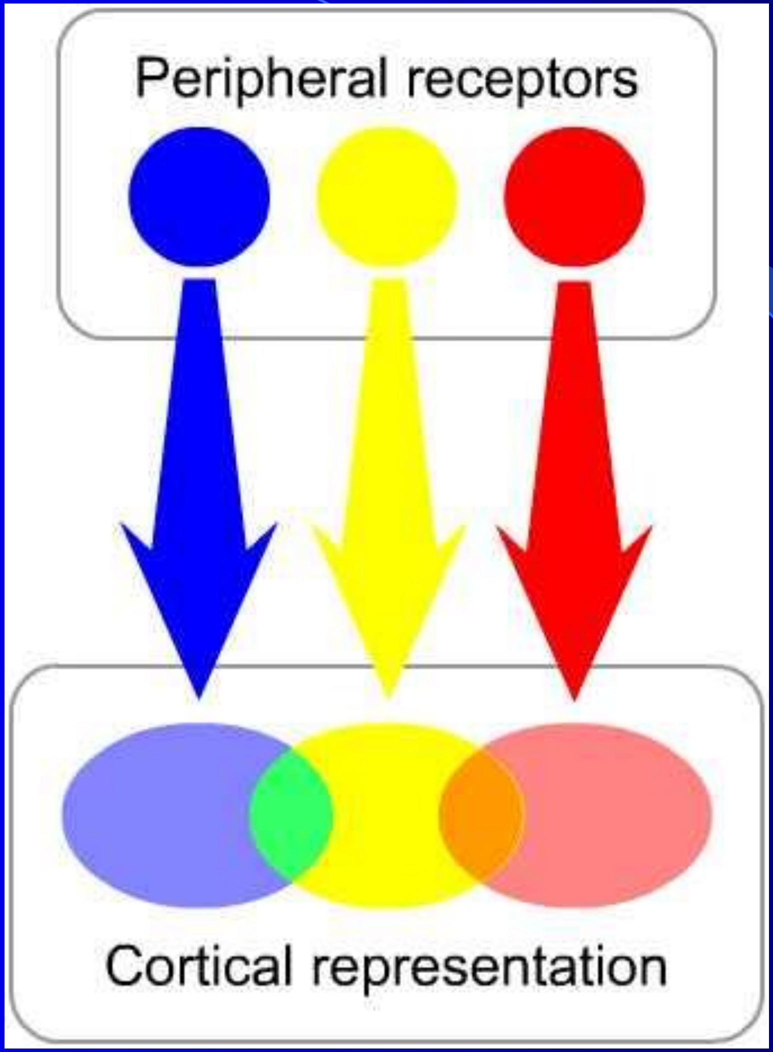
Covariation between rACC and the brainstem



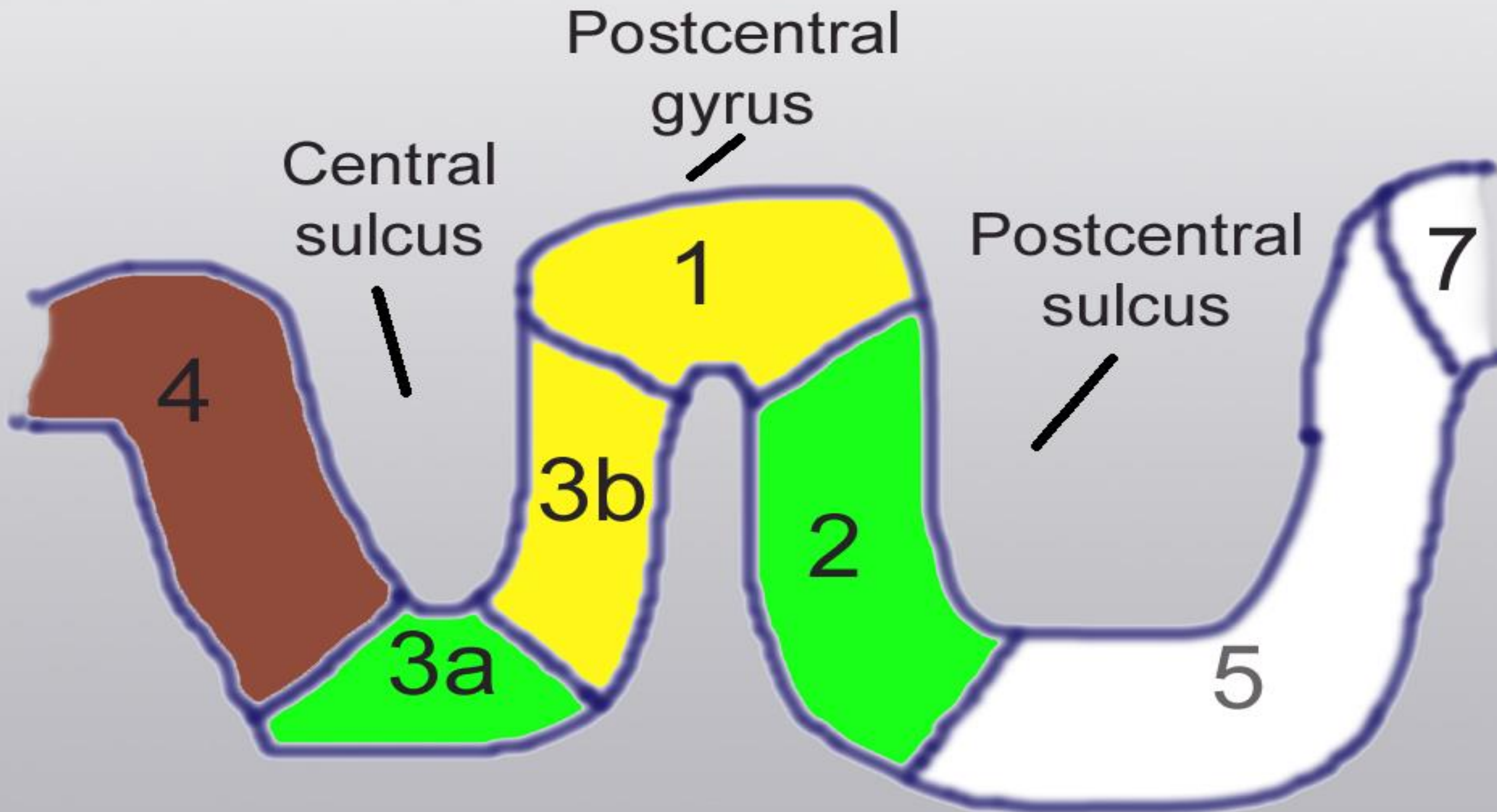
Petrovic, P. et al,

Neuro Rehab Techniques for CNS Reorganization

Propriospinal	Sensory Discrimination	Counter Stimulation	Electromagnetic Stimulation	Cognitive Therapy
• Exercise		• Acupuncture	• TMS	• Cognitive remediation
• Manual Therapy Mobilization Manipulation		• TENS	• TES	• Attention modulation
• Constraint therapy		• Vibration	• PNS	• Environmental enrichment



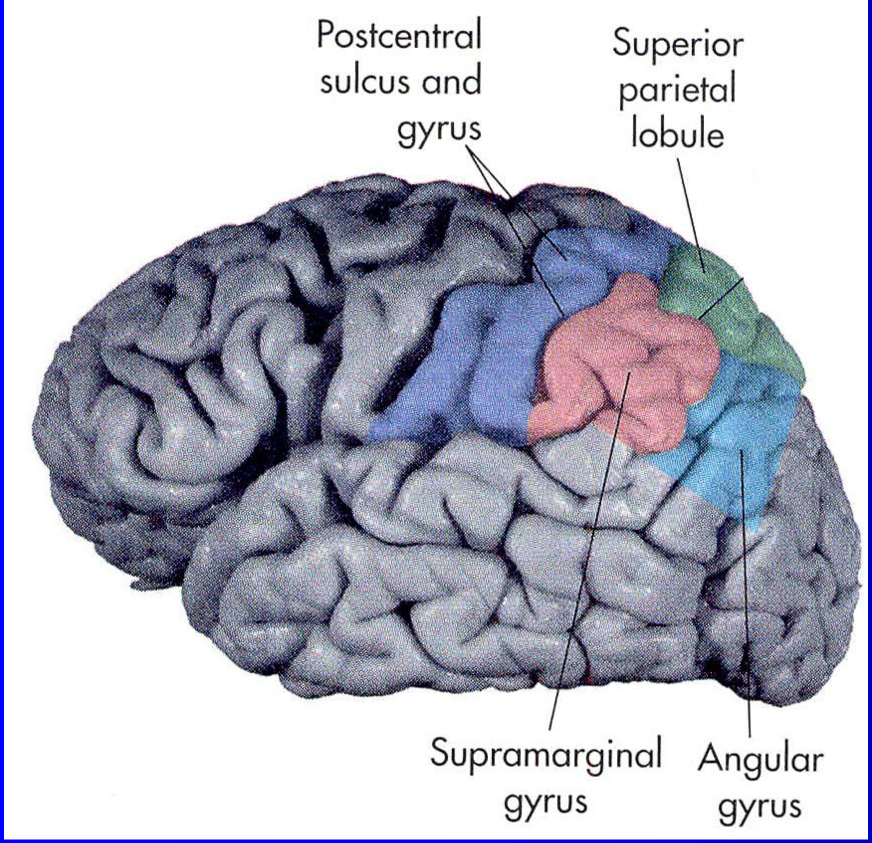
Nelson, 2003

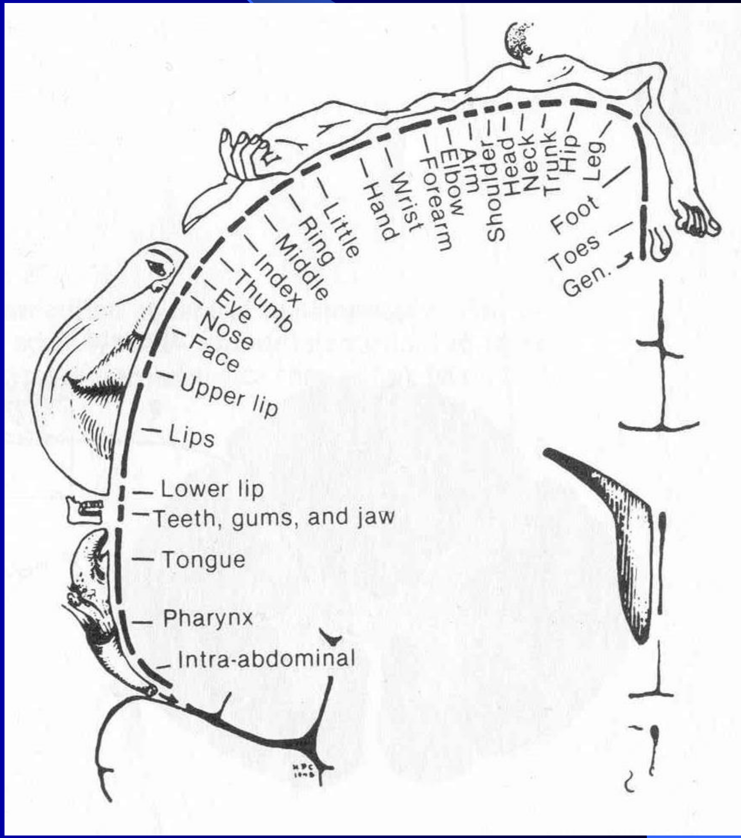


cutaneous reception - 1, 3b
deep reception - 2, 3a
proprioception - 2, 3a, 4

Digital Mapping – S1 Somatotopy

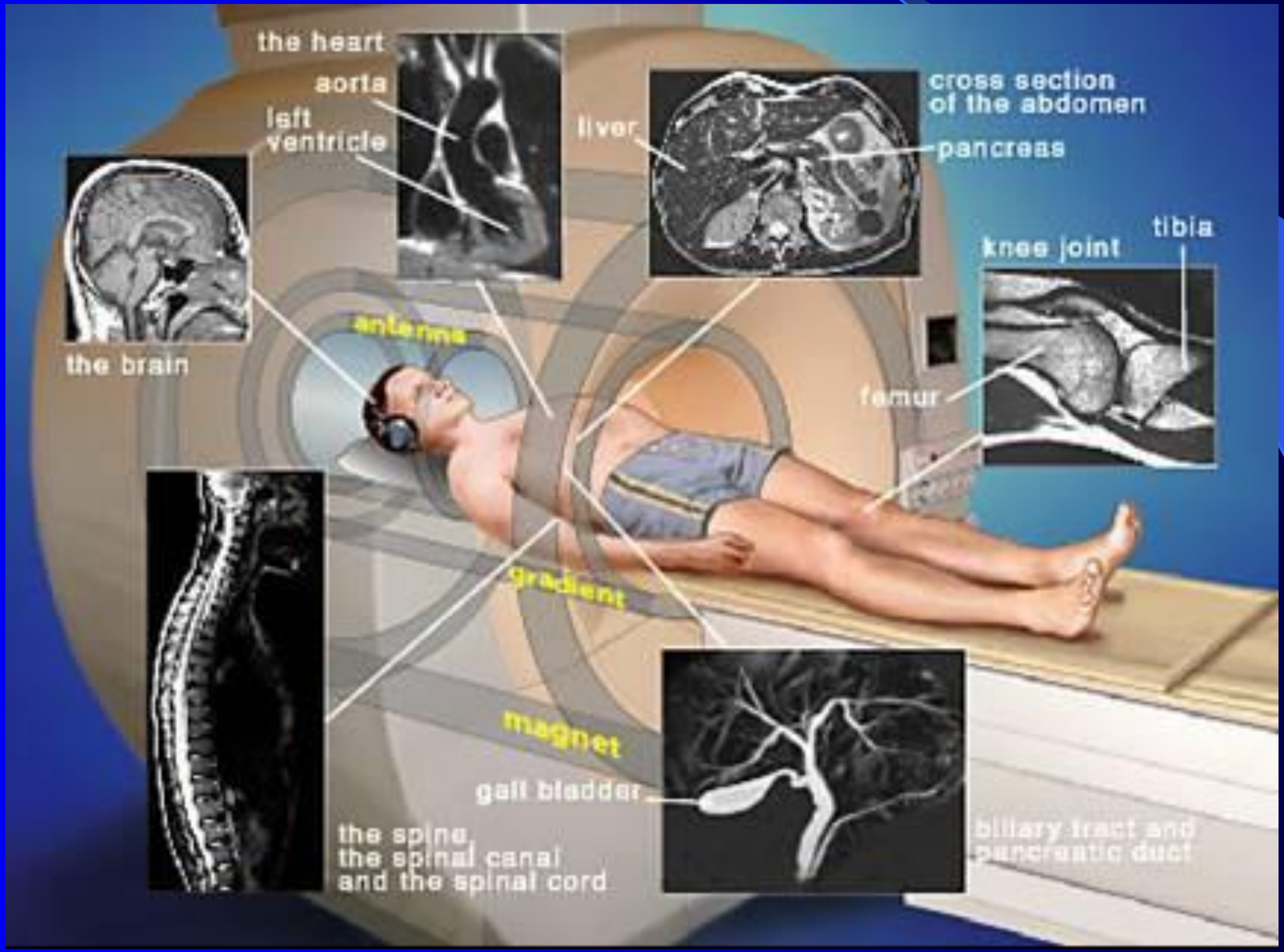
- **The somatotopic digit homuncular organization in the human primary somatosensory cortex (S1) was originally mapped by Penfield in 1937.**





Magnetic Resonance Imaging (MRI)

-Apply RF energy to H^1 in H_2O molecules at high magnetic field (MRI $B>1.5T$;   note: Earth $B \sim 5 \times 10^{-5}$ T, Human $B \sim 10^{-6}$-10^{-9} T)



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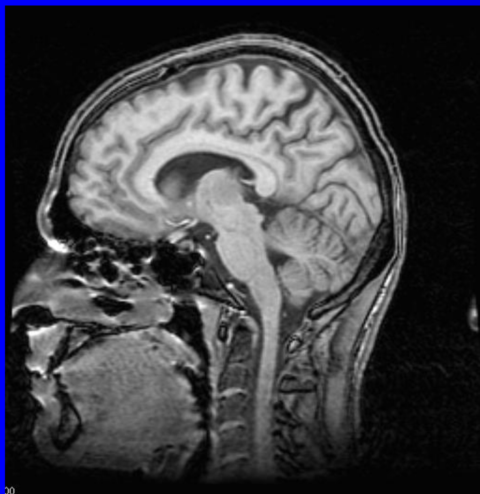
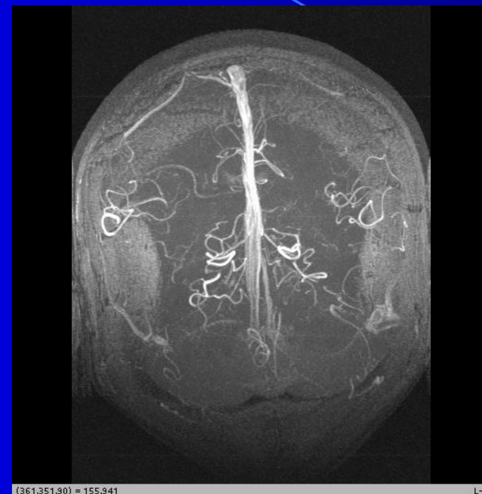
MRI Examples

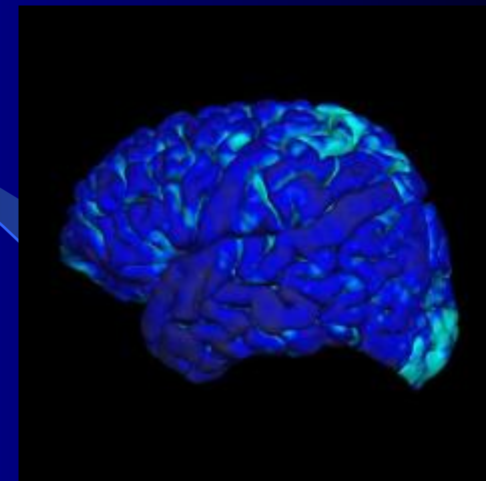
Anatomical MRI (T1-weighted)



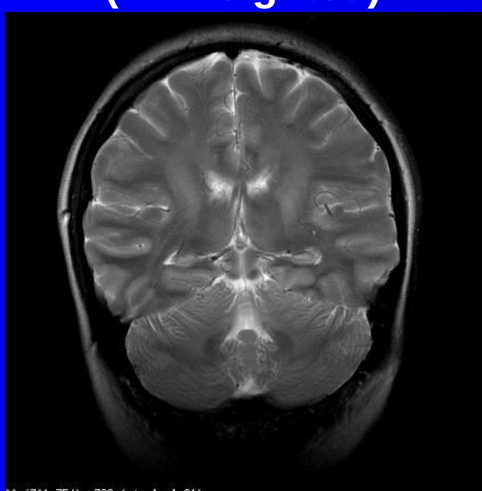
Angiogram (blood vessels map)



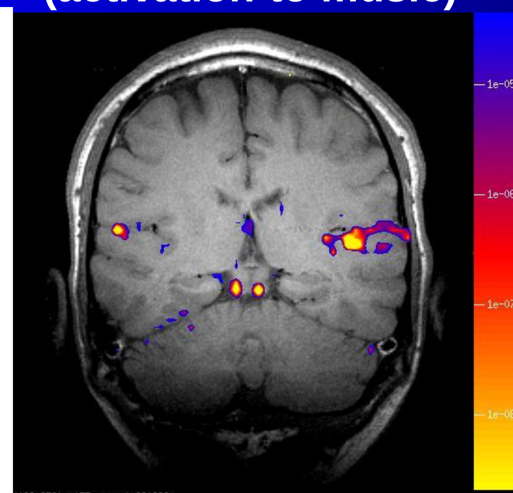
Structural MRI (gray matter thickness map)



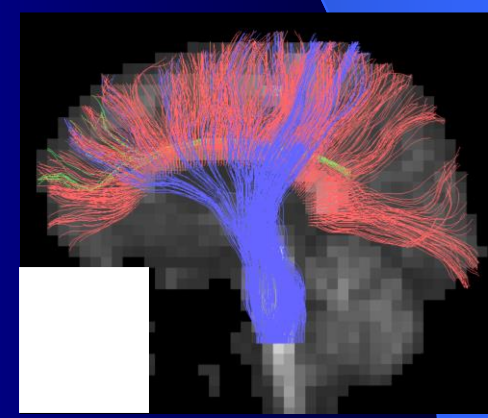
Anatomical MRI (T2-weighted)



Functional MRI (activation to music)



Diffusion Tensor MRI (white matter tracts)



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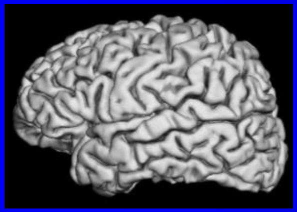
Brain Activation Imaging: "fMRI"

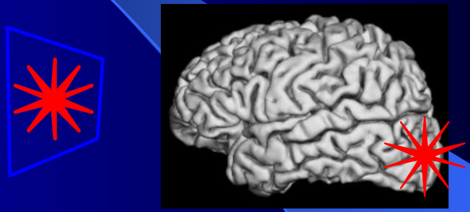
Belliveau et al., Science, Nov. 1991

What is functional MRI?

State (Stimulus **Off**):



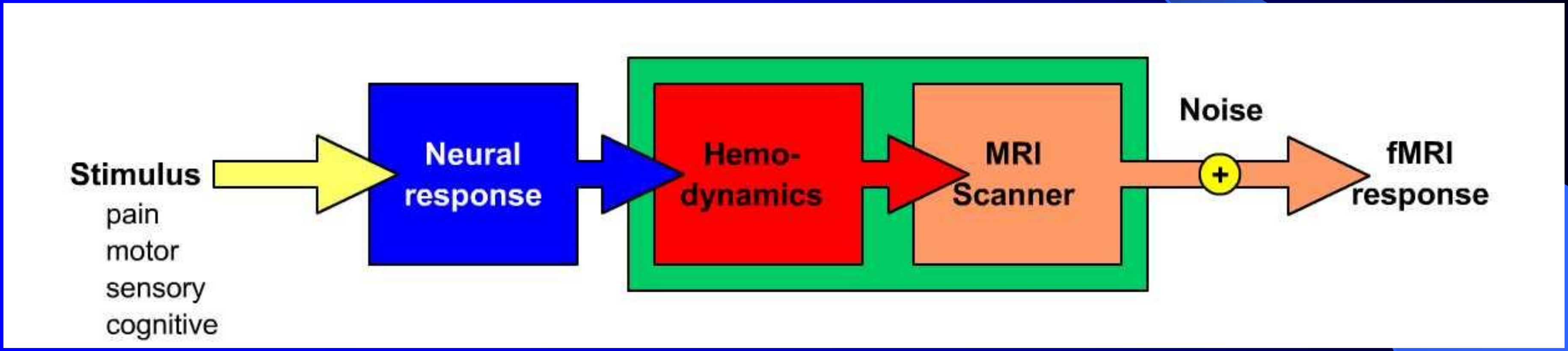
Activated State (Stimulus **On**):



fMRI detects <u>difference</u> in signal (ΔS = ON - OFF)

fMRI is <u>indirect</u> method to infer brain activity (hemodynamic, BOLD)

What is fMRI?



Huettel, 2004

NEURONAL ACTIVITY ⟷ **METABOLIC ACTIVITY** → **FUNCTIONAL BRAIN IMAGING**

"Coupling"

Action potentials/ postsynaptic potentials

CBF / Glucose / O_2

PET / fMRI / SPECT

SYNAPSE

NEURON-GLIA METABOLIC UNIT

IMAGING SIGNALS

Magistretti, et al

The Chain of Events

Increased Neural Activity

↓

Increased Local CBF and CBV

↓

Decreased Deoxyhemoglobin Concentration in Veins (BOLD)

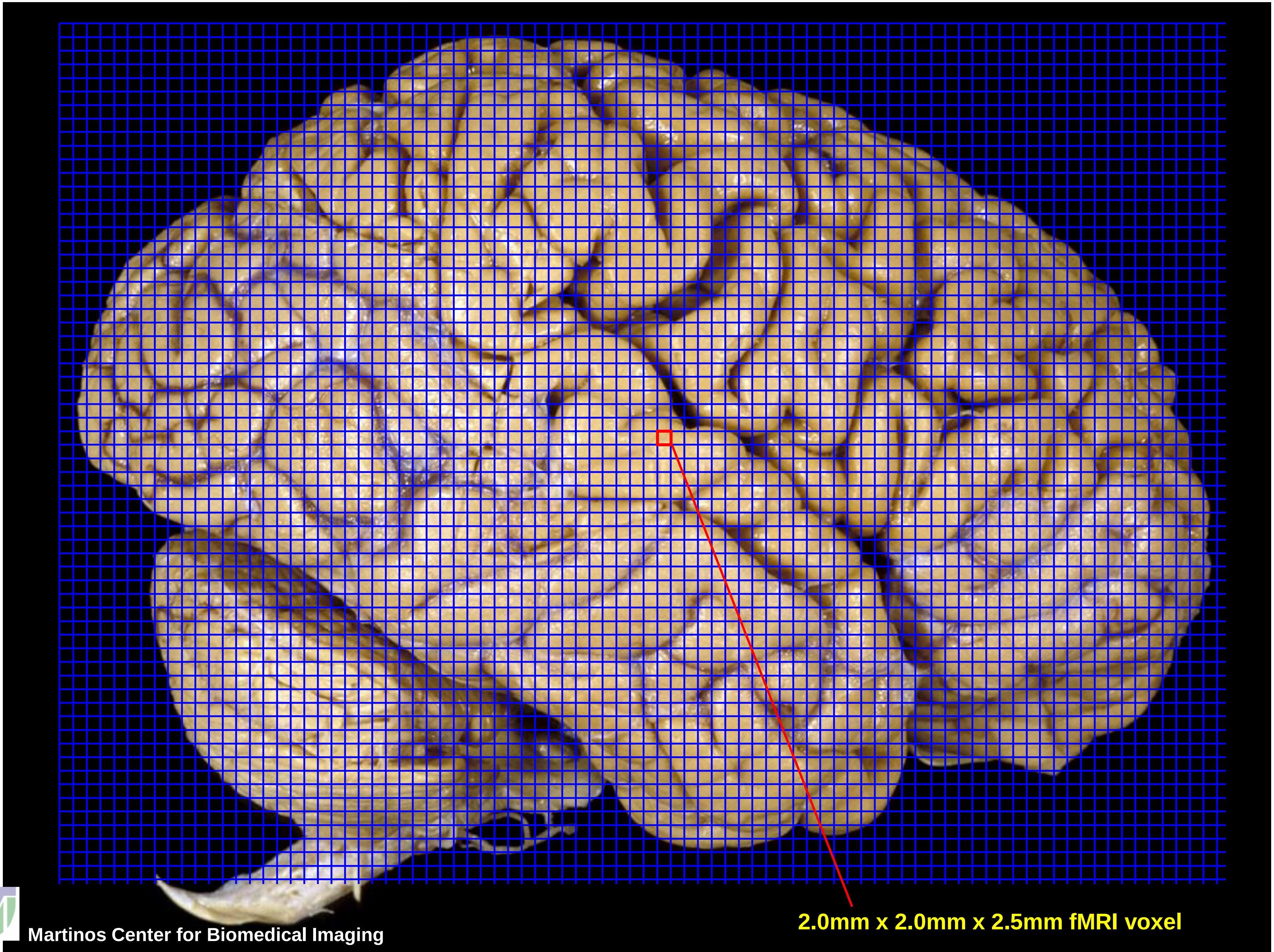
↓

Change in Magnetic Susceptibility

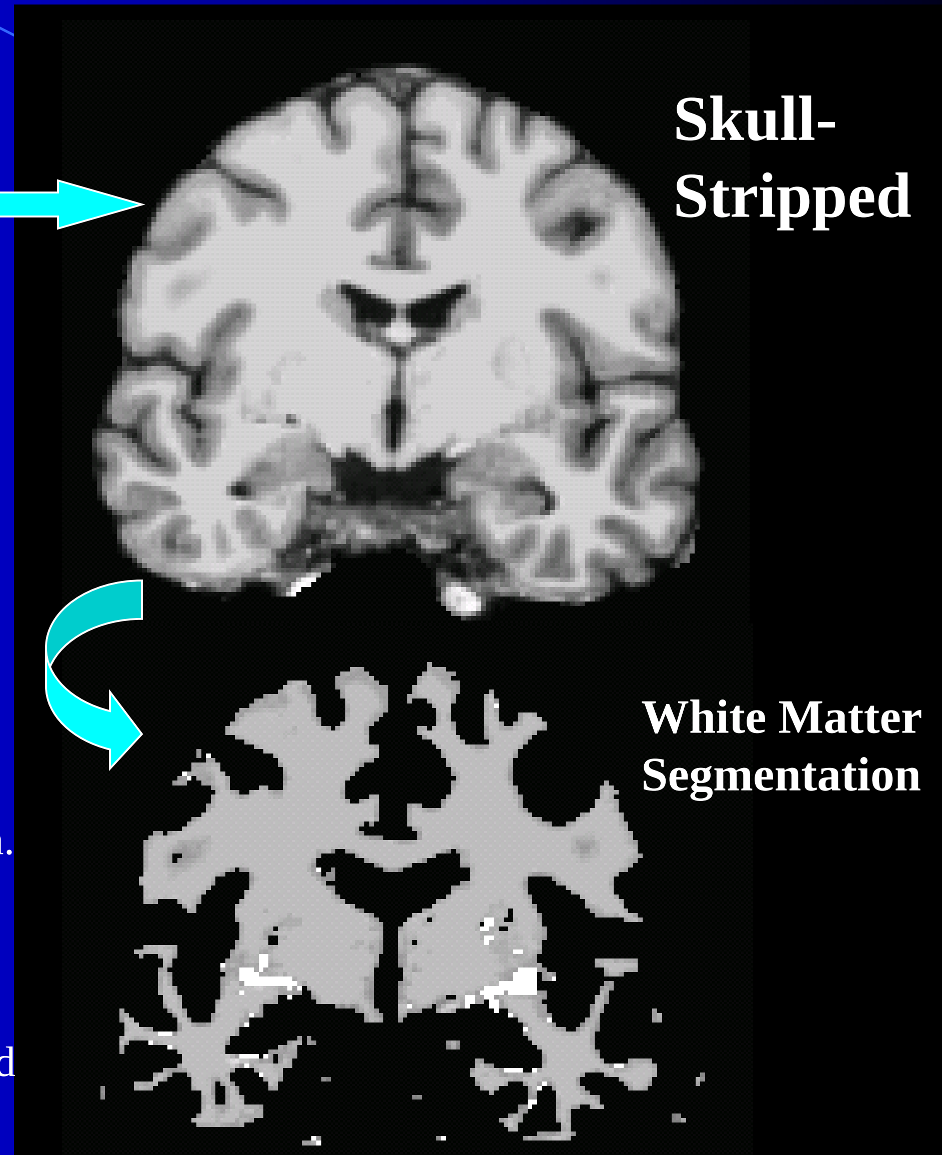
↓

Change in MRI Signal

Splitting the brain into voxels (3D pixels)



Freesurfer – Brain PreProcessing



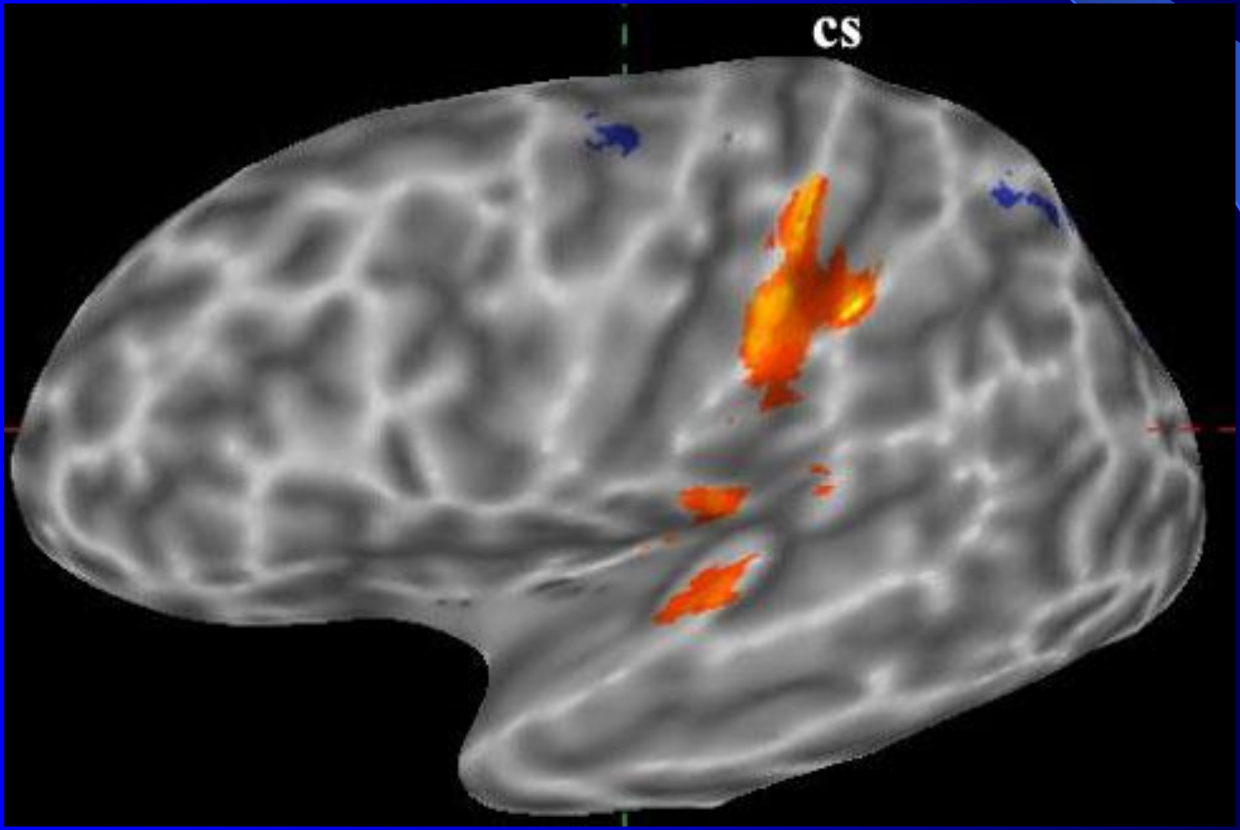
Images courtesy of wideman-one.com

Dale, A.M., et al. (1999). Cortical Surface-Based Analysis I: Segmentation and Surface Reconstruction. **NeuroImage** 9(2):179-194

[2] Fischl, B., et al. (1999). Cortical Surface-Based Analysis II: Inflation, Flattening, and a Surface-Based Coordinate System. **NeuroImage** 9(2):195-207

Inflated Brain Analysis

- Due to the undulating cortical topology, analyses of activation on the cortex are better visualized on an inflated brain surface which shows sulci and gyri as a greyscale texture map.



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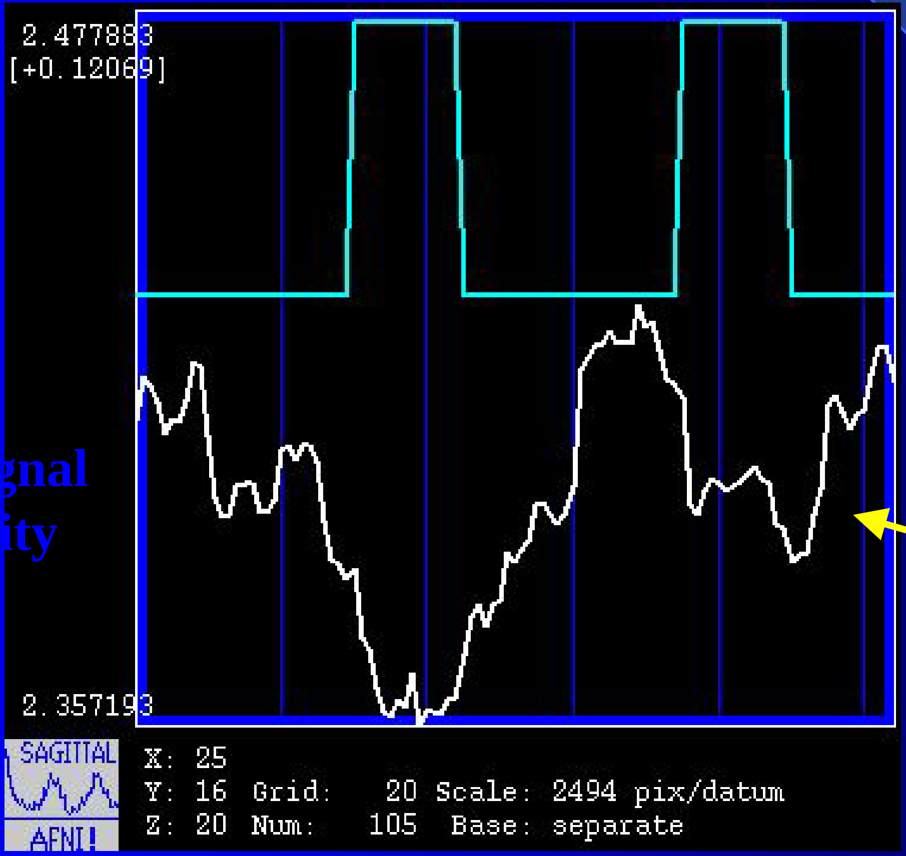
Using Block Design fMRI to infer Stimulus Effect

- A General Linear Model is applied to statistically test whether the MRI signal within any voxel correlates with the applied stimulus.

time



MRI signal from one of ~20,000 brain voxels demonstrates deactivation

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fMRI: Brain Processing of Acupuncture

CTS vs. Healthy Adults

CTS Baseline vs. Post-acupuncture

Acupuncture and CTS - Introduction

- Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy → U.S. prevalence 3.72%[1].

the CTS vicious cycle

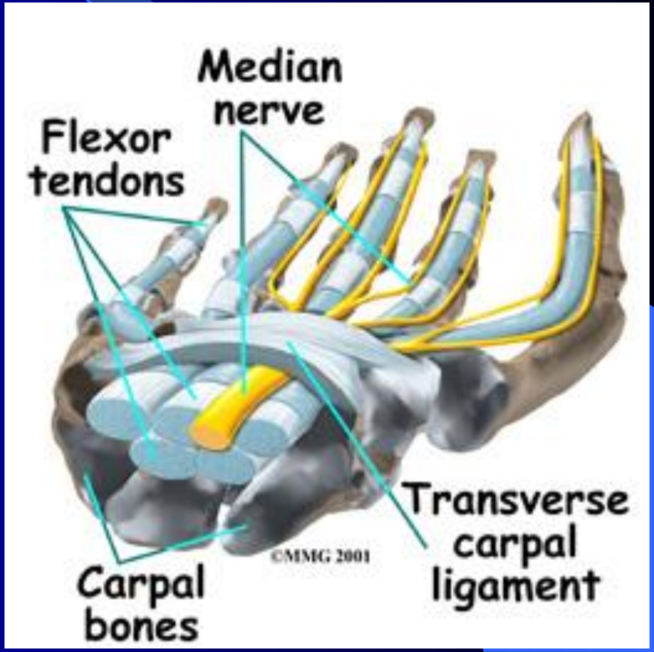
ischemia, inflammation → damage nerve microvasculature

damage nerve microvasculature → exudative edema, fibrosis

exudative edema, fibrosis → ↑ pressure in carpal tunnel

↑ pressure in carpal tunnel → ischemia, inflammation

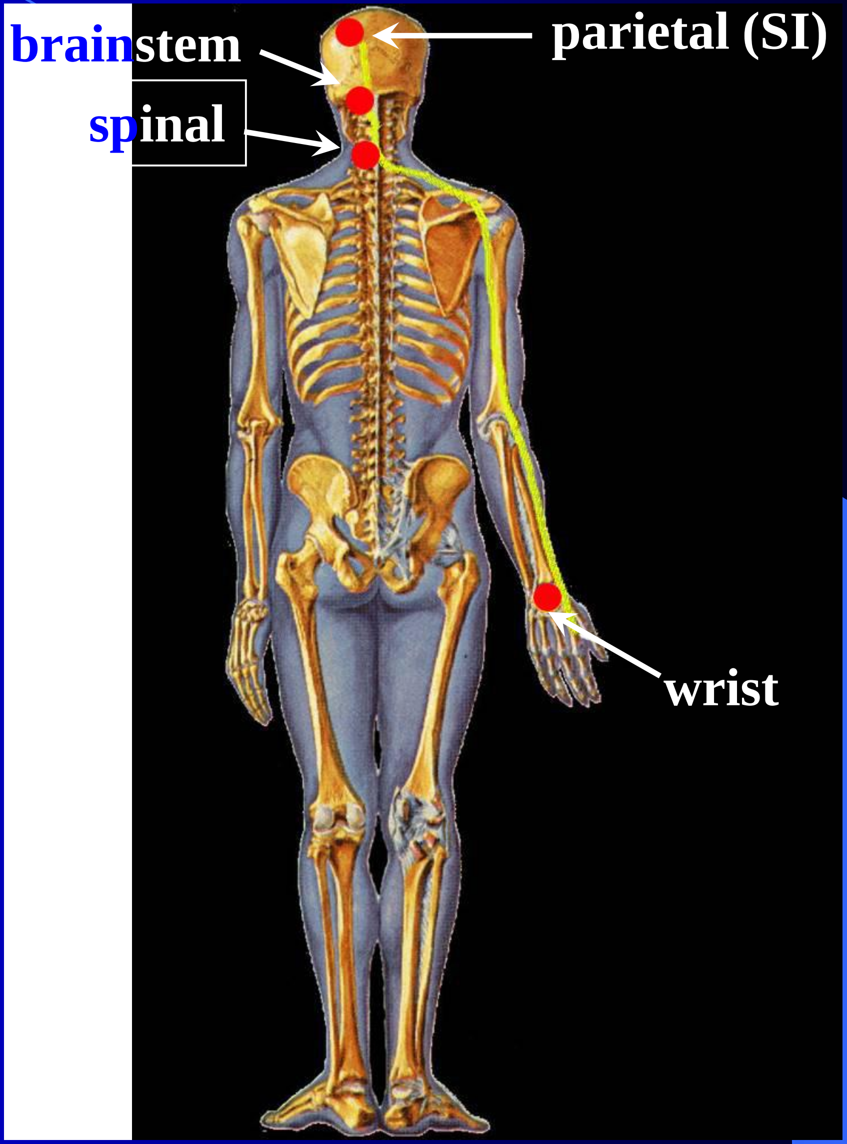
→ pain + paresthesias in 1^{st} to 4^{th} digits



[1]Papanicolaou, et al. J Hand Surg. 2001; 26(3):460-6

CTS Doesn't Just Affect the Wrist

- Median n. injury → abnormal activity within somatosensory system.
- Tinazzi reported somatosensory evoked potentials (SSEPs) abnormally amplified with stimulus to affected side – spinal N13, brainstem P14, parietal N20, P27[1]
- Tecchio reported cortical ECD amplification with MEG[2]



[1] Tinazzi M., et al. **Brain**, 1998. **121 (Pt 9)**:1785-94.
Tecchio, et al. **HBM**, 2002. **17**: 28-36.

Acupuncture Design

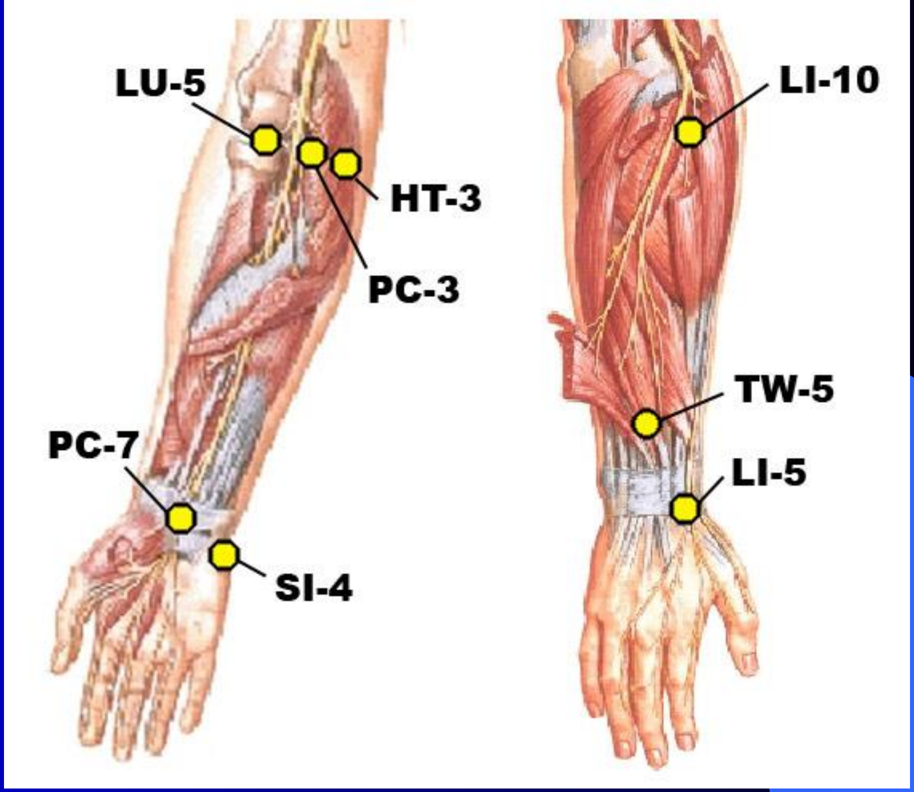
"Semi-Individualized" Protocol

3x/week for 3 weeks + 2x/week for 2 weeks = 13x over 5 weeks:

Needles: 38 guage (0.18mm), 30mm length

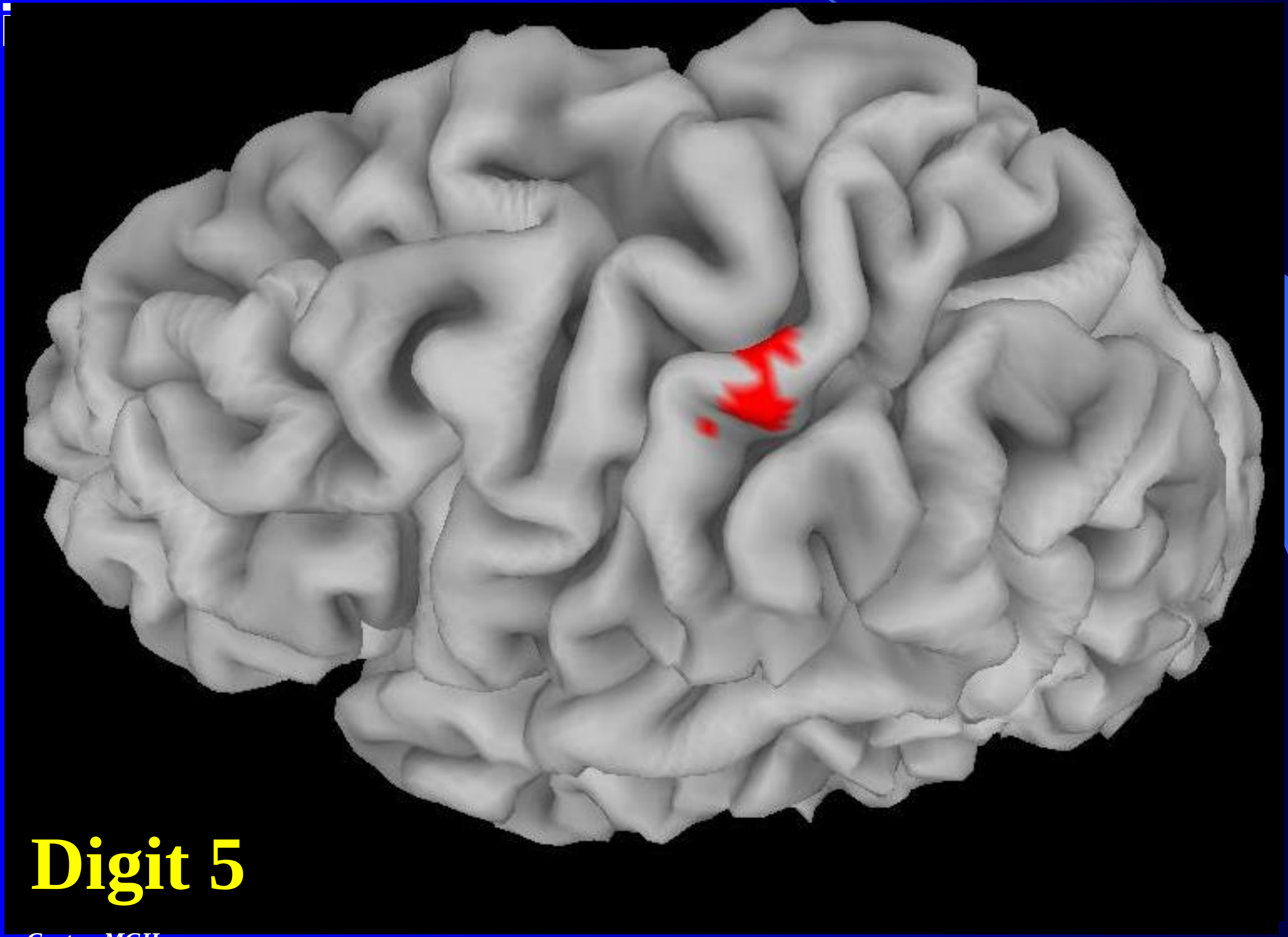
Common Points (every subject): unilateral TW-5 (*interosseous*) to PC-7 (*median*), 2Hz EA, low intensity.

Variable Points (symptom based): acupuncturist chooses 3 of 6 based on diagnosis: HT-3 (*antebrachial cutaneous*), PC-3 (*median*), SI-4 (*ulnar*), LI-5 (*radial*), LI-10 (*radial*), LU-5 (*radial*); manual even needle technique.



fMRI Digit Representations

- fMRI activation was observed in contralateral BA 1 for digits 2, 3, and 5 in most subjects, with digit 2 most ventral and digit 5 most dorsal, demonstrating di



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Methods

CTS (n=10)

baseline

- Clinical testing
- fMRI with sensory stim. on digits 2, 3, 5.
- fMRI w. acup & ctl

→

5 weeks of acupuncture (13 Tx)
+
Clinical test at 2 weeks

→

5 weeks later

- Clinical tests
- fMRI

Healthy Adults (n=9)

baseline

- Clinical testing
- fMRI

→

5 weeks wait

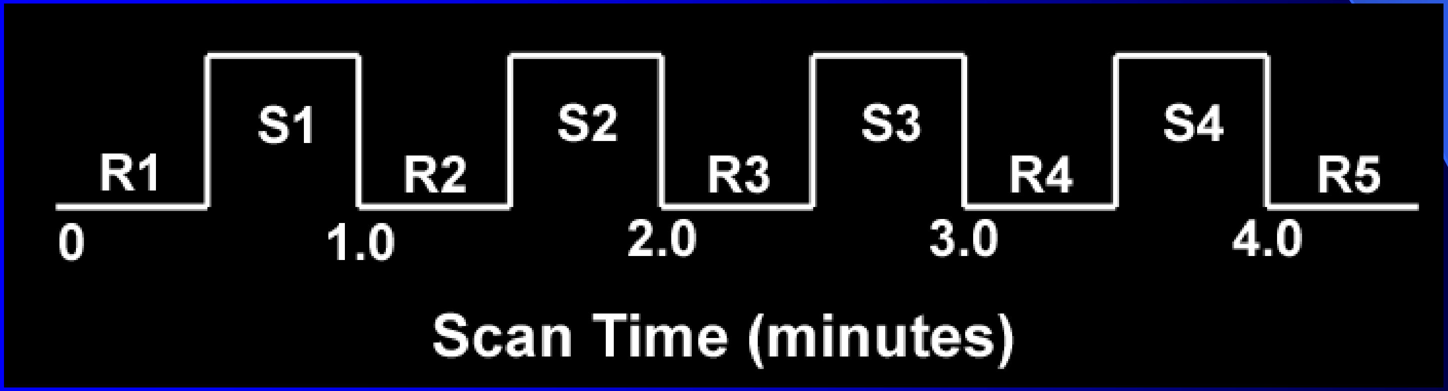
→

5 weeks later

- Clinical tests
- fMRI

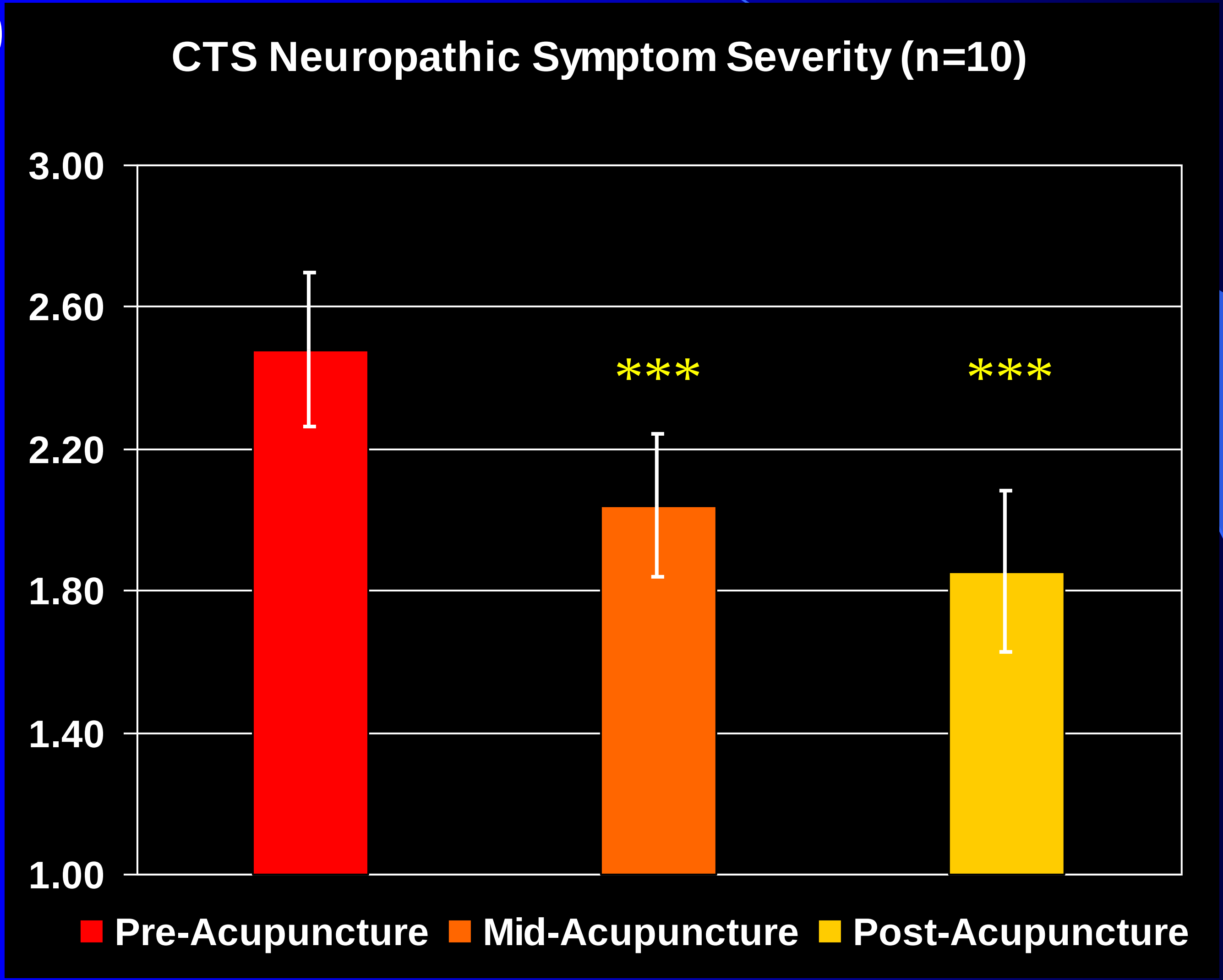
Method:

fMRI Digit Mapping: 100Hz electro-stimulation with surface electrodes on fingers 2, 3, and 5 (pseudorandom order); 0.2 mA below pain sensitivity threshold.

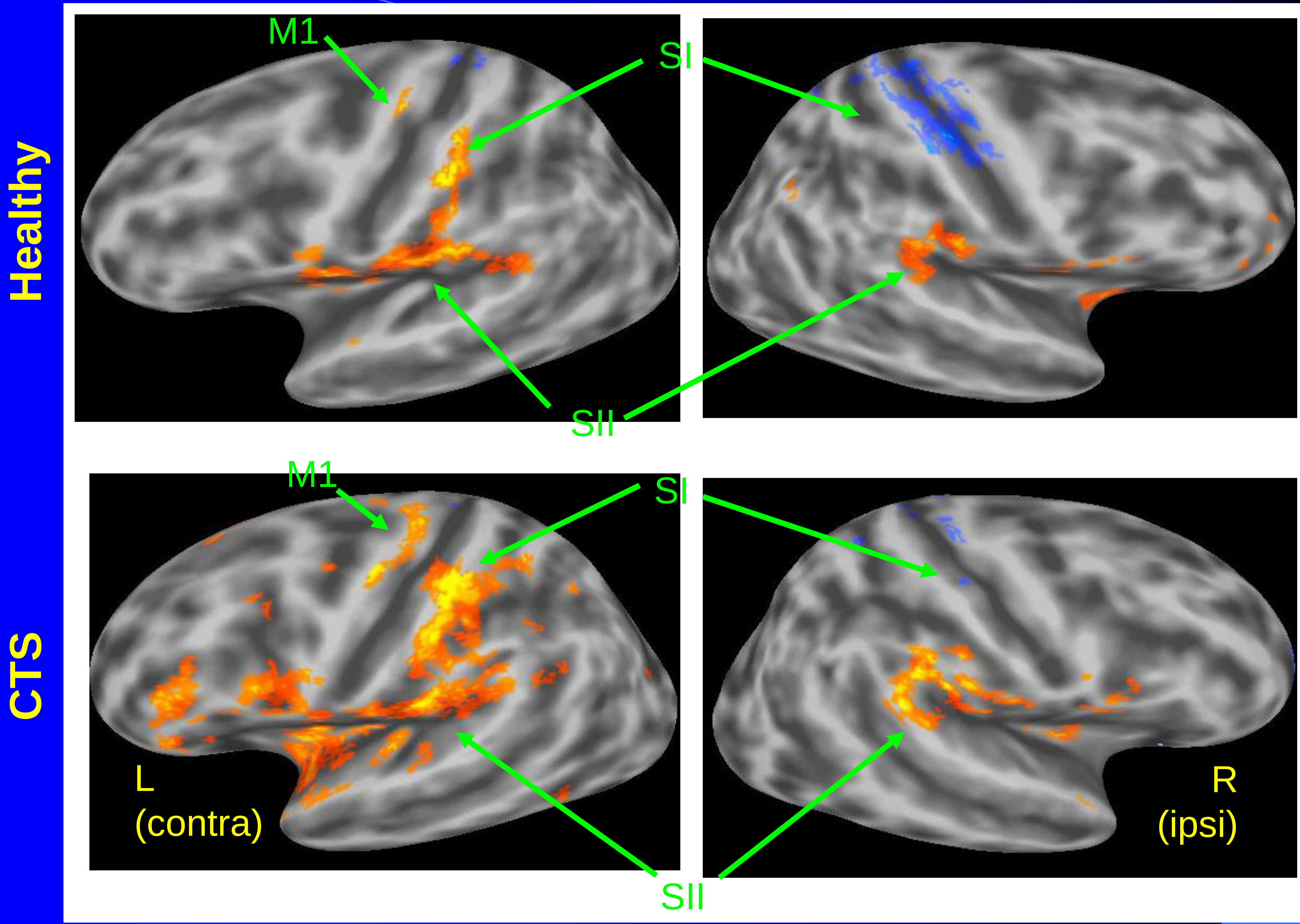


Clinical Results (subjective): Boston CTS Questionnaire

- Acupuncture diminished neuropathic symptom severity, as measured by the Boston CTS Questionnaire (paired t-test: p<0.00



Digit 3



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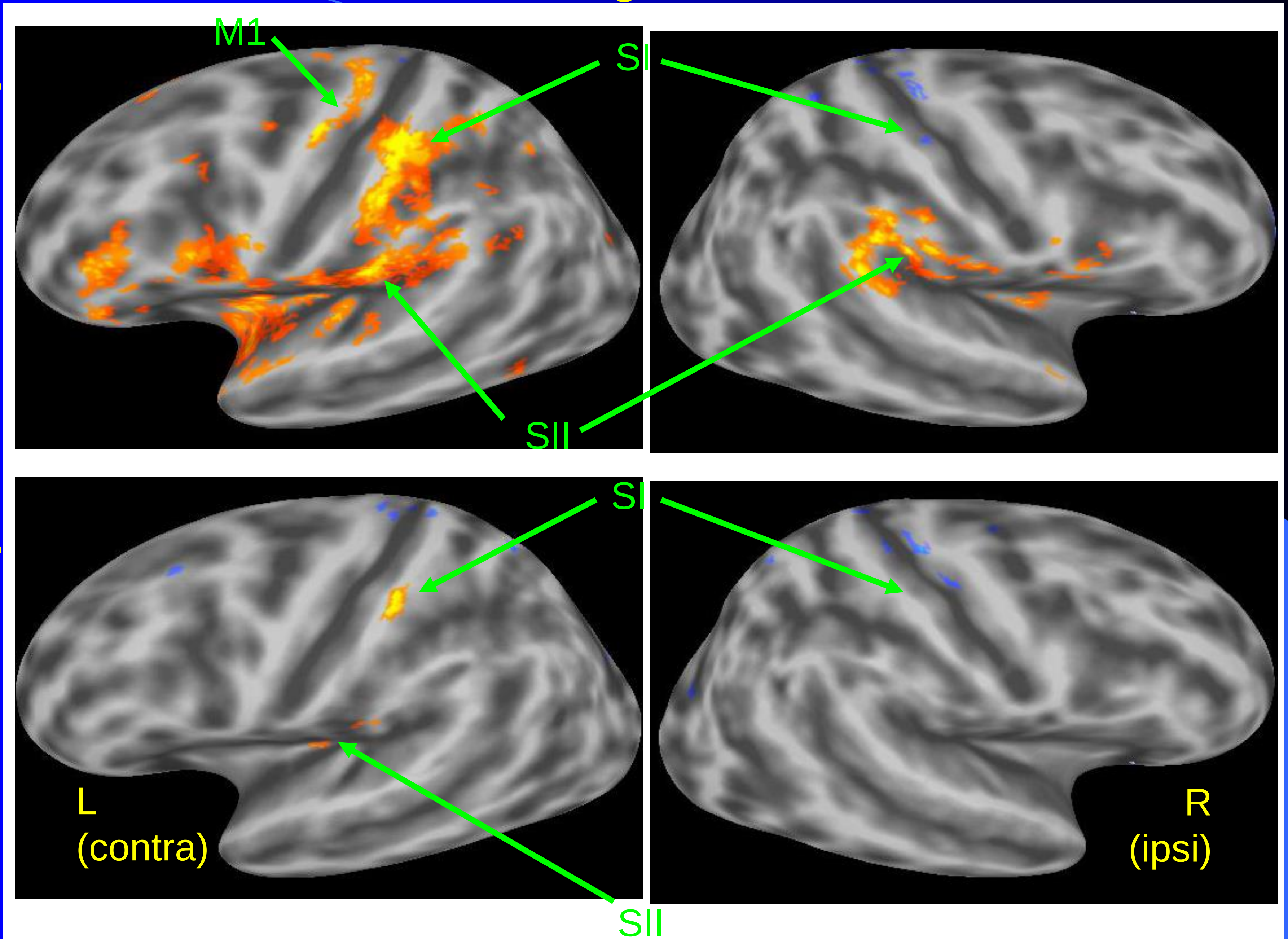
Digit 3

CTS Pre-Acup

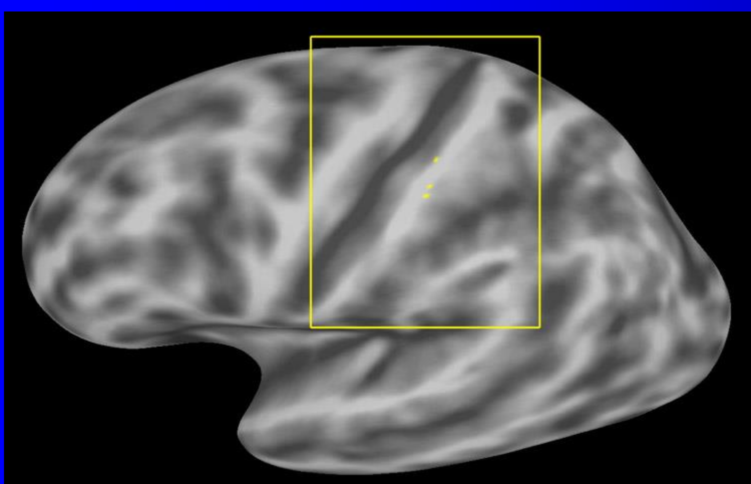
CTS Post-Acup



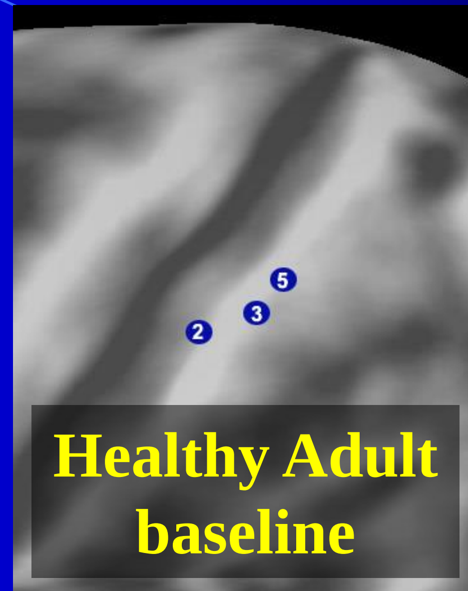
Group Map SI Somatotopy

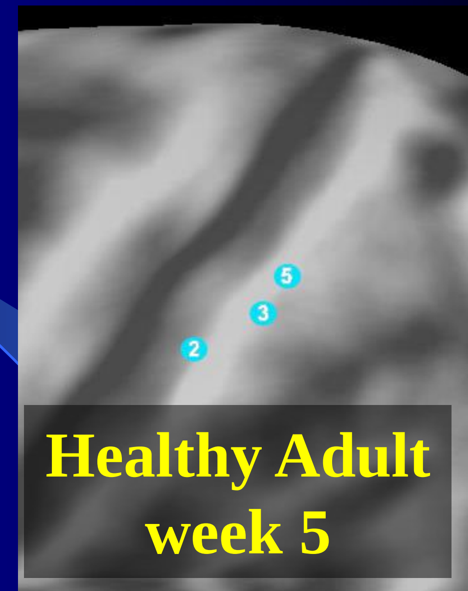
D2 & D3 were closer together for CTS patients than healthy adults

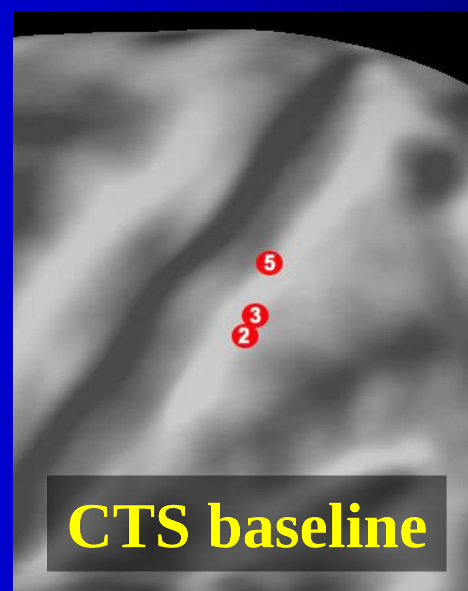
D2 & D3 were more separated post-acupuncture

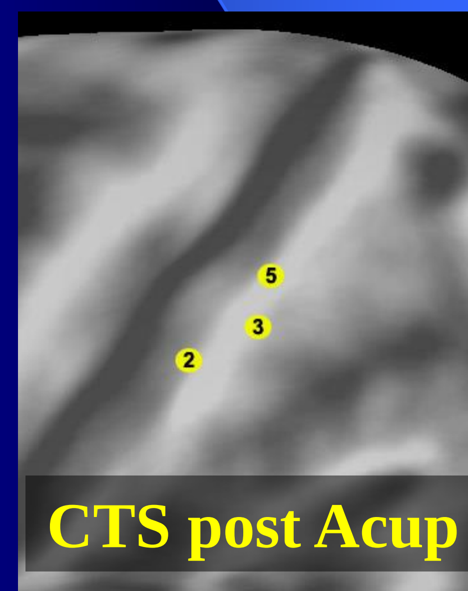


contralateral hemisphere









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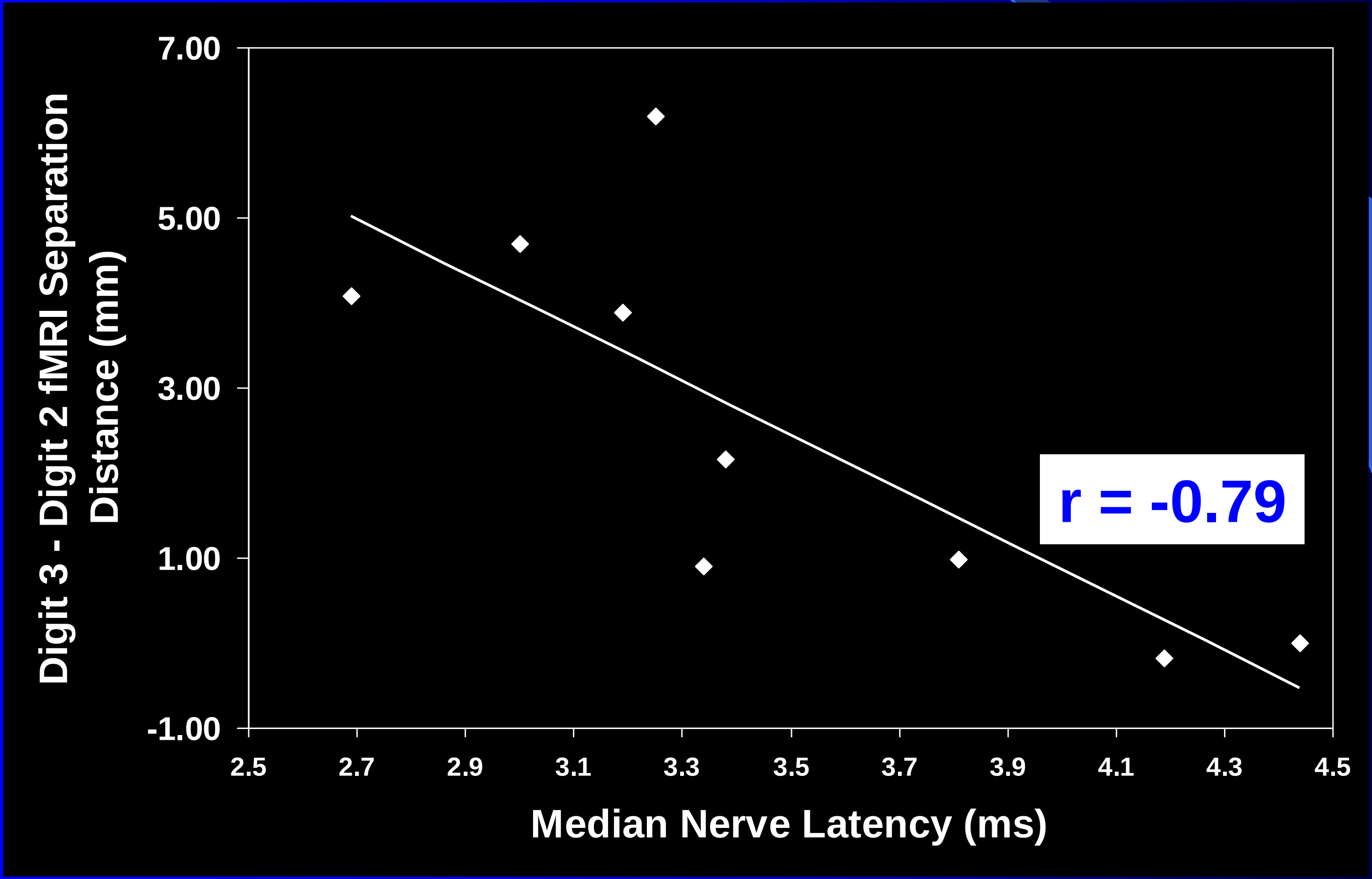
Somatotopic Separation Correlates with Peripheral Pathology in CTS patients

- Negative correlation between digit 3/2 separation distance and D2 nerve conduction delay ($p<0.05$).



CTS – A Central Manifestation of Peripheral Nerve Dysfunction

Carpal Tunnel Syndrome

pain + paresthesias

more frequent and abnormal nerve traffic to brain

disinhibition

more extensive digit representations in cortex

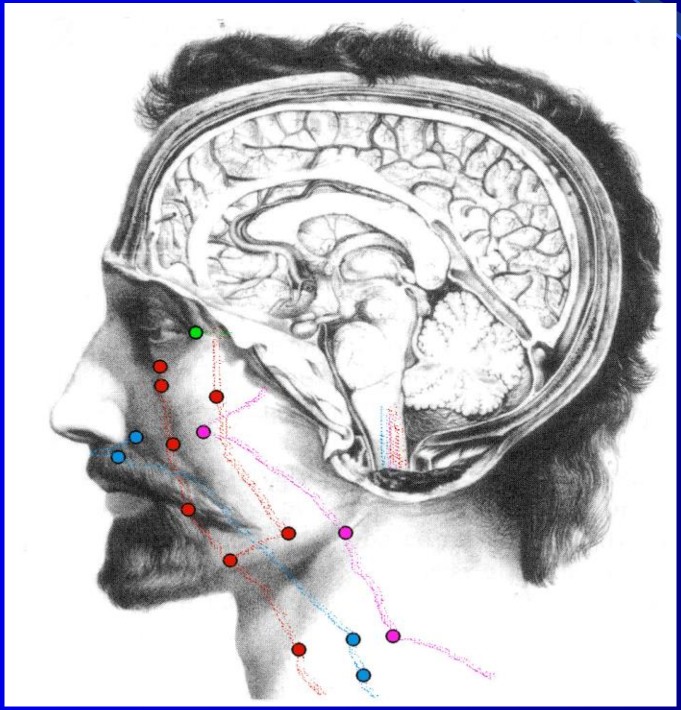
more simultaneous signaling from affected digits

Hebbian plasticity mechanisms

overlapping and blurred digit representation in cortex

Acupuncture Modulates Resting State Connectivity in Default and Sensorimotor Brain Networks

Rupali P Dhond, Calvin Yeh, Kyungmo Park, Norman W Kettner, Vitaly Napadow



Martinos Imaging Center, MGH

Dept. of Radiology, Logan College of Chiropractic,
Athinoula A. Martinos Center for Biomedical Imaging,
MIT, Massachusetts General Hospital, Harvard Medical School

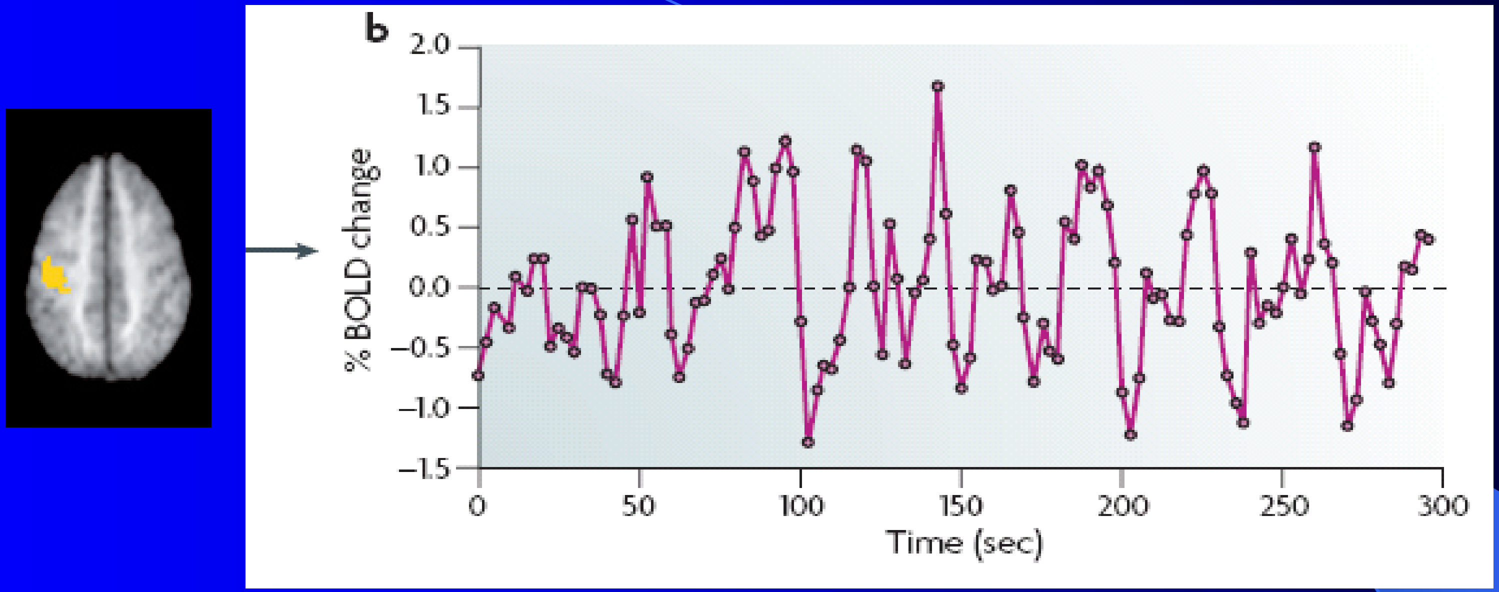
Background

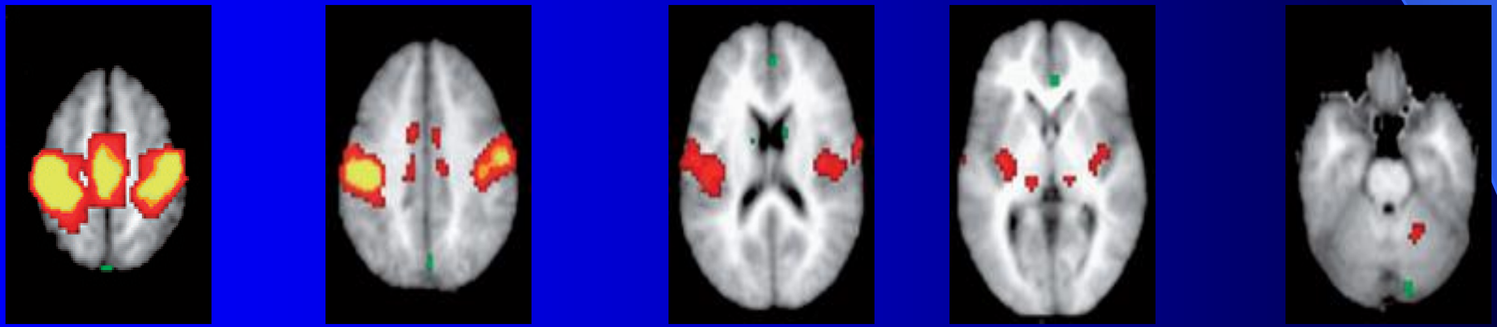
Abnormalities in functional connectivity within inter-related brain regions may contribute to the pathophysiology of idiopathic disorders such as chronic low back pain.

Functional connectivity refers to temporal synchrony and correlation between distinct and spatially remote brain regions.

Low frequency fluctuations in cerebral hemodynamics (0.01- 0.1Hz) have been identified (Biswal 1995) in fMRI data obtained during rest, and are temporally correlated across widely separated brain regions characterizing a functional resting state network (RSN).

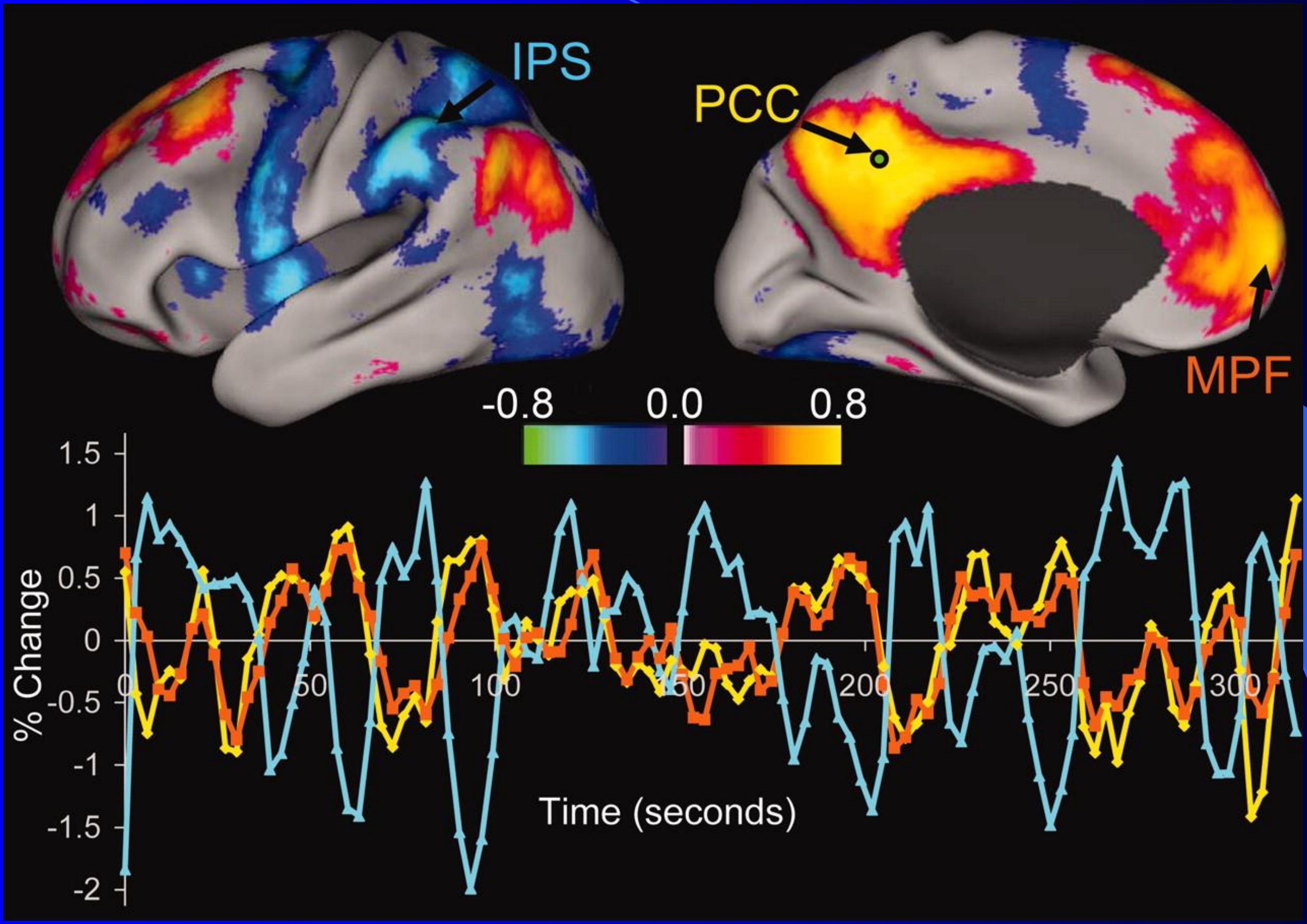
Seed Voxel Method





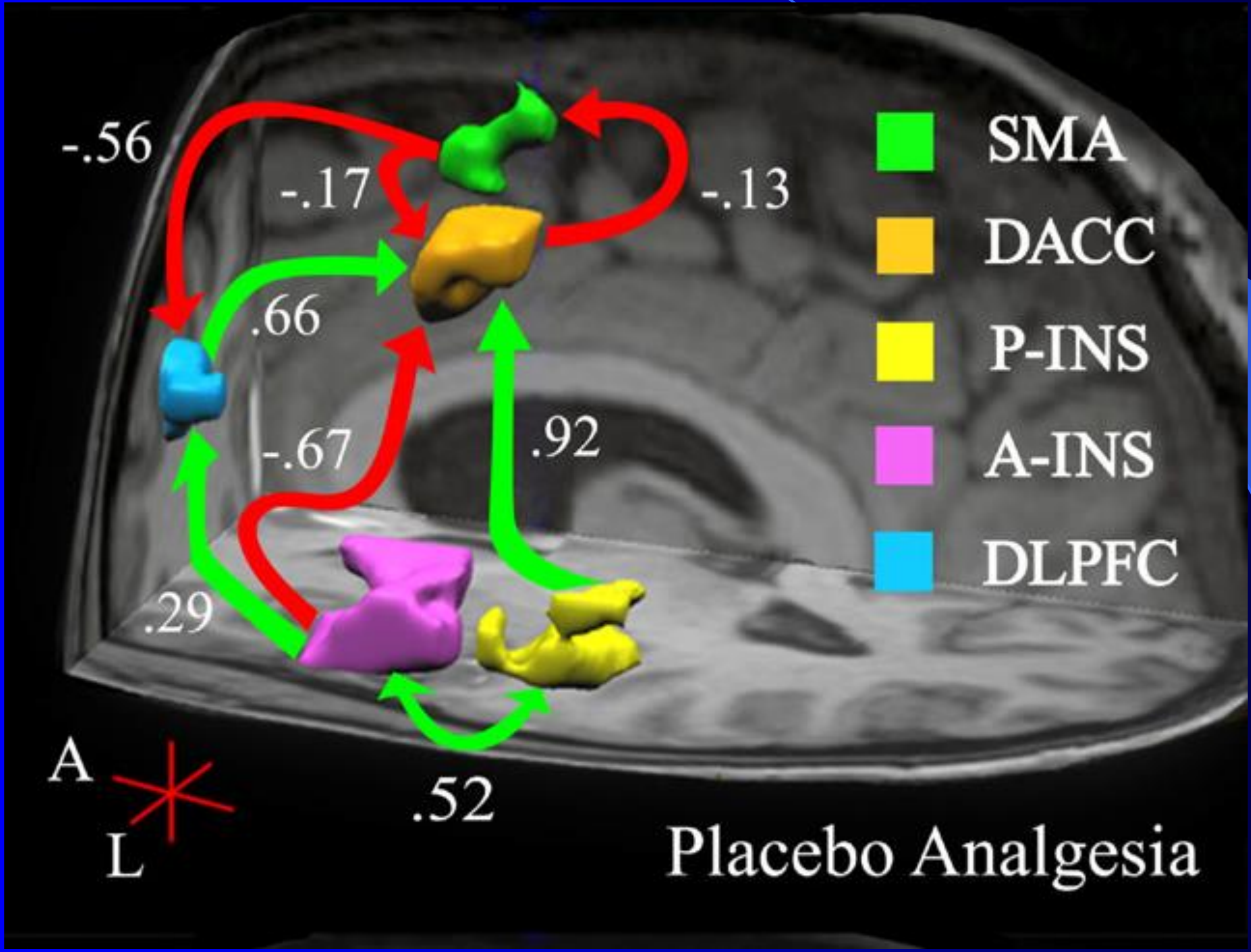
Fox, Raichle Nat Rev Neurosci. 2007

Intrinsic correlations between a seed region in the PCC and all other voxels in the brain for a single subject during resting fixation



Fox, Michael D. et al. (2005) Proc. Natl. Acad. Sci. USA 102, 9673-9678

SEM Method



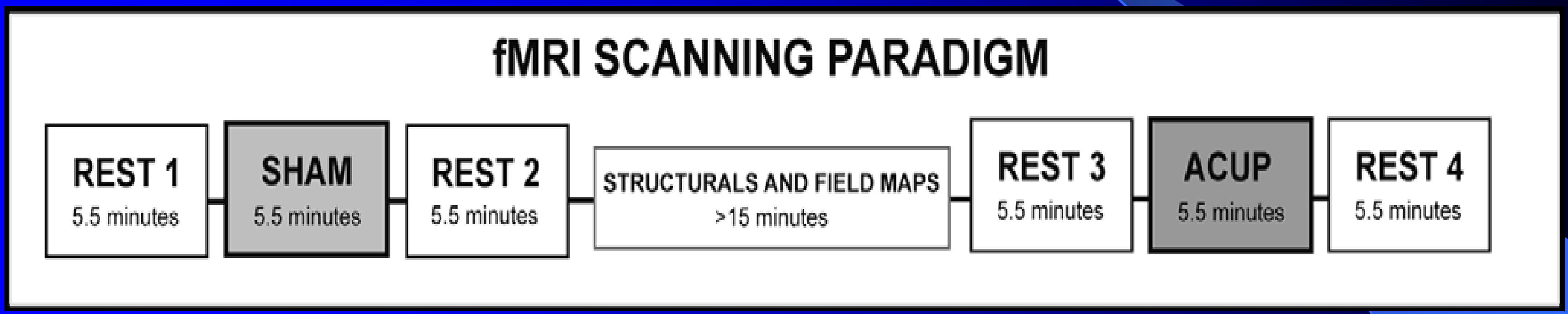
Craggs JG: NeuroImage 2007

Methods

We evaluated the functional connectivity present in non-task, resting fMRI data, both pre and post acupuncture at PC 6 with a non-insertive sham (Semmes -Weinstein filament) as sham.

Functional connectivity was evaluated with two template networks the "default mode" (DMN) and "sensory-motor networks" (SMN).

Data were collected from 15 healthy, right handed adults, 18-50. Manual acupuncture (MA) and sham acupuncture (SA) were used at left PC-6. During rest blocks there was no acupuncture intervention and subjects lay still and fixated on a centrally presented + symbol. The order of MA and SA runs were randomized across subjects.


fMRI SCANNING PARADIGM
REST 1
5.5 minutes
SHAM
5.5 minutes
REST 2
5.5 minutes
STRUCTURALS AND FIELD MAPS
>15 minutes
REST 3
5.5 minutes
ACUP
5.5 minutes
REST 4
5.5 minutes

Data were acquired using a Siemens Trio 3T MRI system equipped for echo planar imaging. Probabilistic independent component analysis (pICA) was performed on all rest runs using FSL-MELODIC to measure functional connectivity in the resting networks.

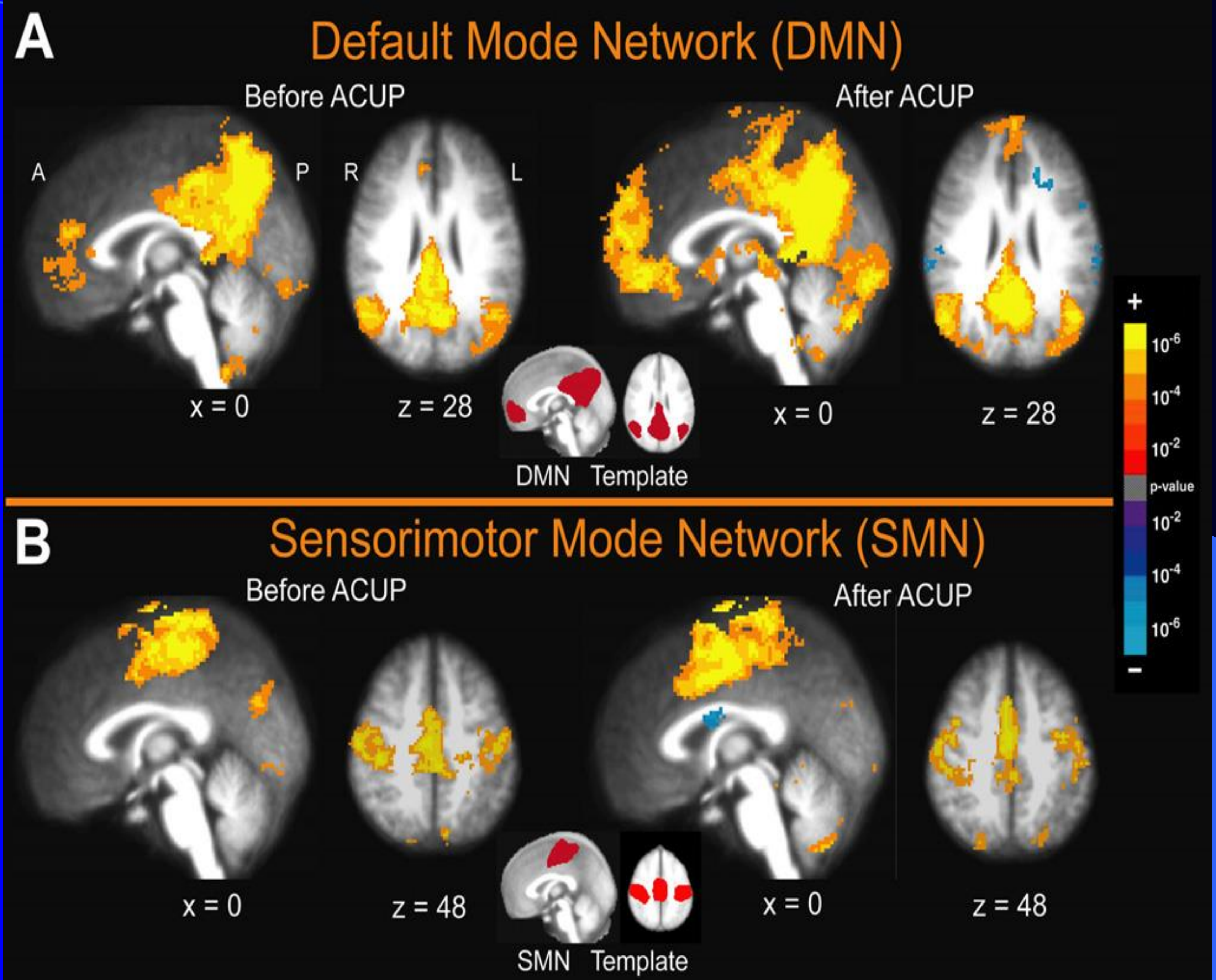
The pICA maps were in the form of a z – statistic for temporally coherent activated or deactivated areas. Components were obtained using “best fit” (average z-scores of voxels greatest inside /outside the template) from each rest run on all subjects.

Group analysis was performed on the selected component maps using a mixed effects model.

Paired and unpaired t-tests between resting state networks (DMN and SMN) before vs. after the acupuncture runs were obtained.

Results

Group maps of the best fitting IC for DMN and SMN showed consistent spatial distribution relative to their templates before and after acupuncture

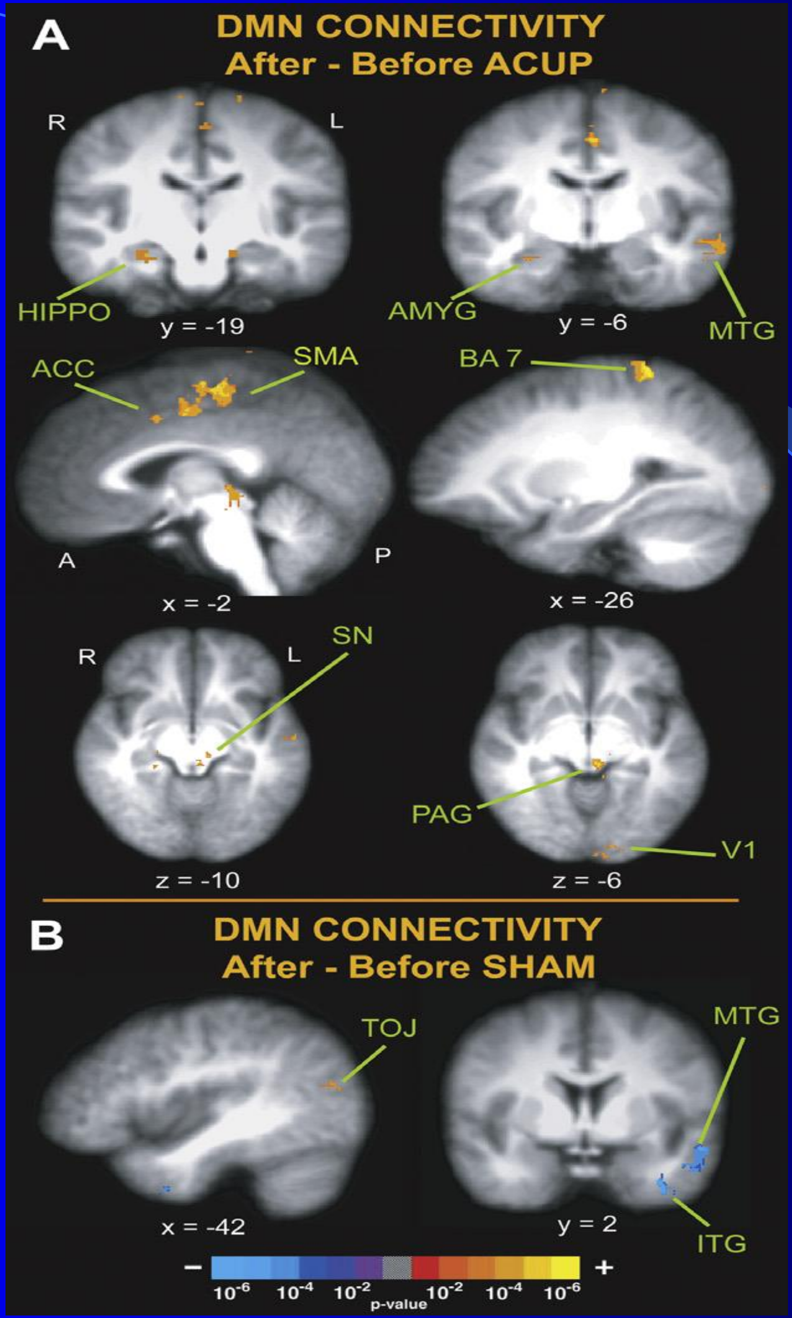


A
Default Mode Network (DMN)
Before ACUP
After ACUP
A
P
R
L
x = 0
z = 28
DMN Template
x = 0
z = 28
B
Sensorimotor Mode Network (SMN)
Before ACUP
After ACUP
x = 0
z = 48
SMN Template
x = 0
z = 48
+
10-6
10-4
10-2
p-value
10-2
10-4
10-6
-

Changes in connectivity (after vs. before) stimulation were observed in group maps for both MA and SA. The MA increased connectivity of the DMN with:

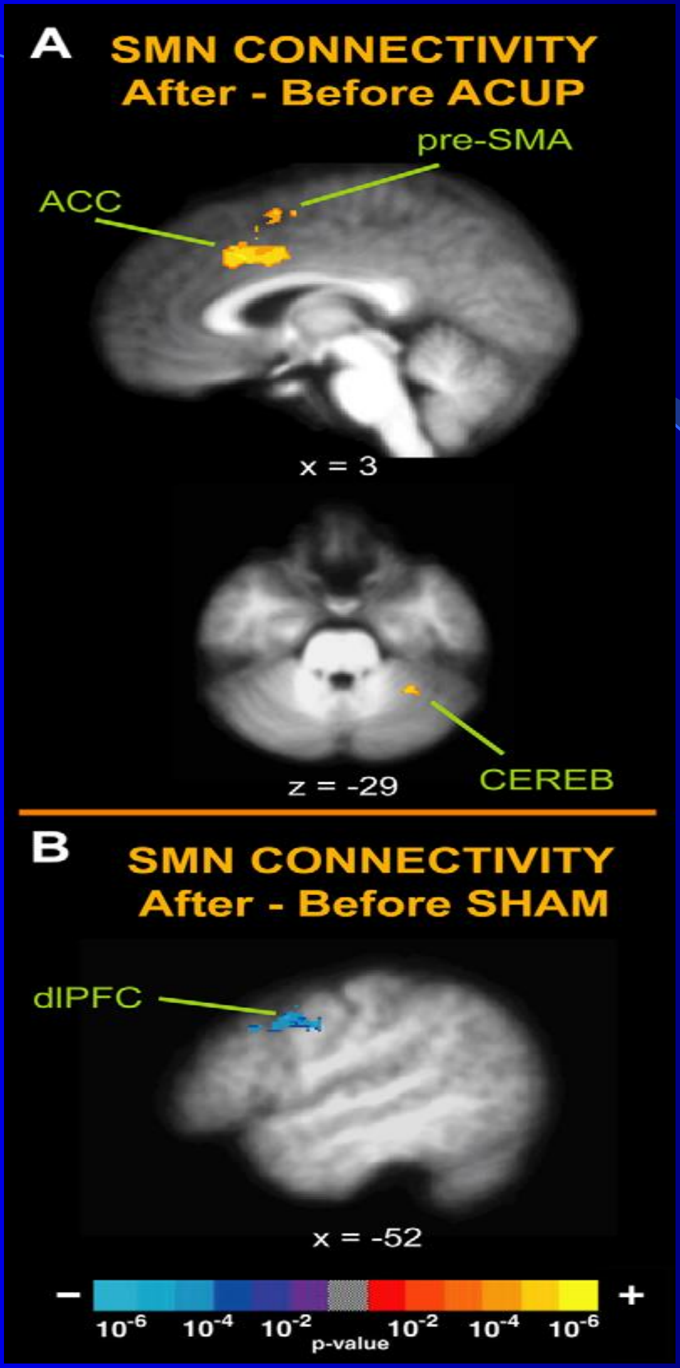
1. limbic and memory related areas (amygdala, hippocampus, middle temporal gyrus)
2. attentional (cingulate)
3. anti-nociceptive (PAG)
4. somatomotor (SMA)
5. spatial/associative (posterior parietal) regions

Following SA, the TOJ, MTG and ITG decreased connectivity with DMN.


A
DMN CONNECTIVITY
After - Before ACUP
R
L
HIPPO
y = -19
AMYG
y = -6
MTG
ACC
SMA
BA 7
A
P
x = -2
x = -26
SN
R
L
PAG
V1
z = -10
z = -6
B
DMN CONNECTIVITY
After - Before SHAM
TOJ
MTG
x = -42
y = 2
ITG
−
+
10-6 10-4 10-2 p-value 10-2 10-4 10-6

Changes in the SMN for MA (but not SA) involved increased connectivity within the somatomotor network (ACC, cerebellum pre-SMA).

For SA, decreased connectivity for SMN was seen in the dorsolateral prefrontal cortex


A
SMN CONNECTIVITY
After - Before ACUP
pre-SMA
ACC
x = 3
z = -29
CEREB
B
SMN CONNECTIVITY
After - Before SHAM
dlPFC
x = -52
−
+
10-6
10-4
10-2
10-2
10-4
10-6
p-value

Conclusions

This study supports the modulation (increase) of the intrinsic functional connectivity of resting state networks (DMN, SMN) in the brain associated with the complex somatosensory stimulation of acupuncture. Future work will study RSN functional connectivity in chronic pain patients.

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NCCAM

M.I.N.D.® Institute

Pain in the Brain: The Role of Functional Neuroimaging

- Biology of Nociception, Pain and Placebo
  - Biopsychosocial model
  - Neuroanatomy of nociception
  - Perception of pain
  - Placebo response
- Functional Neuroimaging Techniques
  - Positron Emission Tomography (PET)
  - Functional Magnetic Resonance Imaging (fMRI)
- Functional Neuroimaging of the Human Brain
  - Imaging the placebo response
  - Imaging chronic pain (CTS)
  - Imaging resting state networks

Conclusion

INAUGURAL JOSEPH W. HOWE ORATION IN DIAGNOSTIC IMAGING

Inaugural
Oration in Diagnostic Imaging
William D. Purser Center, DC Center
Logan College of Chiropractic
St. Louis Missouri
April 3, 2008

Presented by:
James M. Cox, DC, DACBR, FICC
Norman W. Kettner, DC, DACBR, FICC
Terry R Yochum, DC, DACBR,
Fellow, ACCR, FICC