Omneuron

APPLICATIONS OF REAL TIME FMRI: PAIN TREATMENT AND SUBSTANCE ABUSE TREATMENT

MARCH 2007

THIS WORK SUPPORTED BY NIH:

MH067290-01	NS050642-03	DA-4-7748	DA-4-7748	NS049673-01	DA021877-01A1
Applications of Real Time fMRI	Applications of Real Time fMRI - Phase II	Virtual Reality and Real Time fMRI	Virtual Reality and Real Time fMRI - Phase II	Novel Methods for Functional Brain Imaging	Measurement and Control of Patterned Brain Activation

SPECIAL THANKS FOR HELP AND GUIDANCE

Nora Volkow, NIDA
Ro Nemeth, NIDA
Dave Thomas, NIDA
Larry Stanford, NIDA
Linda Porter, NINDS

COLLABORATIVE TEAM

	AFFILIATION
CHRISTOPHER DECHARMS –Chloe Hutton –Susan Landau –Brett Mensh –Kristen Lutomski –Saxon MacLeod –Debbie Scacco –Dave Hagewood	Omneuron
SEAN MACKEY –Axel Lucca –Deepak Soneji	STANFORD
JOHN GABRIELI	MIT
–Fumiko Maeda	STANFORD
–Alison Adcock	UCSF
GARY GLOVER	STANFORD
JOHN PAULY	STANFORD

TALK OUTLINE

OVERVIEW OF REAL TIME FMRI

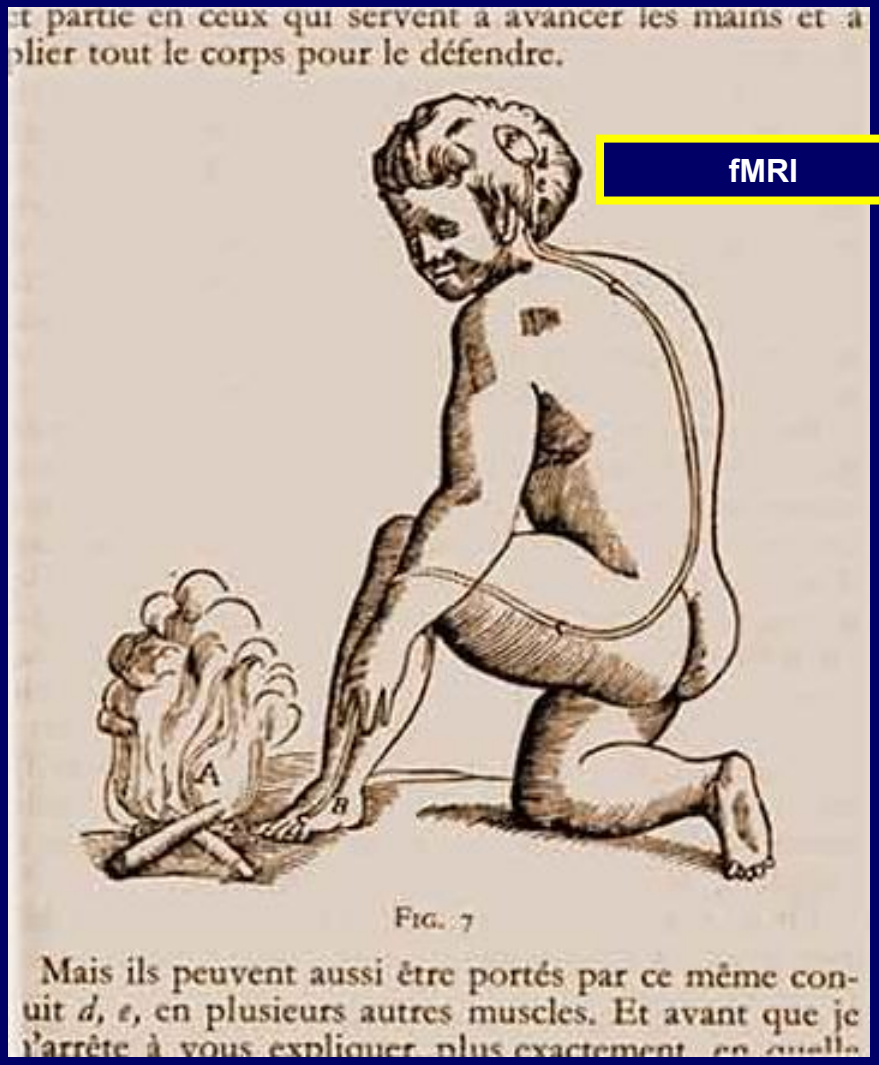
LEARNED CONTROL OVER BRAIN ACTIVATION AND PAIN

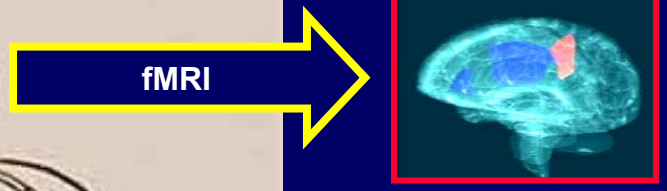
RTFMRI IN CHRONIC PAIN

SUBSTANCE ABUSE - PRELIMINARY EXPERIENCES

DESCARTES VIEW OF BRAIN, AND PAIN

IS IT POSSIBLE TO VISUALIZE THE MECHANISMS UNDERLYING PERCEPTION IN REAL TIME?





CAN MRI BECOME A THERAPEUTIC MODALITY?

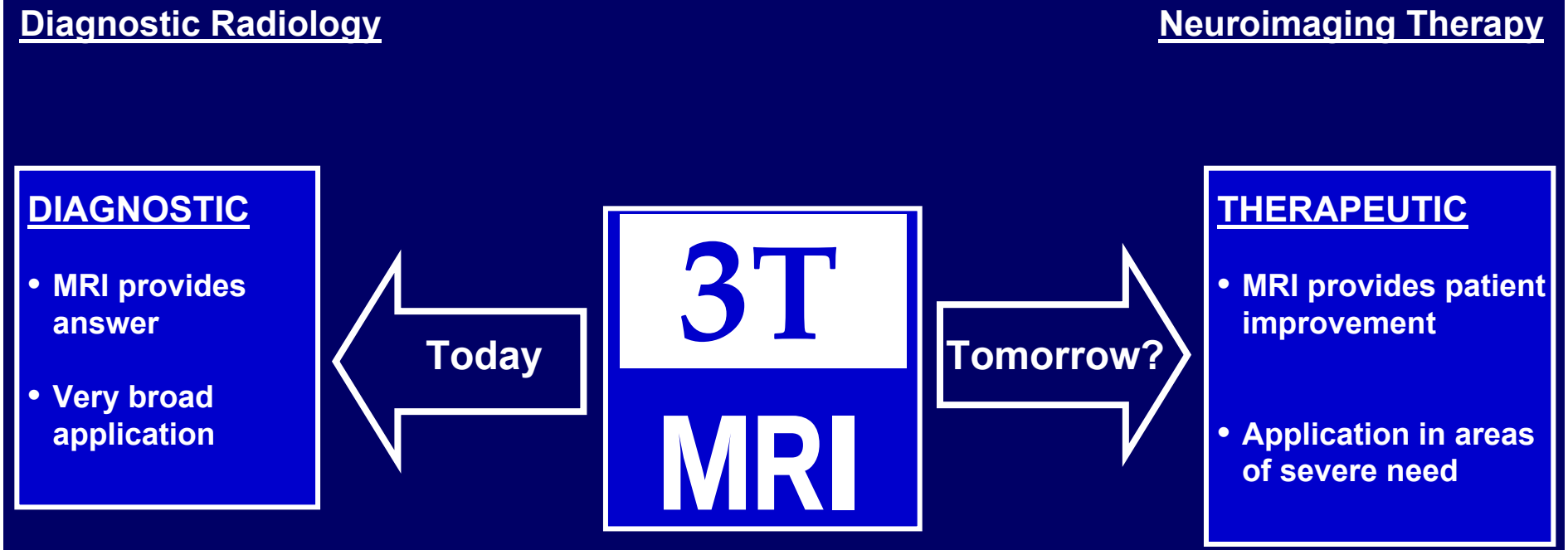
Diagnostic Radiology

DIAGNOSTIC

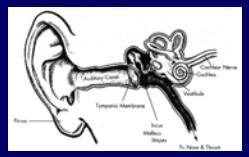
- MRI provides answer
- Very broad application

3T MRI

CAN MRI BECOME A THERAPEUTIC MODALITY?



RTFMRI AS A POTENTIAL NEW INTERFACE TO THE NERVOUS SYSTEM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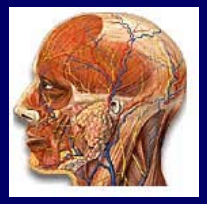
Wires

Cochlear implant

- Restore hearing through direct stimulation of the nervous system in the profoundly deaf
- Potential to move on to vision as well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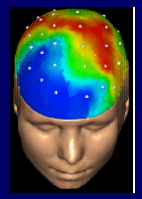
Wires

Deep brain stimulation

- Drive centers in the brain that control global functioning in order to remediate disease
- Currently applied in Parkinson's disease, efforts underway in others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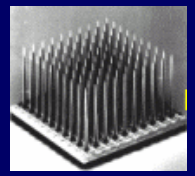
Wires

EEG-based measurement

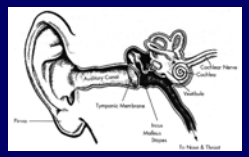
- Used in epilepsy and elsewhere
- EEG Neurofeedback
- Control of screen cursor demonstrated in people


+

Wires

Multi-electrode recording

- Control of screen cursor demonstrated in monkeys
- Potential to control prosthetics

RTFMRI AS A POTENTIAL NEW INTERFACE TO THE NERVOUS SYSTEM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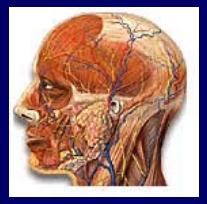
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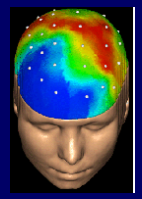
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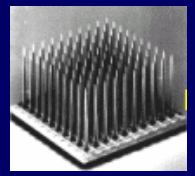
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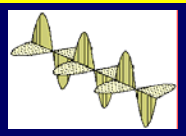
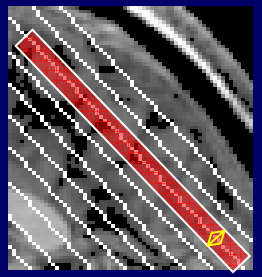

Photons

Neuroimaging/Cognitive

- Non-Invasive
- No tissue damage
- Reasonable localization

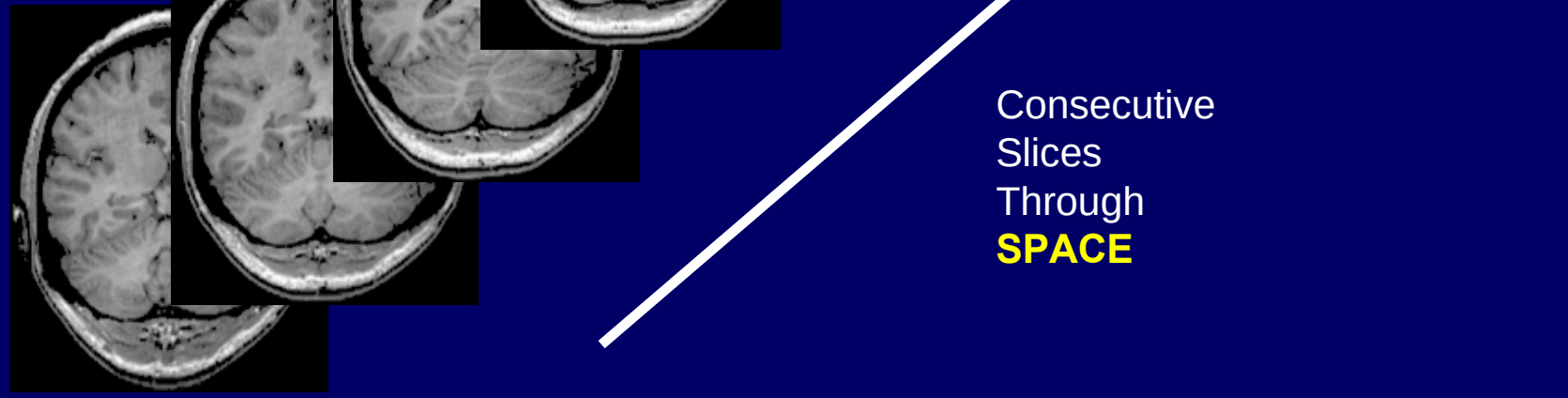
MRI: IMAGES OF ANATOMY – PHYSICAL STRUCTURE



Slice Thickness
e.g., 6 mm

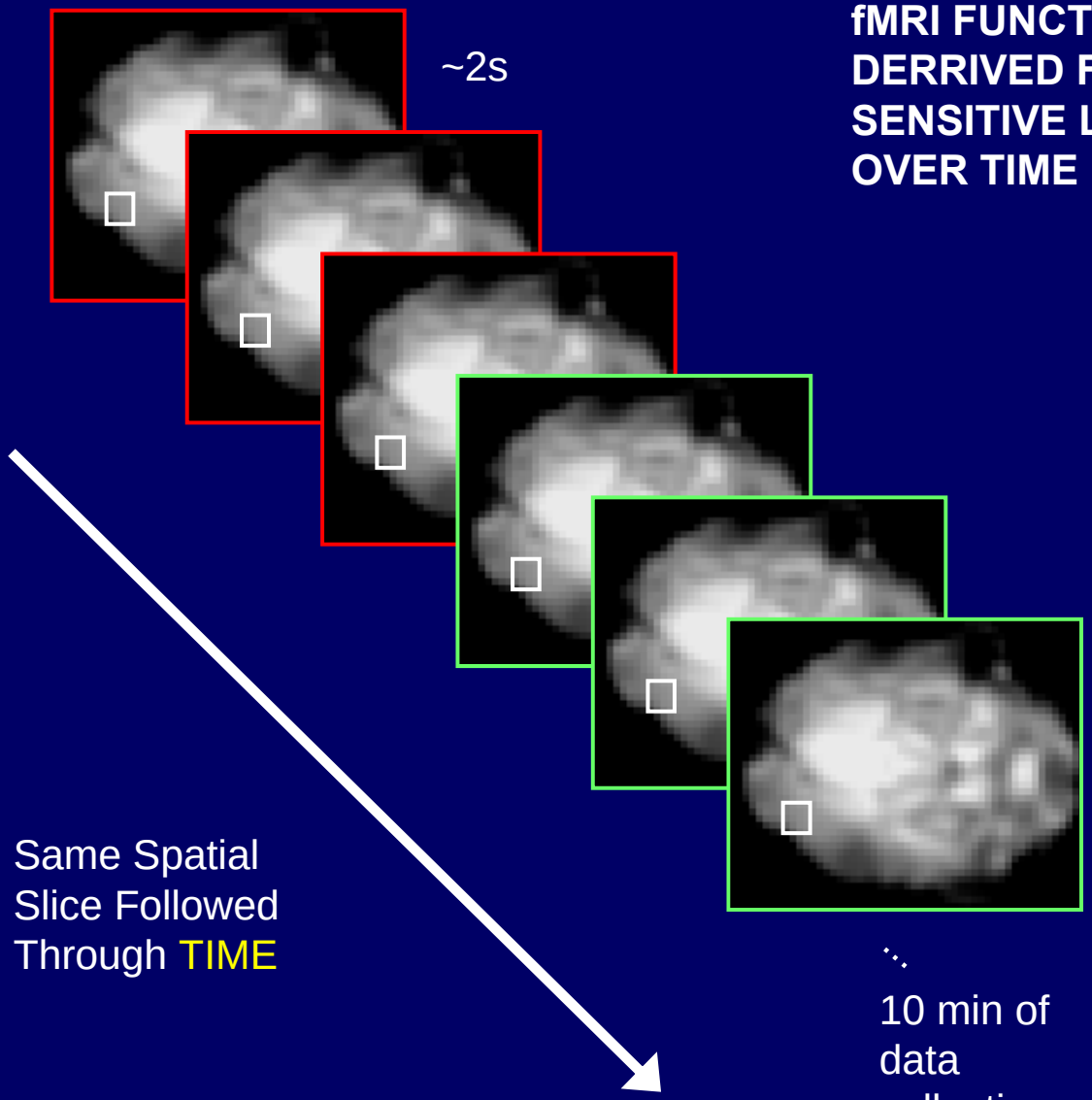
OBLIQUE SLICES

Number of Slices
e.g., 10



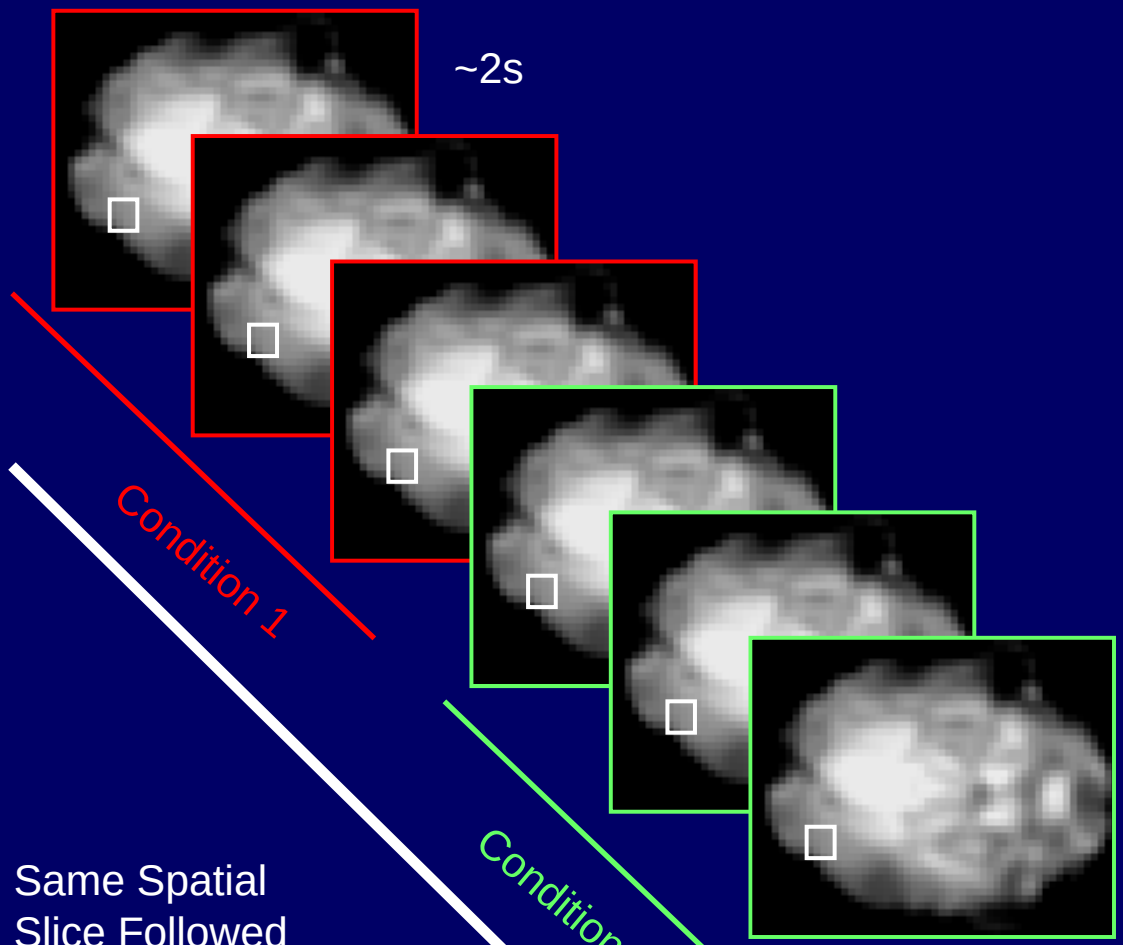
Consecutive
Slices
Through
SPACE

fMRI: IMAGES OF PHYSIOLOGY – FUNCTION



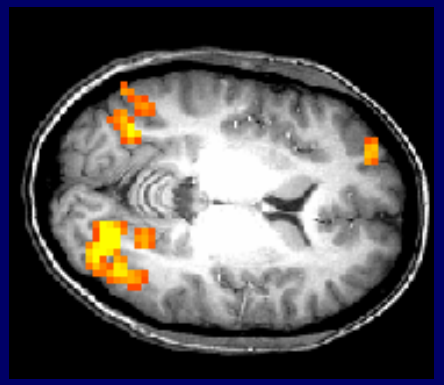
fMRI FUNCTIONAL IMAGES ARE DERRIVED FROM CHANGES IN T2*-SENSITIVE LOW-RESOLUTION IMAGES OVER TIME

fMRI FUNCTIONAL IMAGES ARE DERRIVED FROM DEVIATIONS IN LOW-RESOLUTION ANATOMICAL IMAGES



Hours/days of analysis

Statistical Map superimposed on anatomical MRI image



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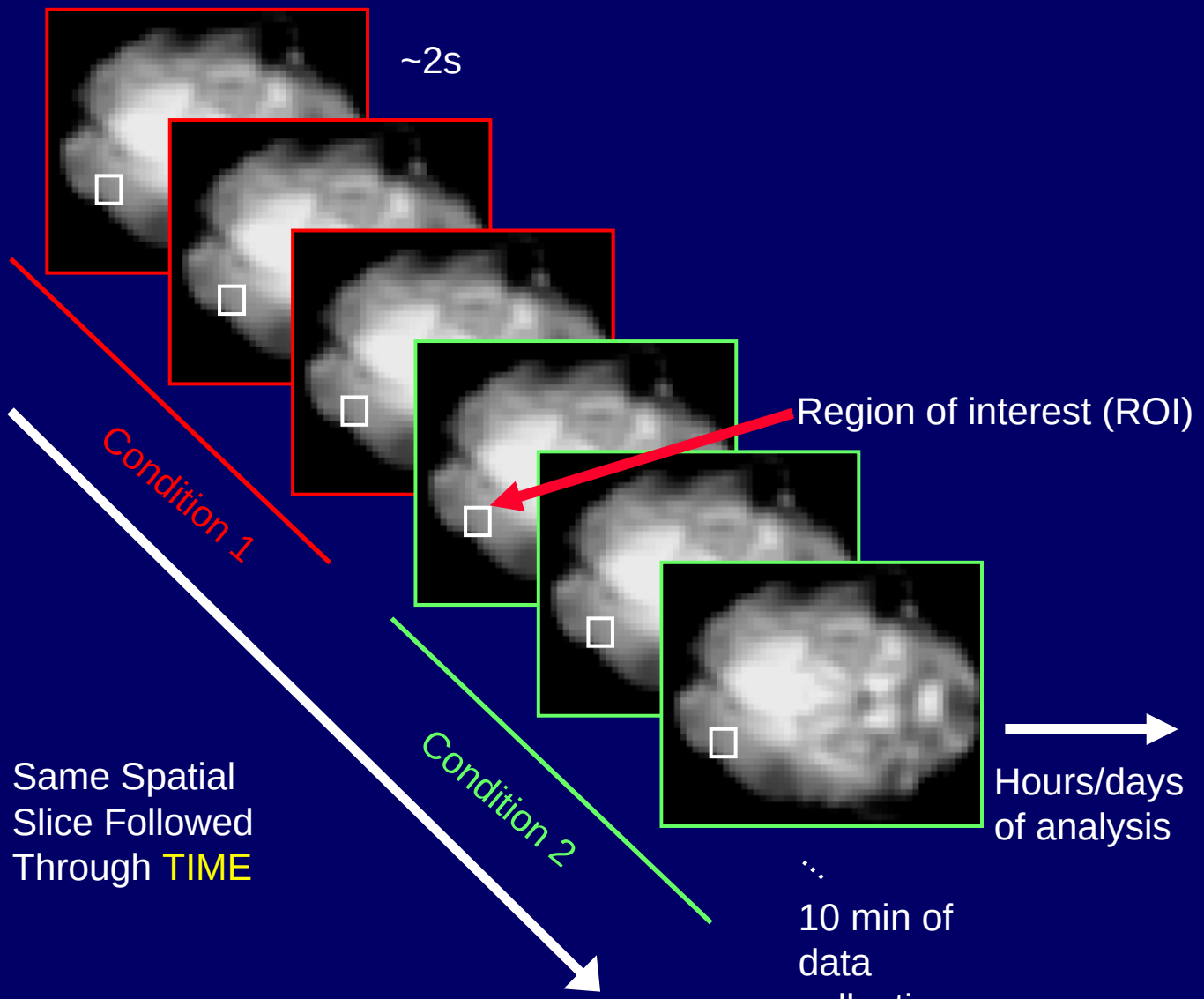

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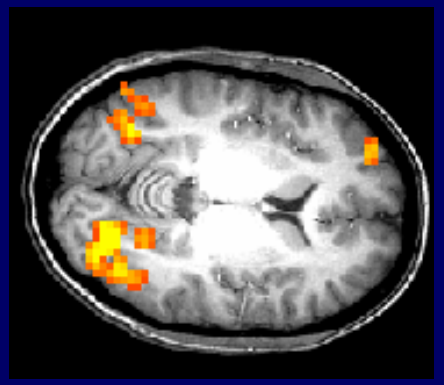

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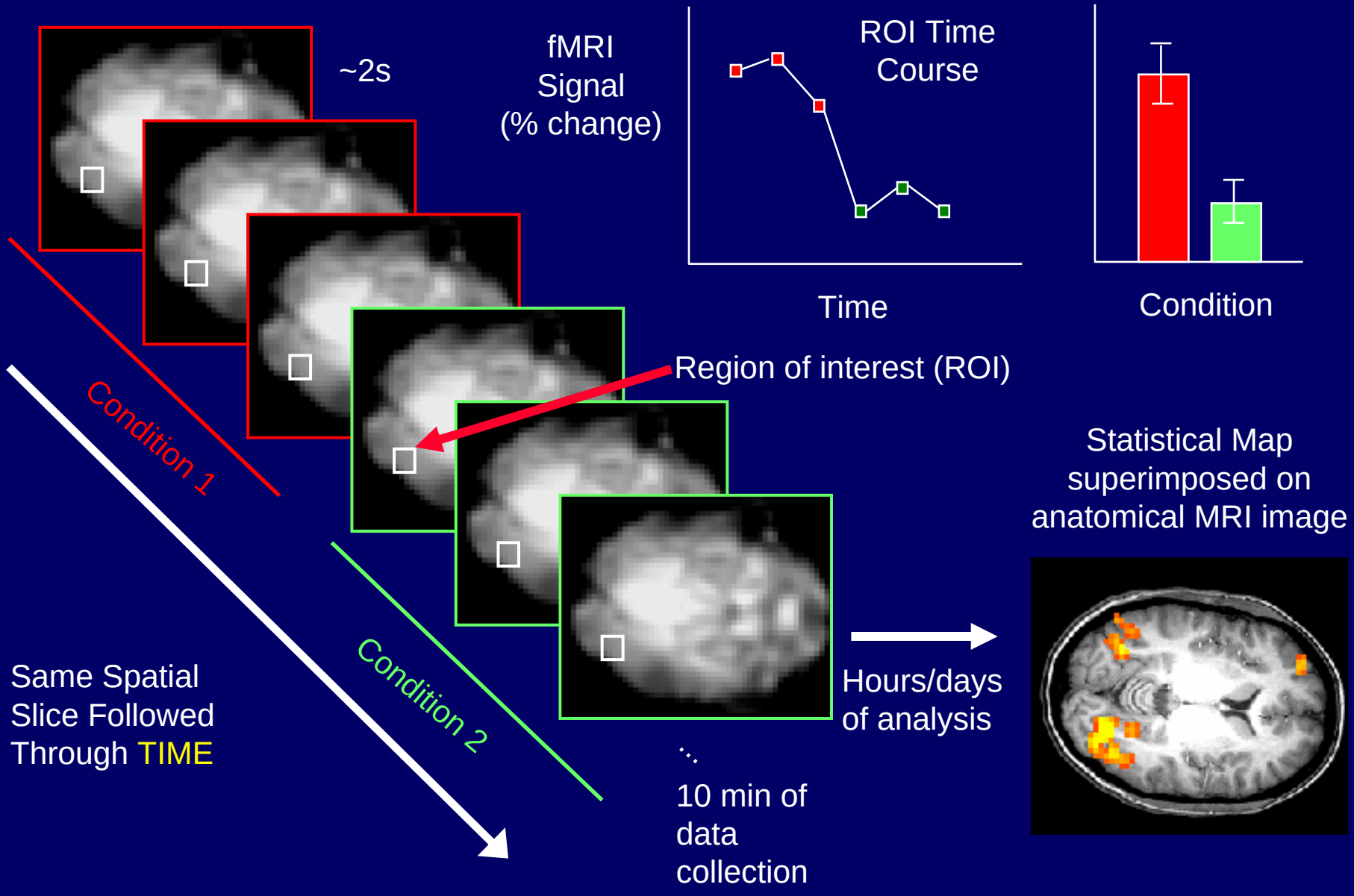


OVERVIEW OF METHOD

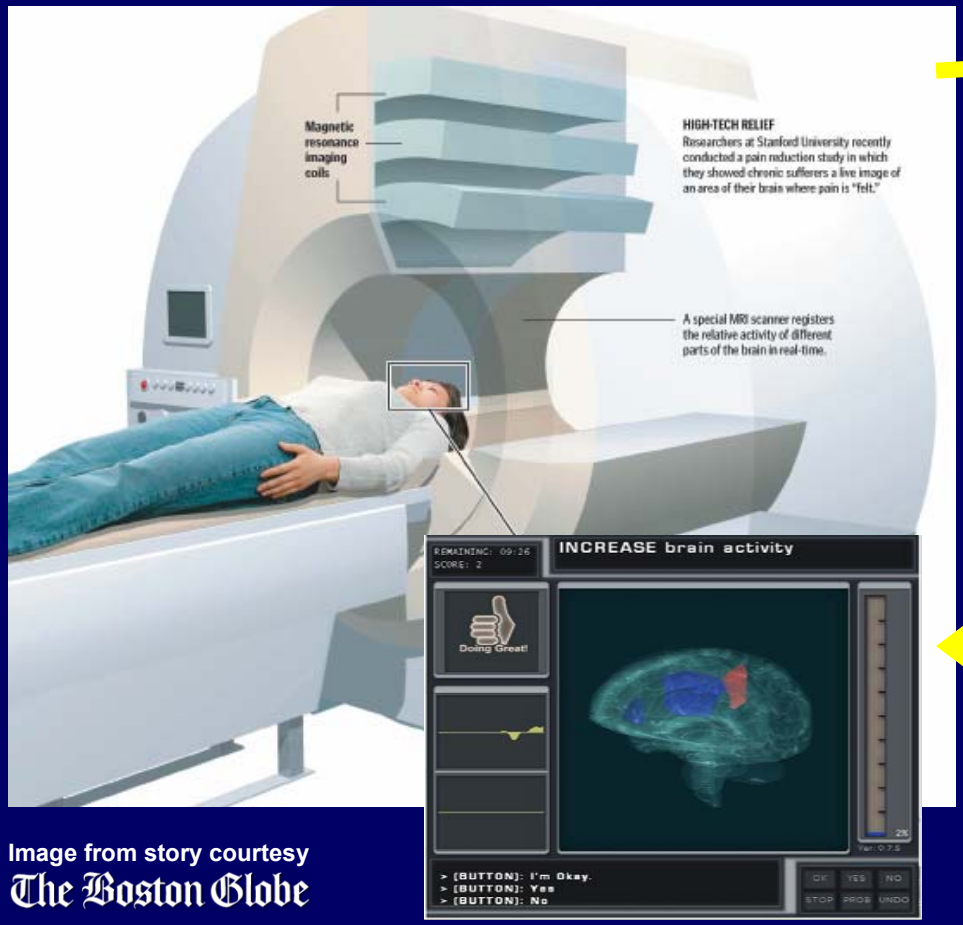


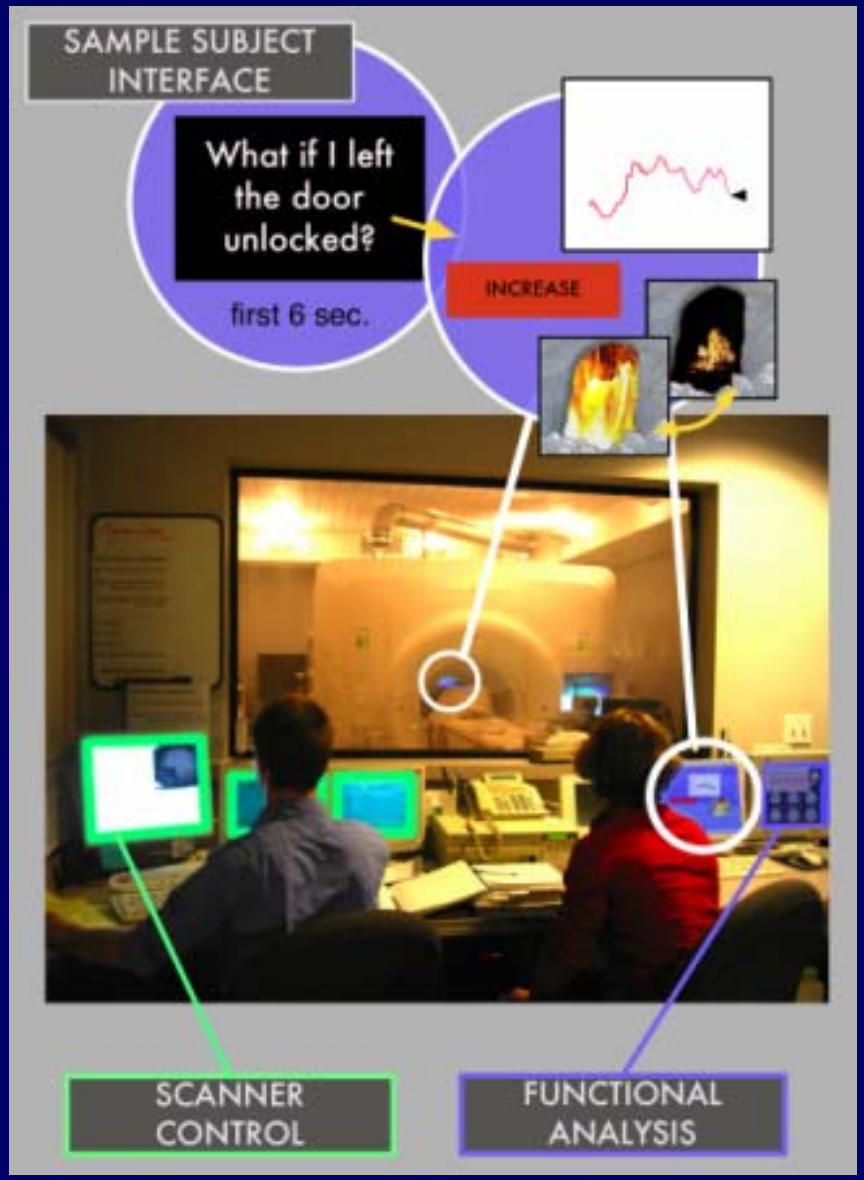
Image from story courtesy
The Boston Globe

MRI acquires real time fMRI data (spiral or EPI)

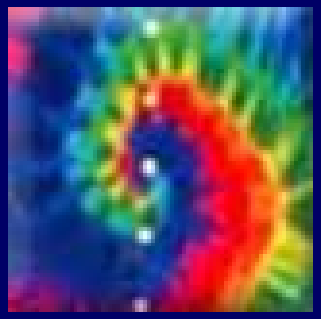
Real time fMRI analysis
- Motion correction
- Temporal filtering
- Spatial filtering
- Event-related averages
- Pattern comparison

Subjects (or patients or clinicians) watch their cognitive processes unfold 'live', depicted as simulated displays

RTFMRI SETUP



RTFMRI-BASED TRAINING – A MORE PRECISE, ANATAMICALLY TARGETED MEASURE THAN TRADITIONAL AUTONOMIC 'BIOFEEDBACK'



	MEASURES	CONSEQUENCES
60's	**AUTONOMIC FUNCTION** Heart Rate Breath Rate Skin Conductance Skin Temperature	Predominantly measures of global arousal. Most useful if you want to teach relaxation

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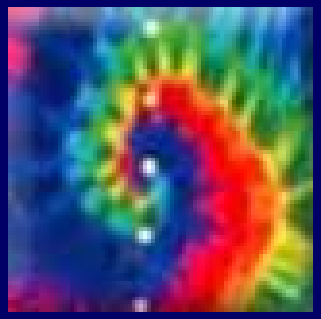

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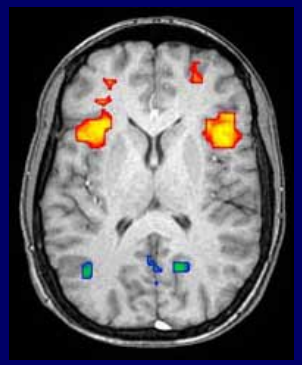

TODAY

BRAIN FUNCTION

Can measure the very specific neurophysiological functions associated with the >100 individual brain areas.

Can measure patterns of activation evolving across multiple brain areas.

Potential to train subjects to produce very specific neurophysiological effects.

CHALLENGES WITH fMRI AS A MEASURE OF BRAIN FUNCTION

"Neurophysiologist reaction"

	PROBLEM	POTENTIAL RESOLUTION
TIMESCALE	Neural activation is on a msec timescale, diseases lead to long-term changes in brain function. fMRI signals evolve over a few seconds.	Cognitive processing is closer to the seconds timescale. We'll use better temporal methods as soon as they come along.
SPATIAL SCALE	There may be ~10^7 neurons in the areas that fMRI is measuring – that's no way to measure the code.	It may not be necessary to control individual neurons to achieve important applications: eg drugs, deep brain stimulation.
$$	Isn't MRI way too expensive to really be practical?	Patient care costs can easily run into $100k/yr/patient for many CNS diseases. Invasive CNS procedures can easily cost this much for a single procedure.

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OVER TIME, IMAGING TECHNOLOGY WILL EVOLVE TO NEW USES:

RTFMRI AND COGNITIVE TRAINING TAKE-HOME EXERCISE

POSSIBLE CREDIT	ASSIGNMENT	DUE DATE
	Produce 1% modulation in rACC activation	Next Wed

RTFMRI AND COGNITIVE TRAINING TAKE-HOME EXERCISE

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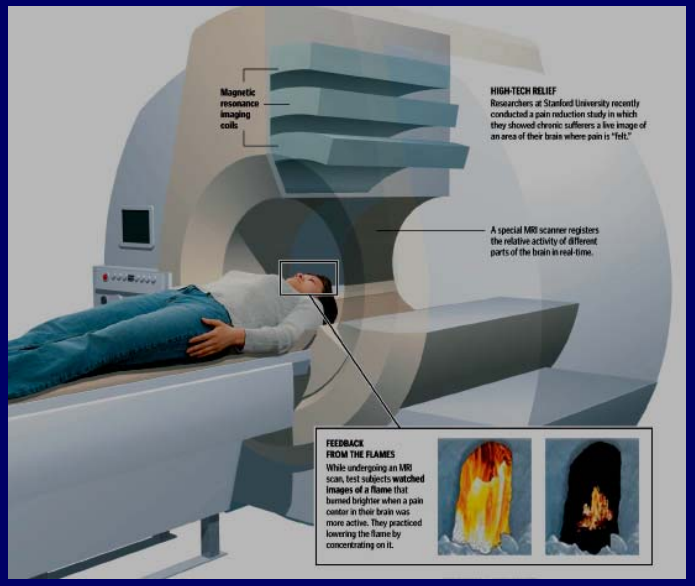
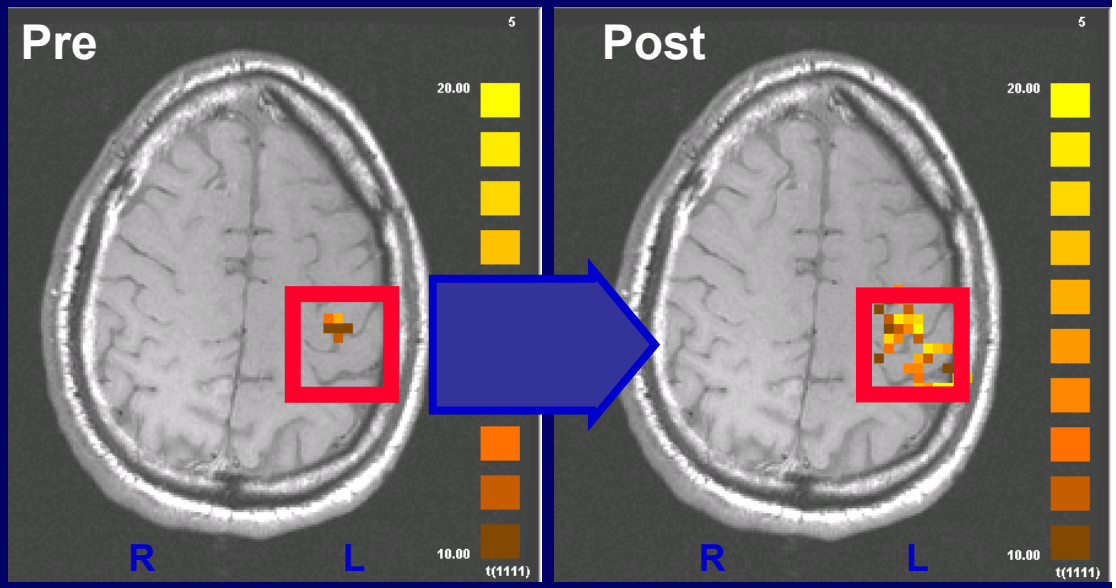
	Take control over your own reward and endorphin systems…	**??**

RTFMRI AND COGNITIVE TRAINING TAKE-HOME EXERCISE

POSSIBLE CREDIT	ASSIGNMENT	DUE DATE
	Produce 1% modulation in rACC activation	**Next Wed**
	Take control over your own reward and endorphin systems…	**??**
	Decrease pain and suffering	**Future**

REAL TIME FMRI TRAINING OF BRAIN FUNCTION

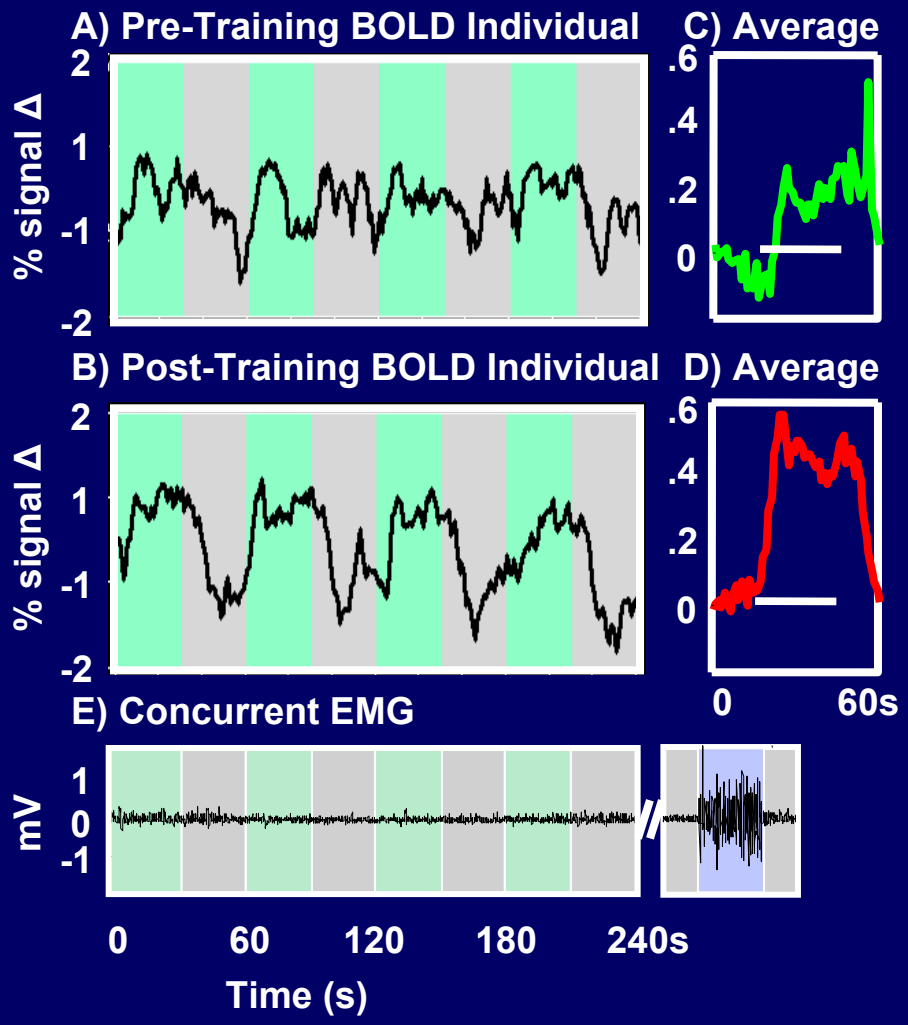




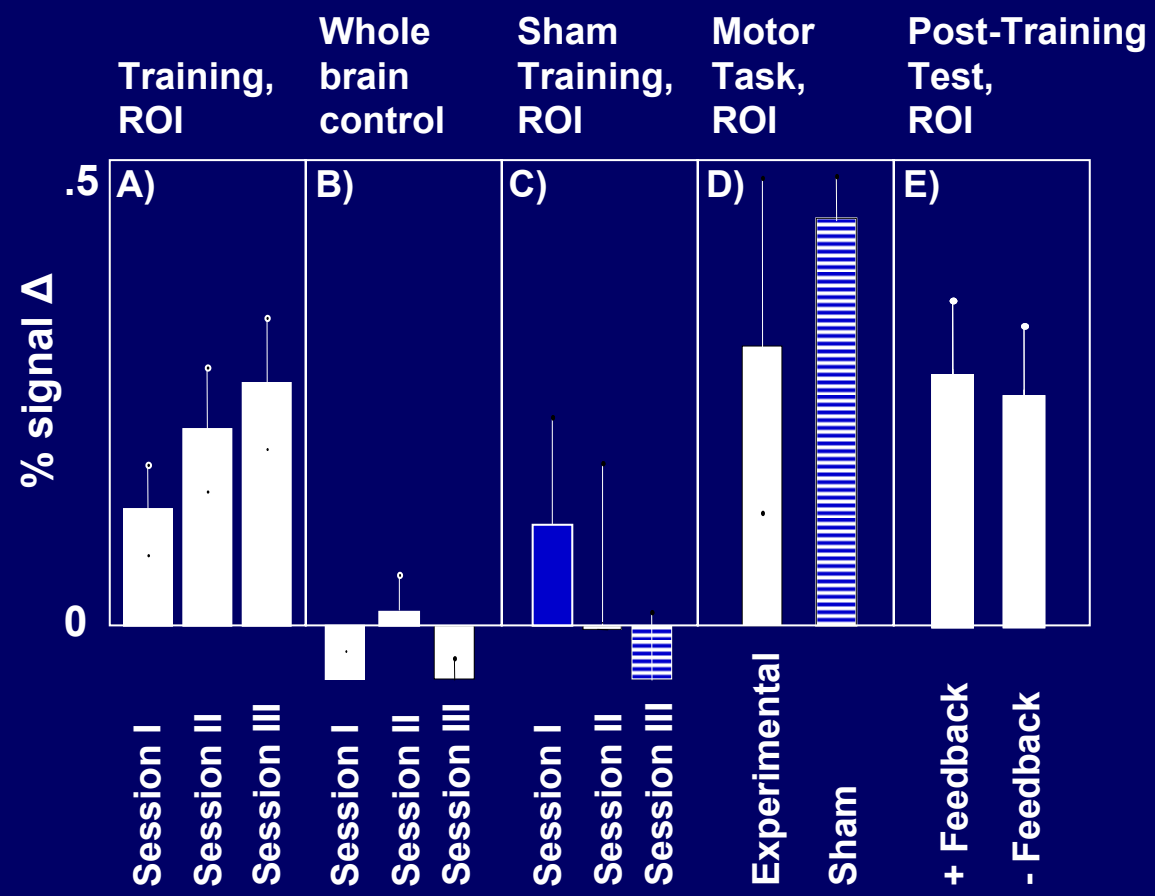
Activation target

Learned regulation of spatially localized brain activation using real-time fMRI.
NeuroImage (2004) 21, 436-443
deCharms, R. C., Christoff, K., Glover, G. H., Pauly, J. M., Whitfield, S., and Gabrieli, J. D.

IMPACT OF RTFMRI TRAINING ON BRAIN ACTIVATION



TIME COURSE OF TRAINING EFFECT AND CONTROLS

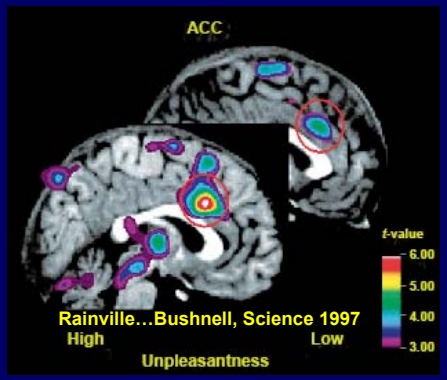


CAN THIS APPROACH BE USED IN CLINICALLY IMPORTANT AREAS?

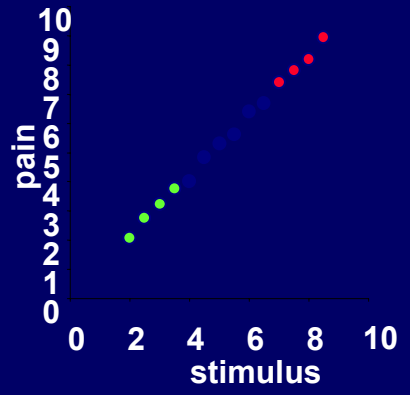
TRANSLATING BASIC RESEARCH IN PAIN INTO A NEW POTENTIAL THERAPEUTIC APPLICATION AREA: NEUROIMAGING

BASIC RESEARCH

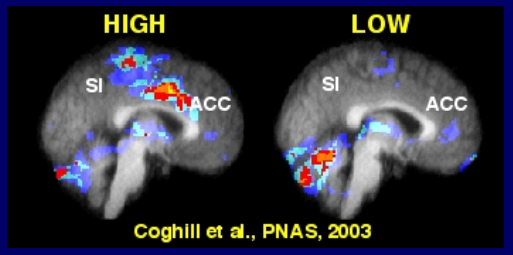
Pain can be powerfully modulated by cognitive processes including attention, placebo effect, hypnosis, and many others involving a matrix of brain regions



There are large individual differences in pain perception…



…and subjects with different pain sensitivities show differences in a similar group of brain regions



Pain, and brain, can be changed substantially by mechanisms of plasticity

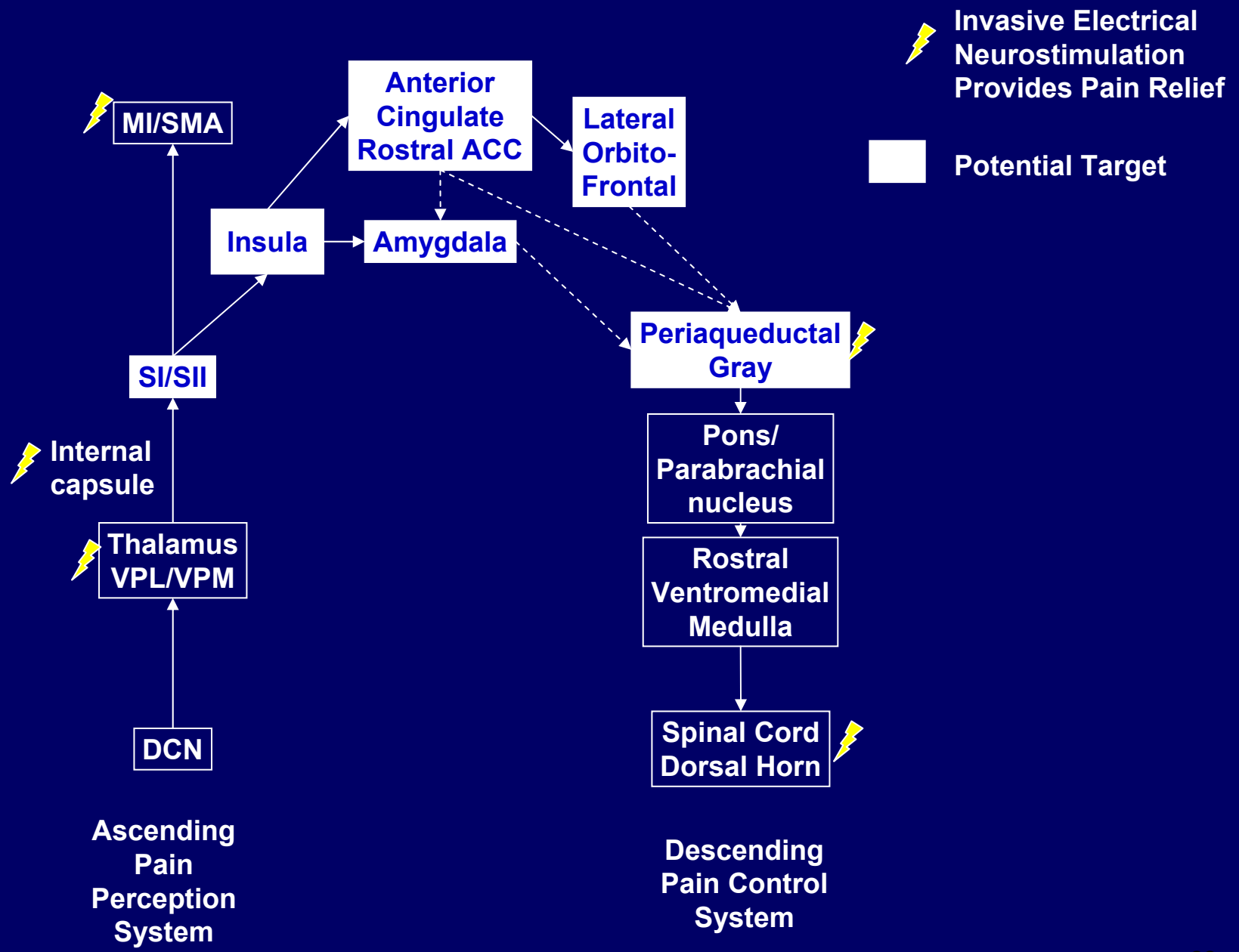
APPLIED QUESTION

CAN SUBJECTS BE TRAINED TO MORE EFFECTIVELY COGNITIVELY CONTROL PAIN?

CAN SUBJECTS SHIFT THEIR PAIN TOLERANCE OR PERCEPTION?

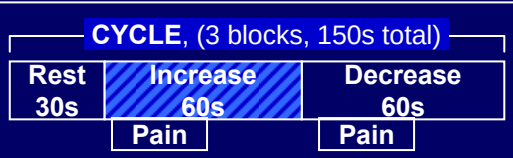
CAN NEURAL PLASTICITY BE ANATOMICALLY TARGETED?

POTENTIAL TARGETS IN THE PAIN CONTROL SYSTEM



RTFMRI TRAINING PROTOCOL IN HEALTHY SUBJECTS

BLOCK DESIGN



Control over brain activation and pain learned by using real-time functional MRI.
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deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., Gabrieli, J. D., and Mackey, S. C.

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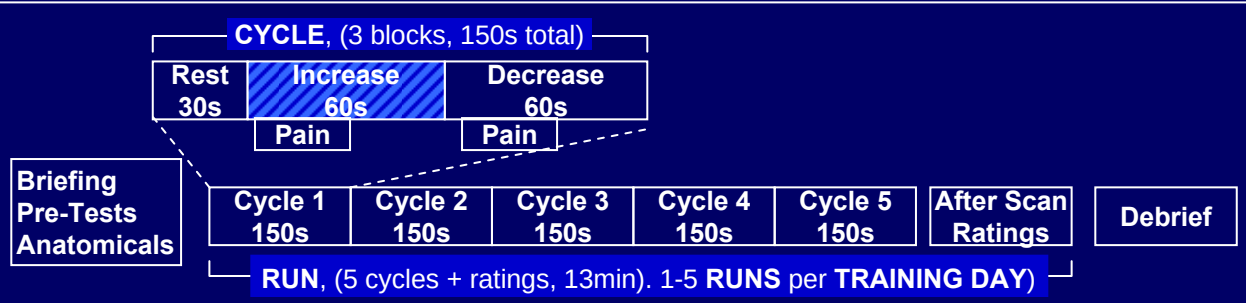

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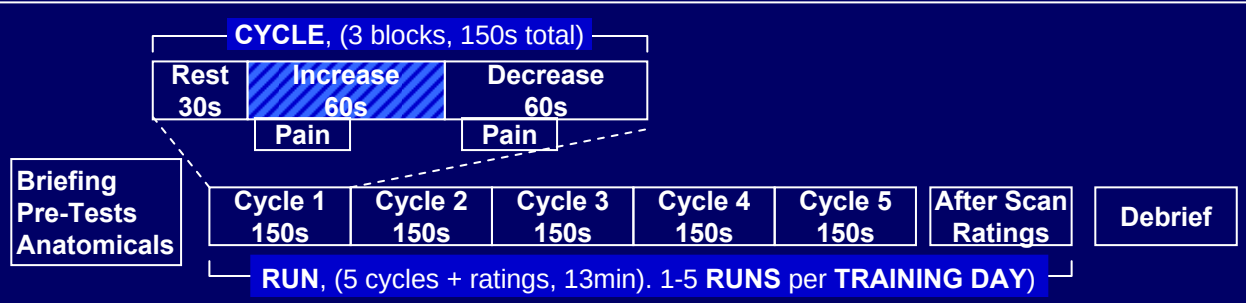
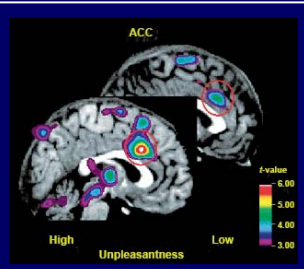
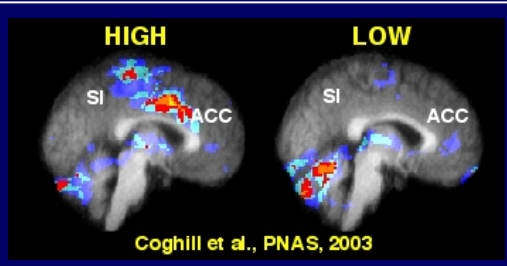


ROI TARGET: rostral Anterior Cingulate Cortex





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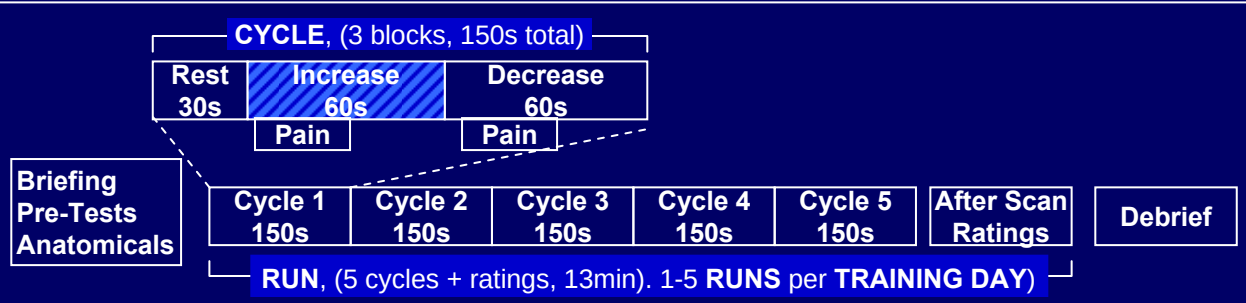

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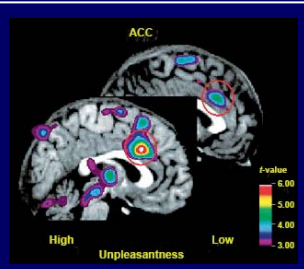
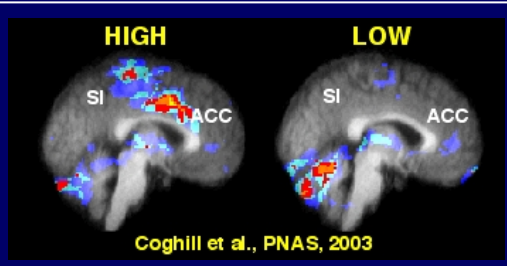


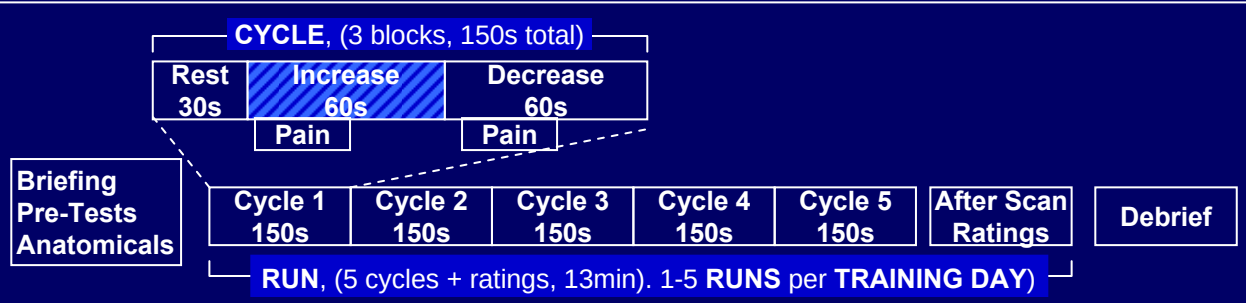


SUBJECT INSTRUCTIONS: Written text describing cognitive modulation of pain

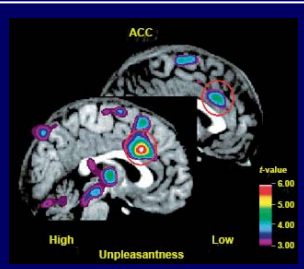
- Attend to pain vs. attend away
- Perceive the pain as more intense vs. less intense
- Perceive the pain as harmful vs. only a tactile sensation

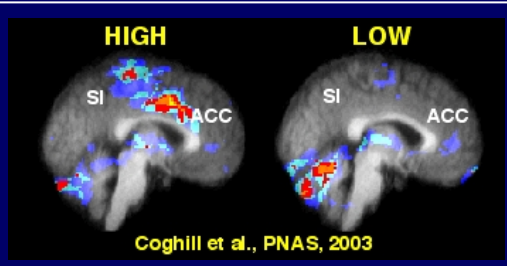
RTFMRI TRAINING PROTOCOL IN HEALTHY SUBJECTS

BLOCK DESIGN



ROI TARGET: rostral Anterior Cingulate Cortex

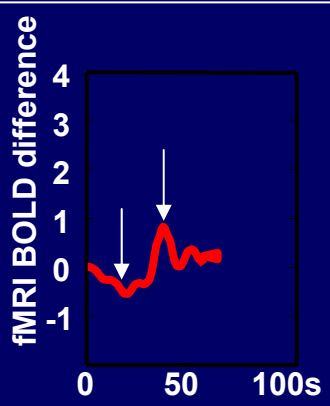




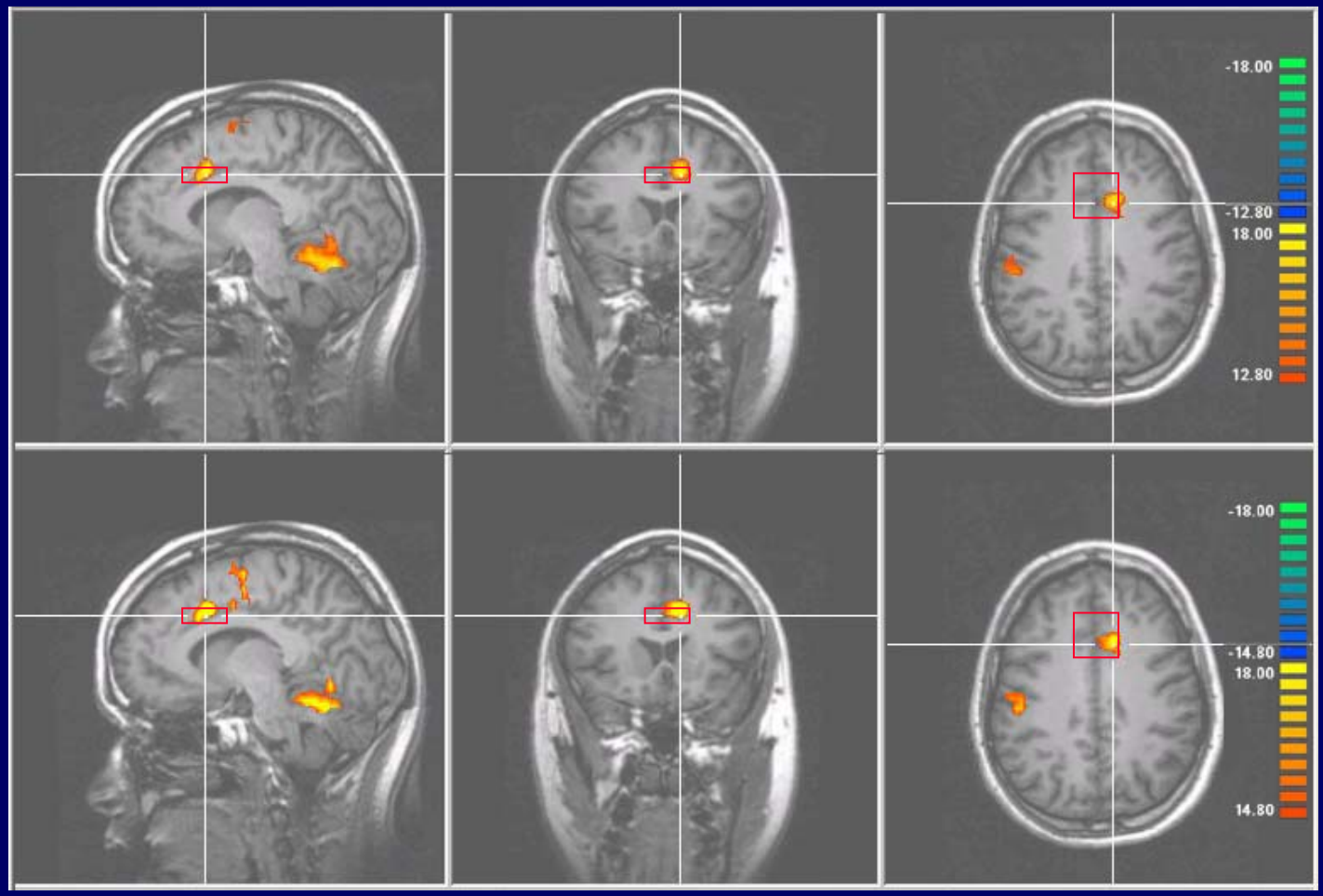
SUBJECT INSTRUCTIONS: Written text describing cognitive modulation of pain

- Attend to pain vs. attend away
- Perceive the pain as more intense vs. less intense
- Perceive the pain as harmful vs. only a tactile sensation

SUBJECT DISPLAYS

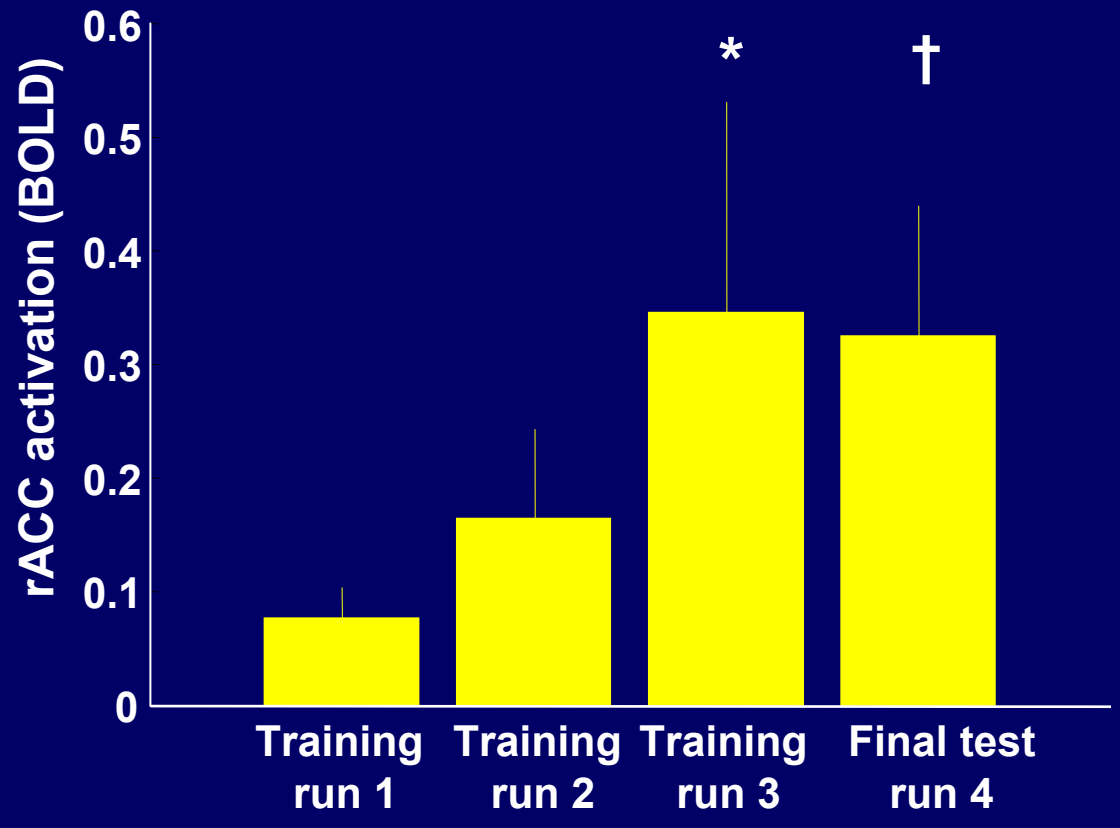


rtfMRI-BASED TRAINING LEADS TO SPATIALLY-SPECIFIC CHANGES IN BRAIN ACTIVATION



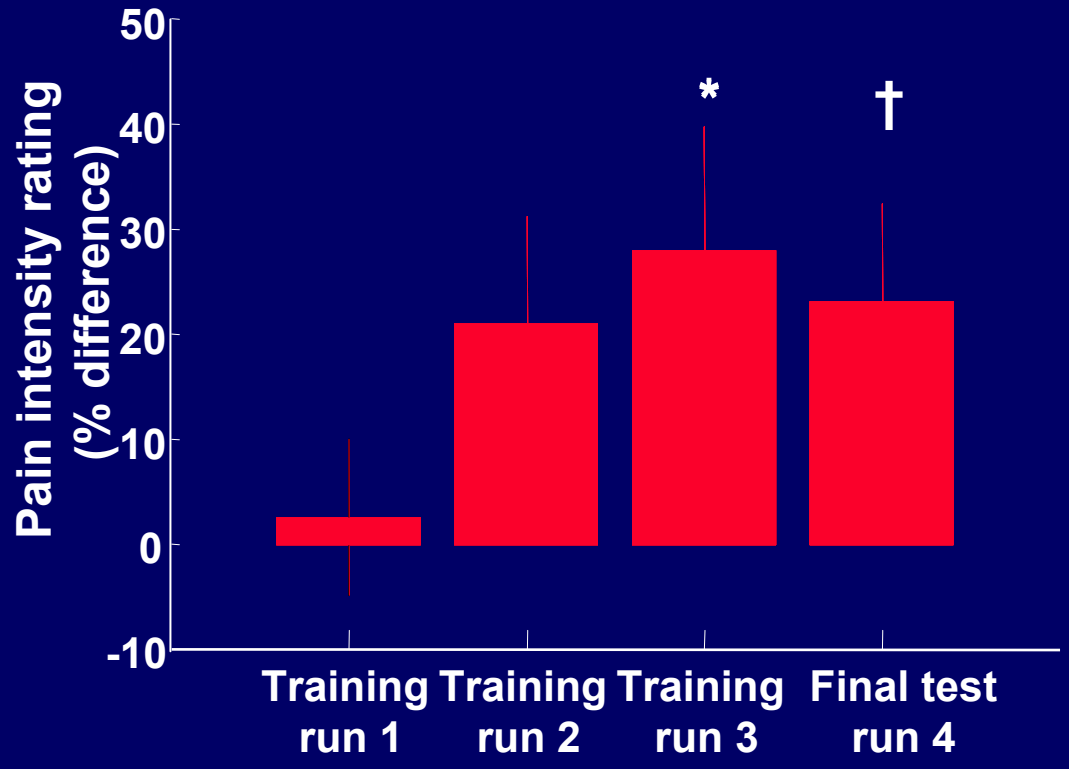
MEASURE: Thresholded T-statistic,
(INCREASE – DECREASE) $_{\text{last run}}$ VS. (INCREASE – DECREASE) $_{\text{first run}}$

HEALTHY SUBJECTS LEARN INCREASED CONTROL OVER BRAIN ACTIVATION THROUGH THE COURSE OF TRAINING



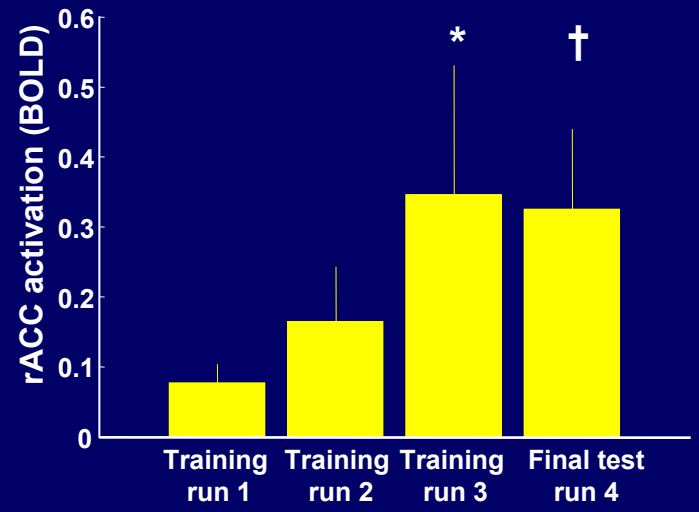
MEASURE: Brain Activation, BOLD % Signal Change,
(Increase Period – Decrease Period) from each pair of blocks,
Averaged over N=8 Subjects

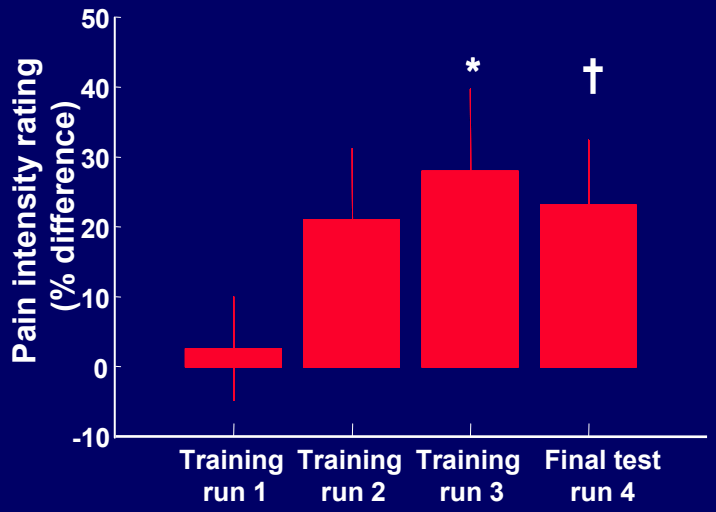
HEALTHY SUBJECTS LEARN INCREASED CONTROL OVER PAIN THROUGH THE COURSE OF TRAINING



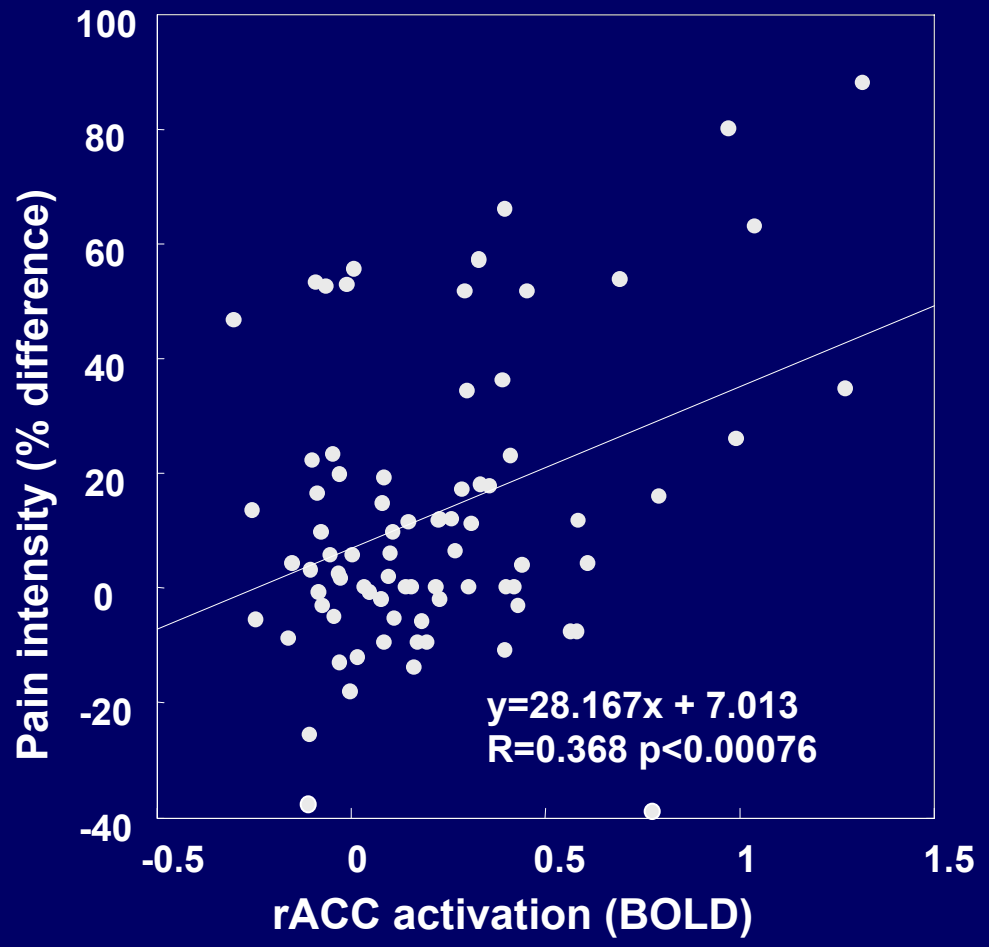
MEASURE: Pain Intensity Rating % Difference,
(Increase Period Rating – Decrease Period Rating)/Average from each pair of blocks,
Averaged over N=8 Subjects

THE TIMECOURSE OF LEARNING OF CONTROL OVER BRAIN ACTIVATION MIRRORS THE TIME COURSE FOR CONTROL OVER PAIN





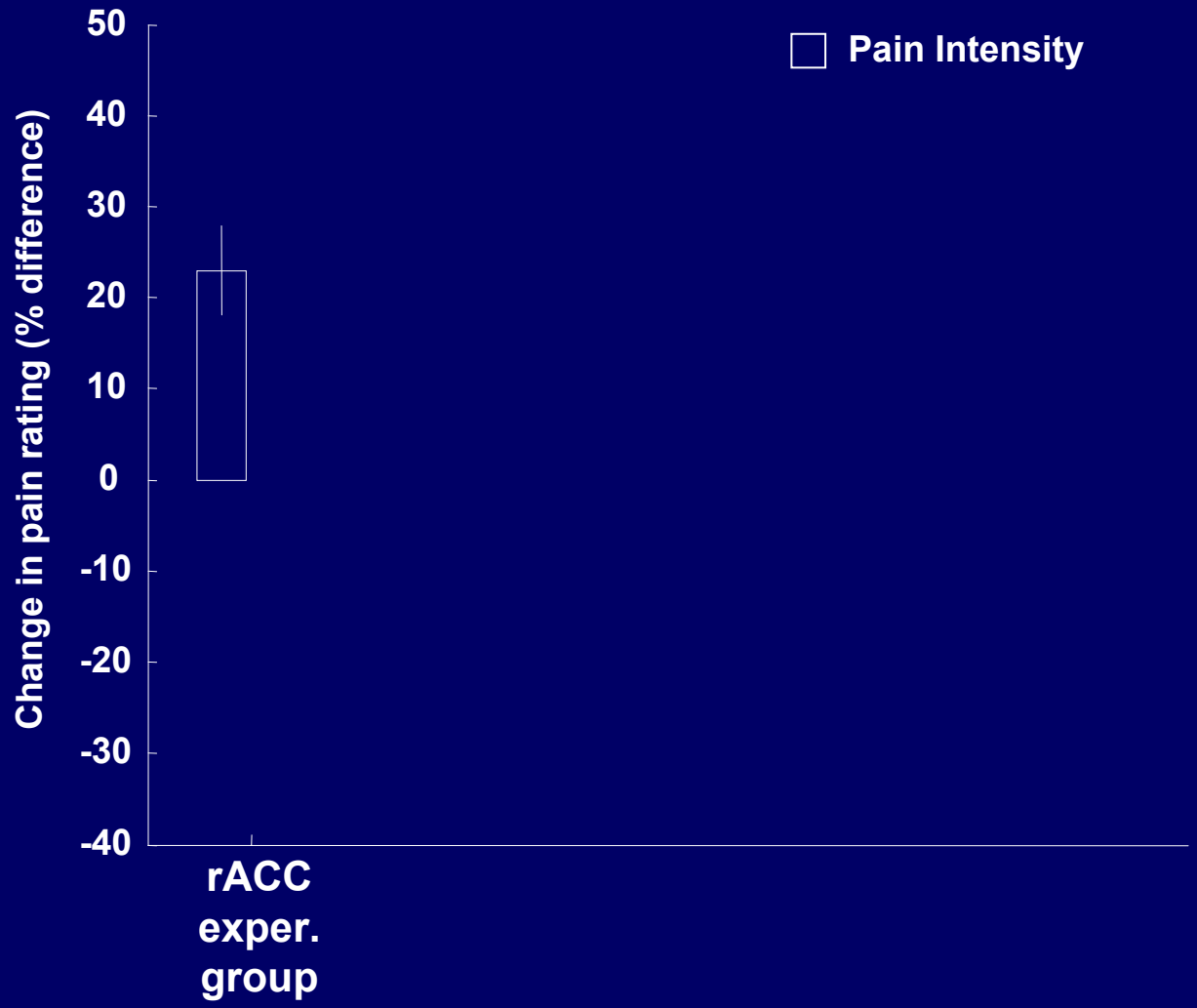
LEARNED CONTROL OVER BRAIN ACTIVATION IN RACC LEADS TO CORRESPONDING CHANGES IN PAIN INTENSITY RATINGS FOR A CONCURRENT THERMAL STIMULUS



FOUR CONTROL GROUPS WERE TRAINED USING SIMILAR OR IDENTICAL PROCEDURES BUT IN THE ABSENCE OF RACC RTFMRI INFORMATION

GROUP I	**Received purely behavioral training for twice as long as the experimental group, but they had no rtfMRI feedback. They were additionally instructed to focus attention on the thermal stimuli during "increase" periods.**	**Control for effects of extended attention training**
GROUP II	**Received identical instructions to the experimental group, and the same period of training, but with no rtfMRI information, to test the effect of identical practice alone.**	**Control for identical training without rtfMRI**
GROUP III	**Received identical training to the experimental group, but using rtfMRI information derived from a posterior cingulate cortex region not involved in pain processing, to examine spatial and physiological specificity.**	**<u>BLIND CONTROL</u> Control for spatial and physiological specificity**
GROUP IV	**Received identical training to the experimental group, but unknown to them the rtfMRI displays that they saw corresponded to activation from a previously-tested experimental subject's rACC, rather than their own rACC.**	**<u>BLIND CONTROL</u> Control for cognitive effects.**

THE LEARNED CONTROL OVER PAIN REQUIRES SPATIALLY-SPECIFIC RTFMRI INFORMATION



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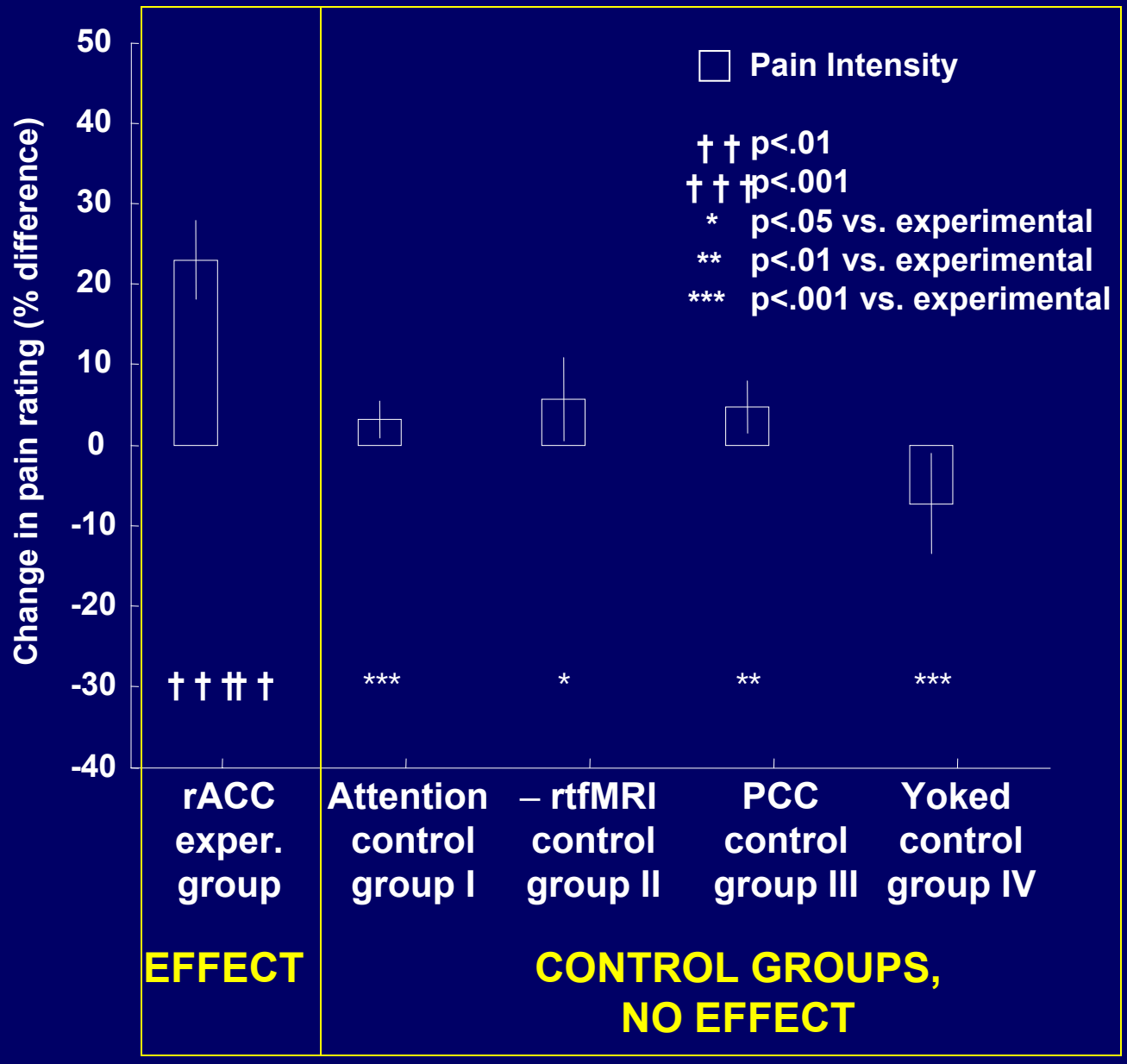

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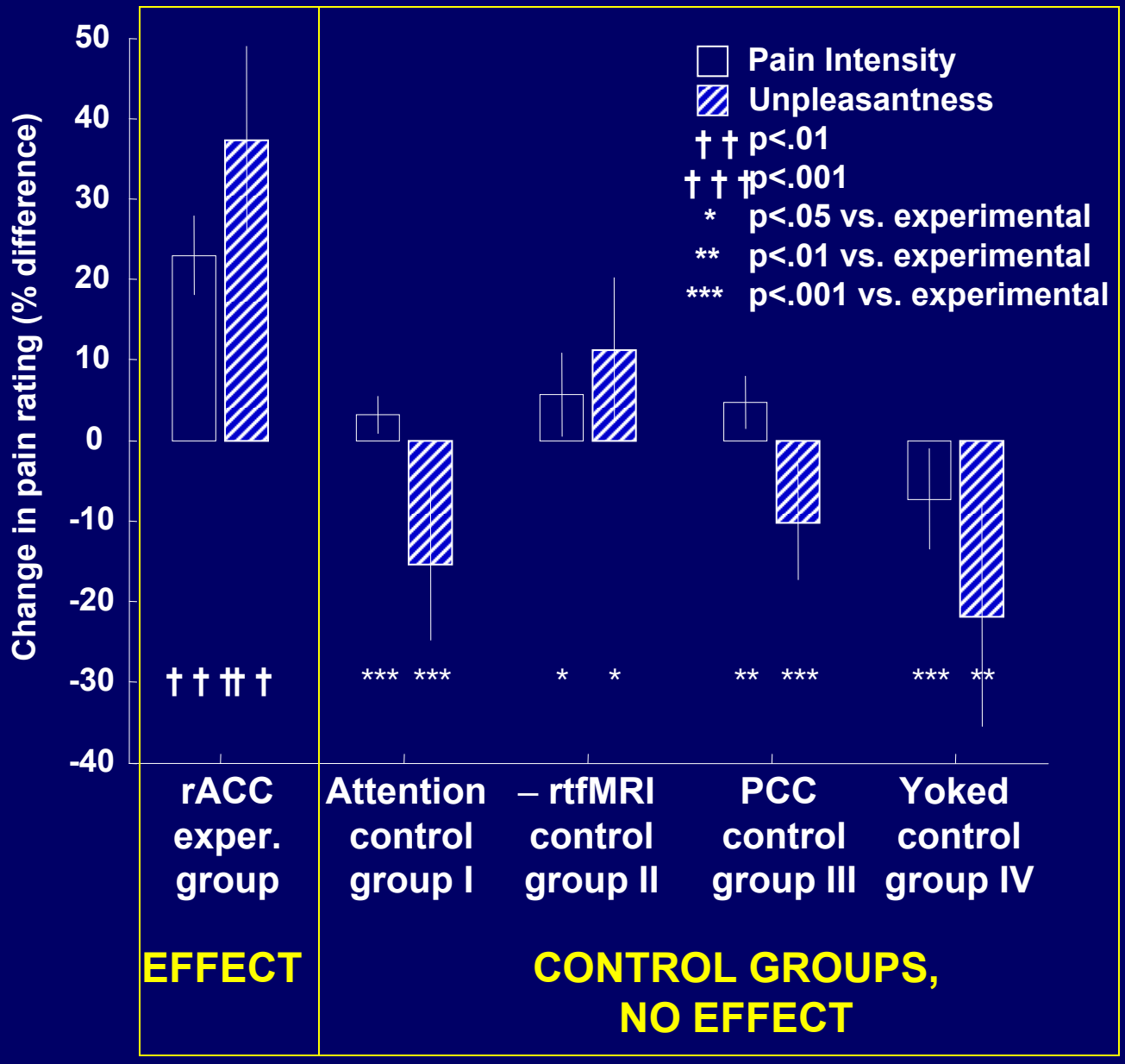
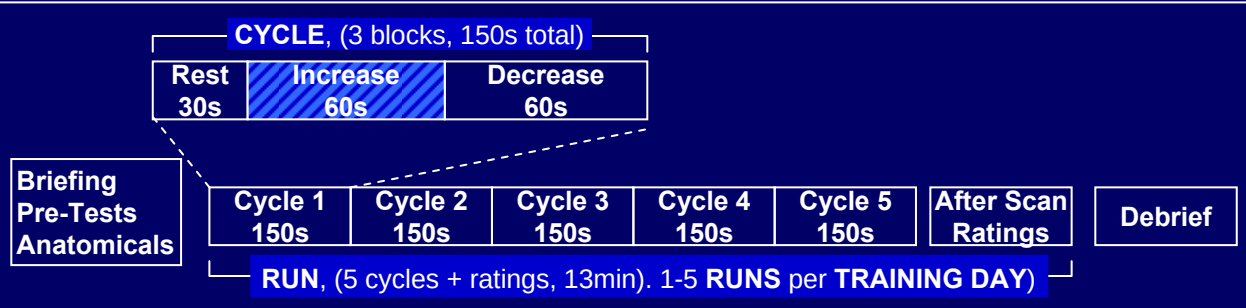


CAN THE PICTURES OF YOUR HEAD PROVIDE RELIEF?

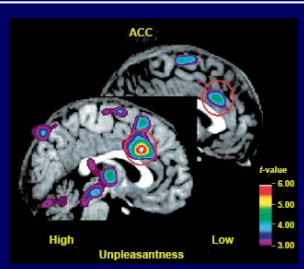
RTFMRI TRAINING PROTOCOL IN PAIN PATIENTS

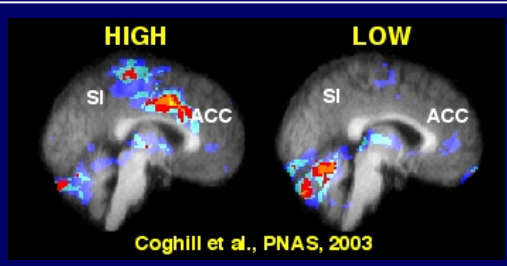
BLOCK DESIGN

NO PAINFUL EXTERNAL STIMULI



ROI TARGET: rostral Anterior Cingulate Cortex





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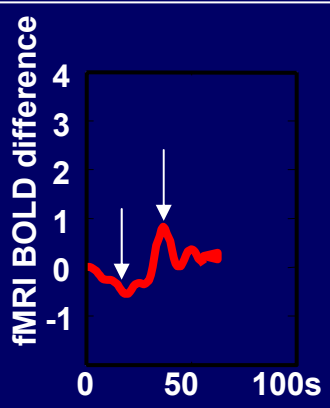
SUBJECT DISPLAYS



PATIENT REPORT OF PAIN MEASURES

PRIOR TO SCANNING

Pain Rating Index

		None		Mild		Moderate		Severe
a	Throbbing		1		2	✓	3	
	Shooting		1		2	✓	3	
	Stabbing		1		2	✓	3	
	Sharp		1		2	✓	3	
	Cramping	✓	1		2		3	
	Gnawing	✓	1		2		3	
	Hot-Burning		1		2		3	✓
	Aching		1		2	✓	3	
	Heavy		1	✓	2		3	
	Tender		1		2	✓	3	
	Splitting		1	✓	2		3	
b	Tiring/Exhausting		1	✓	2		3	
	Sickening	✓	1		2		3	
	Fearful		1	✓	2		3	
	Punishing/Cruel	✓	1		2		3	

II. Present Pain Intensity (PPI)–Visual Analog Scale (VAS). Tick along scale below for pain:

No pain — Worst possible pain

PATIENT REPORT OF PAIN MEASURES

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	Sharp		1		2	✓	3	
	Cramping	✓	1		2		3	
	Gnawing	✓	1		2		3	
	Hot-Burning		1		2		3	✓
	Aching		1		2	✓	3	
	Heavy		1	✓	2		3	
	Tender		1		2	✓	3	
	Splitting		1	✓	2		3	
b	Tiring/Exhausting		1	✓	2		3	
	Sickening	✓	1		2		3	
	Fearful		1	✓	2		3	
	Punishing/Cruel	✓	1		2		3	

II. Present Pain Intensity (PPI)–Visual Analog Scale (VAS). Tick along scale below for pain:

No pain — Worst possible pain

AFTER SCANNING

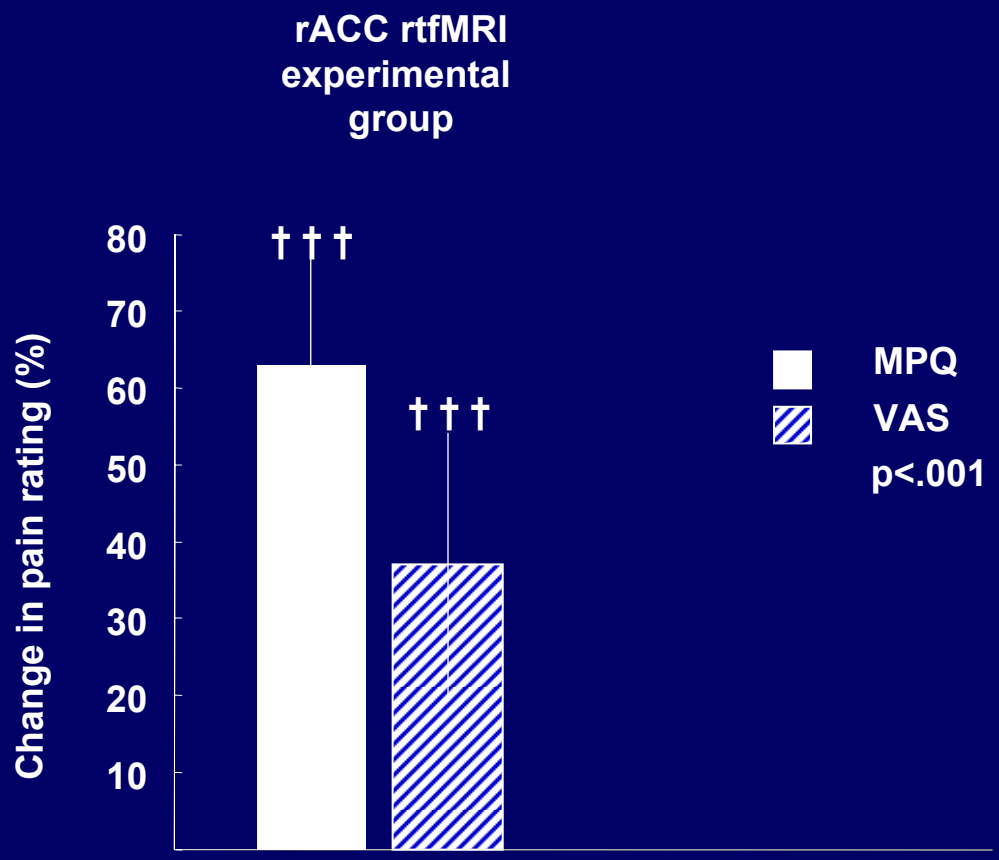
Pain Rating Index

	None		Mild		Moderate		Severe
Throbbing		1	✓	2		3	
Shooting		1	✓	2		3	
Stabbing		1	✓	2		3	
Sharp	✓	1		2		3	
Cramping	✓	1		2		3	
Gnawing	✓	1		2		3	
Hot-Burning		1	✓	2		3	
Aching	✓	1		2		3	
Heavy	✓	1		2		3	
Tender	✓	1		2		3	
Splitting	✓	1		2		3	
Tiring/Exhausting		1	✓	2		3	
Sickening	✓	1		2		3	
Fearful	✓	1		2		3	
Punishing/Cruel	✓	1		2		3	

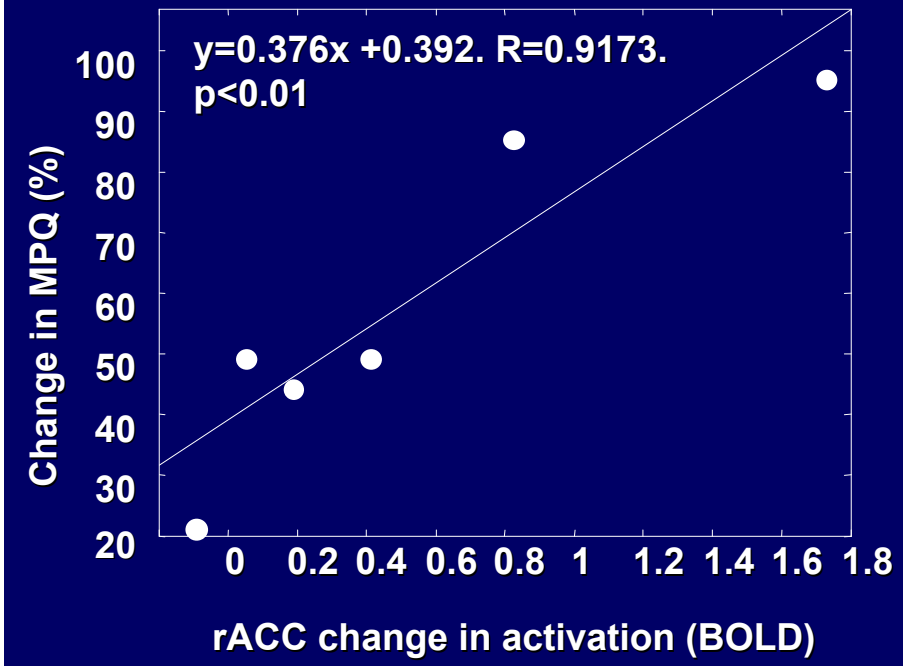
I. Present Pain Intensity (PPI)–Visual Analog Scale (VAS). Tick along scale below for pain:

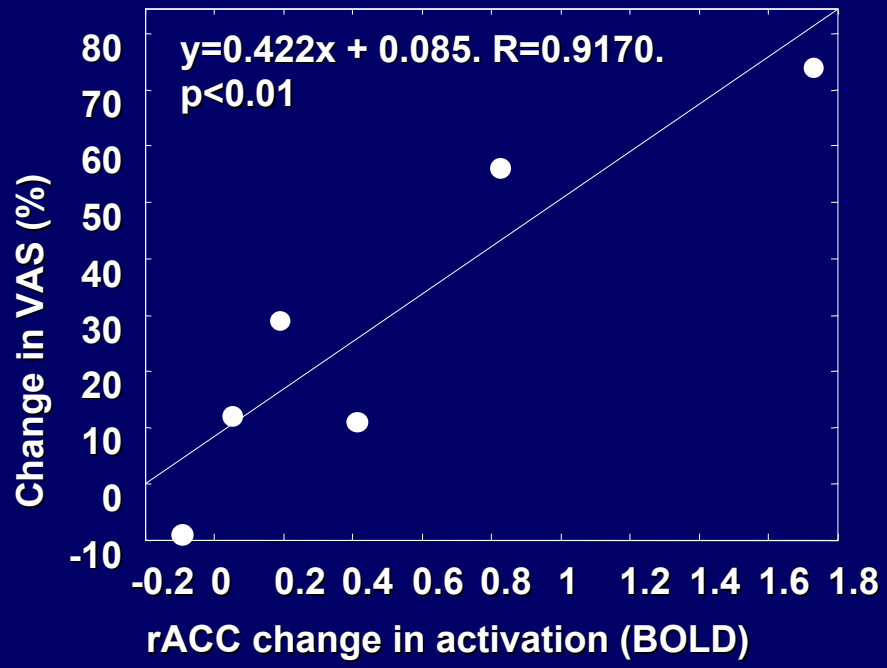
No pain — Worst possible pain

CHANGE IN PAIN RATINGS FOLLOWING RTFMRI TRAINING IN CHRONIC PAIN PATIENTS

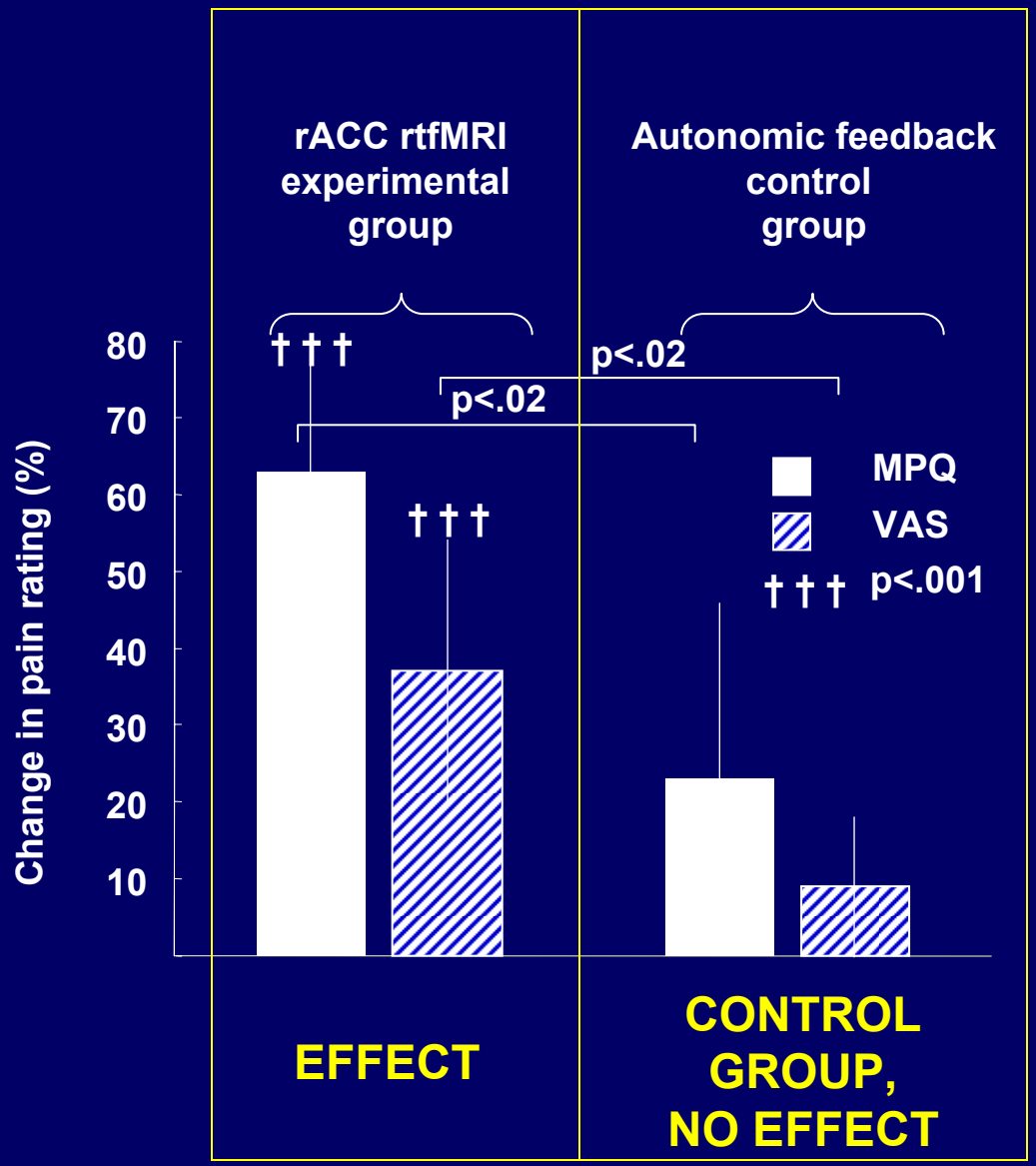


PATIENTS WHO LEARNED TO CONTROL RACC ACTIVATION SHOWED A CHANGE IN PAIN, OTHERS DID NOT





A CONTROL GROUP, TRAINED USING AUTONOMIC BIOFEEDBACK, DID NOT SHOW THE SAME CHANGES IN PAIN



MOTIVATIONS FOR NEUROIMAGING THERAPY IN CHRONIC PAIN TREATMENT

	IMPLICATION	RATIONALE
NON-PHARMACOLOGIC	Uses endogenous physiological, neurotransmitter systems	No drug-related side effects.
REVERSIBLE	Can be terminated if unsuccessful.	Potentially low risk.
NON-INVASIVE	No physical intervention required.	No surgery.
PHYSICIAN'S OFFICE IMAGING MAY BECOME FEASIBLE	Less expensive	Technology grows to meet need:


CAN THIS APPROACH COOL THE FIRES OF CHRONIC PAIN?

INTERFACE FOR CHRONIC PAIN PATIENTS

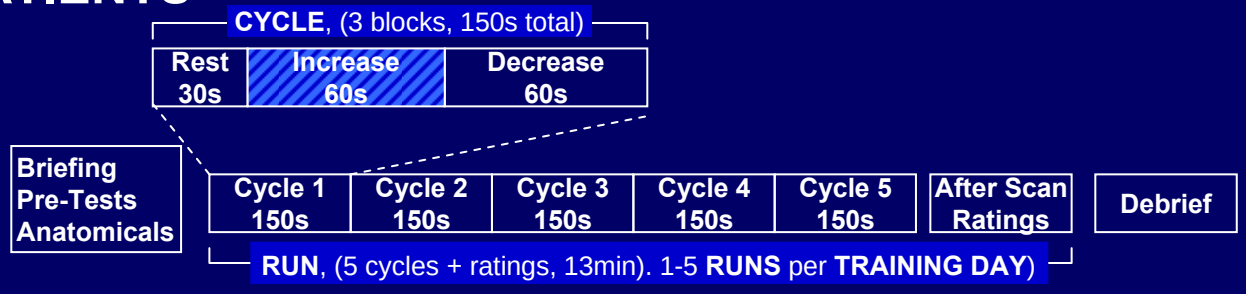
A Better View of Brain Disorders
***Science* 313, 1377-1379 (8 Sept, 2006)**
Miller, G

CAN REAL TIME FMRI LEAD TO A NEW, MECHANISTICALLY-BASED, COMPUTER GUIDED FORM OF COGNITIVE INTERVENTION?

ONGOING STUDY: LONG-TERM RTFMRI TRAINING PROTOCOL IN PAIN PATIENTS

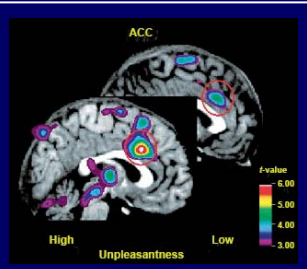
BLOCK DESIGN

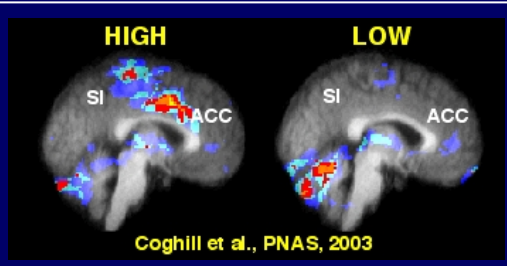
NO PAINFUL EXTERNAL STIMULI



ROI TARGETS: (Two groups)

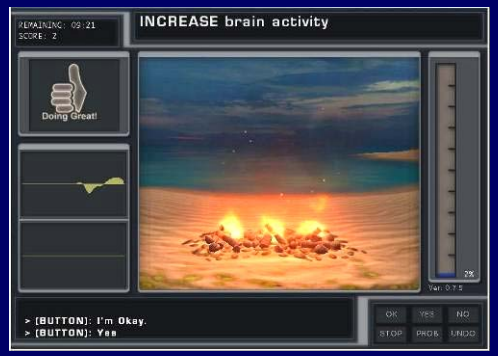
1. rostral Anterior Cingulate Cortex
2. Training using rACC and bilateral insula





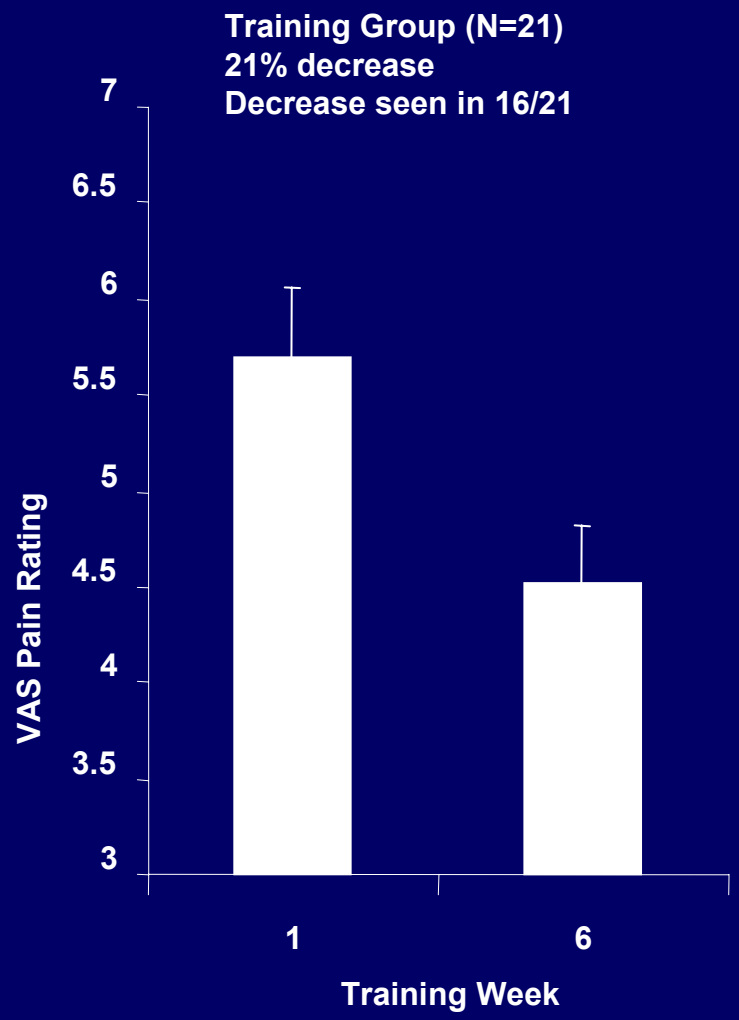
PROTOCOL: Training over 6 consecutive sessions, approximately 6 weeks

SUBJECT DISPLAY



WILL NEUROIMAGING THERAPY PRODUCE LONG-TERM DECREASES IN CHRONIC PAIN?

NOTE:
Preliminary, Unpublished Data!
No Control Group to Date
Placebo Effects Are Likely



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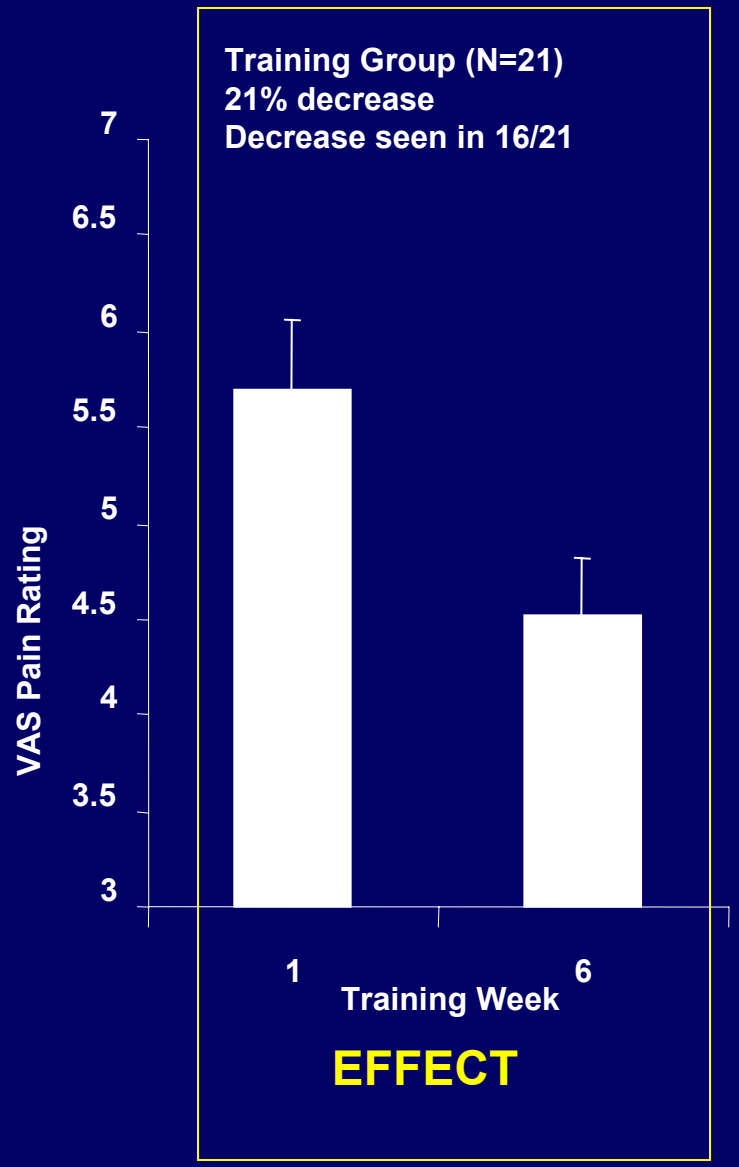

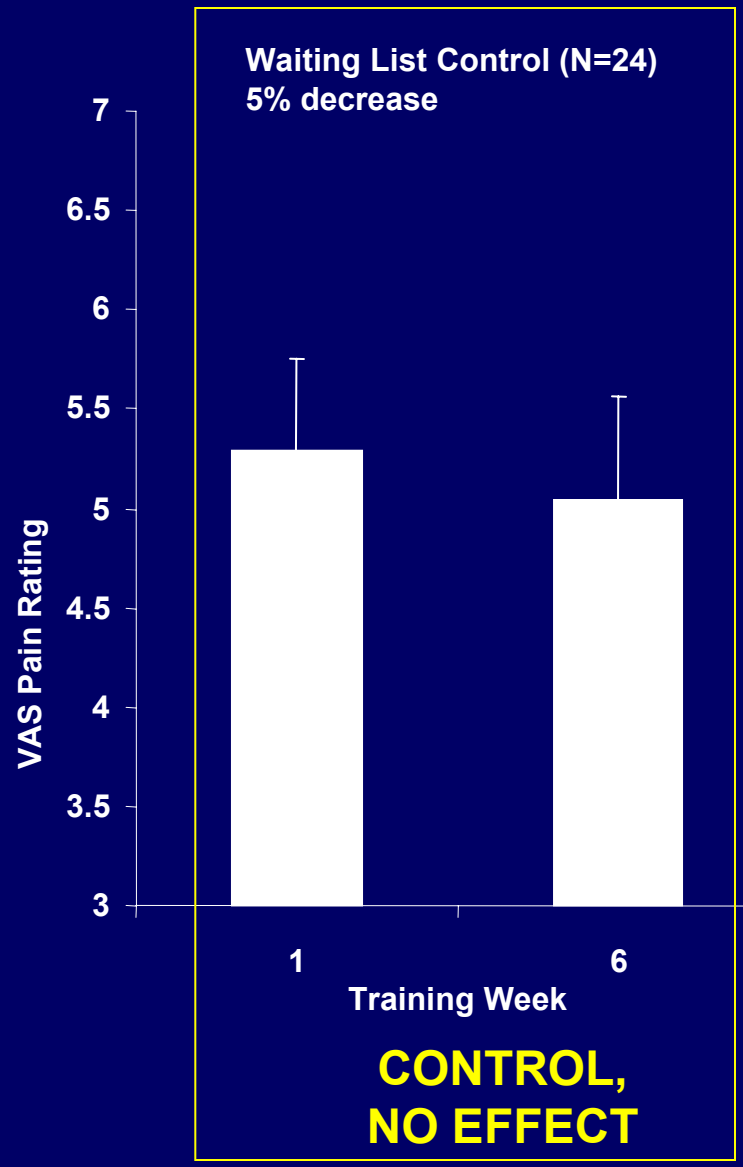

COMPARISON OF EFFECT ACROSS TWO TRAINING SITES/SCANNERS

NOTE:
Preliminary, Unpublished Data!
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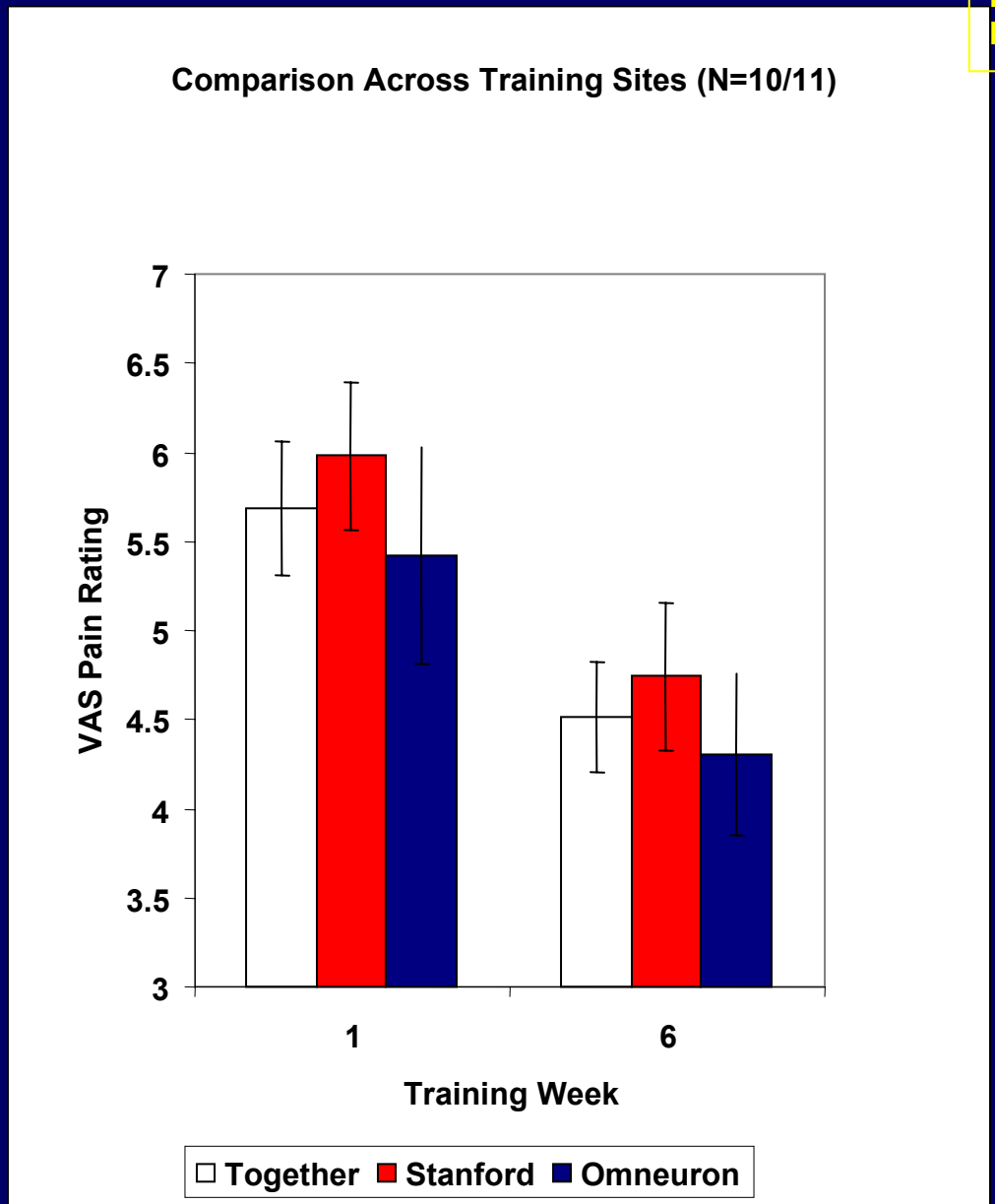
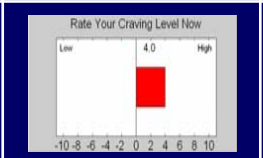
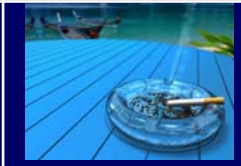
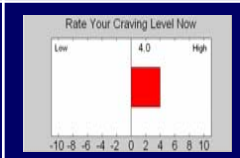
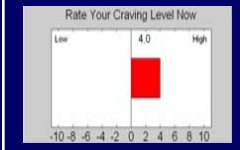
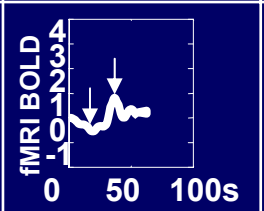
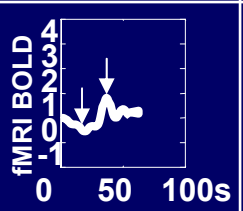
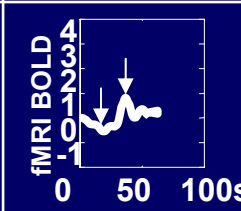
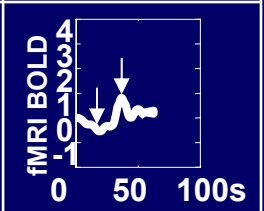


CAN RTFMRI-BASED TRAINING BE USED IN SUBSTANCE ABUSE? PROTOCOL DETAIL

OVERVIEW OF DISPLAY TO SUBJECTS

	INCREASE 30s	RATE 20s	REST 30s	DECREASE 30s	RATE 20s	REST 30s
STIMULUS-INDUCED CRAVING TASK	 INCREASE CRAVING		REST	 DECREASE CRAVING		REST
SELF-INDUCED CRAVING TASK	INCREASE CRAVING		REST	DECREASE CRAVING		REST
RTFMRI TRAINING TASK	 GRAPH UP		 REST	 GRAPH DOWN		 REST

WE ARE ACTIVELY ENROLLING CHRONIC PAIN PATIENTS FOR OUR CURRENT TRIAL

THANK YOU…

SOME REFERENCES

Control over brain activation and pain learned by using real-time functional MRI.
Proceedings of the National Academy of Sciences (2005)
deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., Gabrieli, J. D., and Mackey, S. C.

Learned regulation of spatially localized brain activation using real-time fMRI.
NeuroImage (2004) 21, 436-443
deCharms, R. C., Christoff, K., Glover, G. H., Pauly, J. M., Whitfield, S., and Gabrieli, J. D.

Functional brain imaging using a blood oxygenation sensitive steady state.
Magn Reson Med (2003) 50, 675-683
Miller, K. L., Hargreaves, B. A., Lee, J., Ress, D., deCharms, R. C., and Pauly, J. M.