Functional MRI for studying the interaction between pain and cognition

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Pain – a multidimensional experience (Melzack R & Casey KL, 1968)

Components

- Sensory – discriminative
- Affective – motivational
- Cognitive - evaluative

Why study brain response to pain?

- Fundamental
  -pain is related to consciousness:
  mind – brain problem
- Clinical
  -better pain management
  -designing new analgesics

Pain matrix

- Sensory - discriminative : brainstem, thalamus, somatosensory cortices SI (primary) and SII (secondary);
- Affective - motivational : insula, hypothalamus, amygdala, hippocampus, ACC (limbic system);
- Cognitive - evaluative : posterior parietal cortex (PPC), prefrontal cortex (PFC), supplementary motor area (SMA) and primary motor cortex;

Pain network - shares components with other cognitive functions

- A common experience: pain can affect the ability to carry out complex cognitive tasks
- Chronic pain patients (chronic migraine, low back pain,…) are affected in everyday life

- Neuroimaging studies:

  Attention and cognition influence the perception of pain (Bantick et al., 2002)

  Interactions between cognition and emotion (Drevets et al., 1998)

How does pain interact with the cognitive activity?

- Brain dynamics is not linear : a new cognitive component B, added to the task, modify the implementation of the preexisting component A (Friston KJ et al., NeuroImage, 1996)

Questions

- What is the neurophysiological substrate of this interaction?
- Does the modulation effect depend on the
  - -type of cognitive task?
  - -difficulty level of the task?
  - -psychological variables?

Experiment

- Two cognitive tasks*:
  - -semantic
  - -mental arithmetic
- 2x2 factorial design
  - -2 levels of sensory stimulation
  - -2 levels of difficulty in each cognitive task

*Rémy et al., NeuroImage 2003

Methods

- 12 healthy volunteers (24.2 ± 3.4 years old)
- 3T head-only system
- Functional imaging:

  Gradient-echo single-shot EPI

  16 contiguous axial-oblique slices, 5-mm thickness
- FOV = 20 cm, matrix 64x64

  Volume (16 slices) acquired in TR = 3 s

TASKS

PAIN

- Thermode with a 3x3 cm^2 flat probe on the palm of the left hand
- Alternate periods of rest (9 s) and stimulation (15 s), 4 cycles
- Painful stimulation: 46 to 49°C (pain threshold)
- Warm stimulation (baseline): 39°C

TASKS

COGNITIVE

- Visual presentation through goggles
- Synchronized with the thermal profile

SEMANTIC

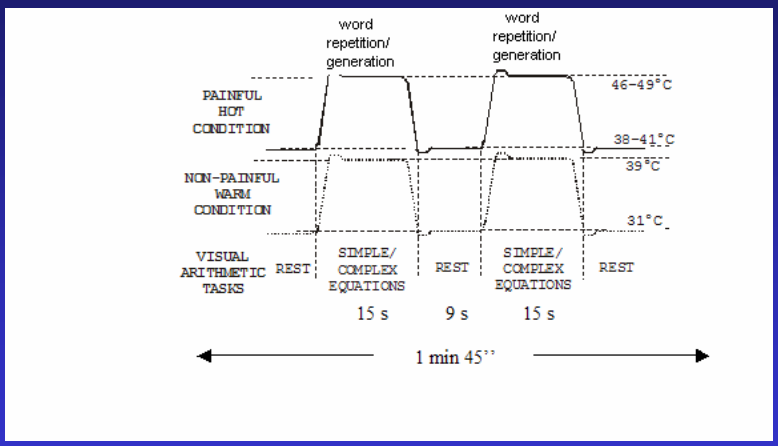
- Word repetition
- Word generation within a given category

TASKS

MENTAL ARITHMETIC

- Simple equations – one digit numbers multiplication (ex. 4x6=24, displayed for 3 s each)
- Complex arithmetic – one digit by two digit numbers multiplications (ex. 16x9=144, displayed for 7.5 s each)

Experimental paradigm



Experimental design

- SEMANTIC TASK
- 4 scanning conditions

(1) warm stimulation + word repetition (WR)

(2) warm stimulation + word generation (WG)

(3) painful stimulation + word repetition (PR)

(4) painful stimulation +word generation (PG)

Behavioral data

	Pain intensity	Unpleasantness	Task difficulty
WR	**1.2**	**1.2**	**0.1±0.3**
WG	**1.2**	**1**	**1.6±1.5**
PR	**6.1±1.4**	**6.2**	**1.4±1.5**
PG	**6.5±1.5**	**6.2**	**2.7±2.0**

P<0.017

P<0.075

P<0.026, paired t-test

- Easy task significantly perceived more difficult during pain

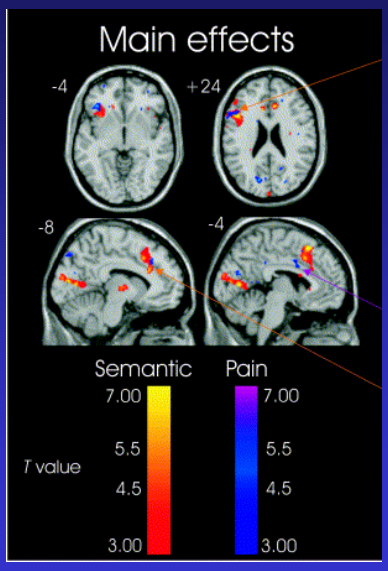
fMRI results

Main effect of Pain

DLPFC (BA9), Broca's area (BA44), MidCG (BA24'),occipital (BA18), precuneus (BA7), L insula, Post. CG, R thalamus R parietal cortex.

Main effect of semantic task

L occippital cortex BA17/BA18, SFG/MidCG (BA8/BA32'), L insula, L SMA, Thalamus, auditory assoc. area (BA22), L lenticular nucleus.



Broca's area (BA44)

MidCG BA24'

MidCG BA32'

(Rémy et al., Neuroimage 2003)

Main Effect of pain masked by main effect of semantic

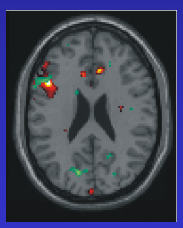
Regions of the semantic network, showing increased activity when pain is superposed

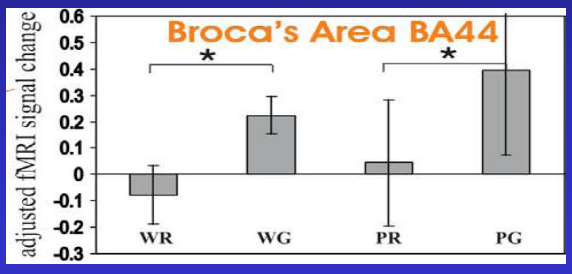
- L occipital cortex (BA19 to BA18)
- L Broca's area (BA45, BA44)
- L SMA (BA6/4)
- midCG (BA32')
- R thalamus
- Posterior CG (BA31)

RESULTS: COGNITIVE NETWORK

- Language area (Broca's area)
  - Similar increase observed with a disturbing interference during cognition (Ghatan et al., 1998)

z = 24 mm

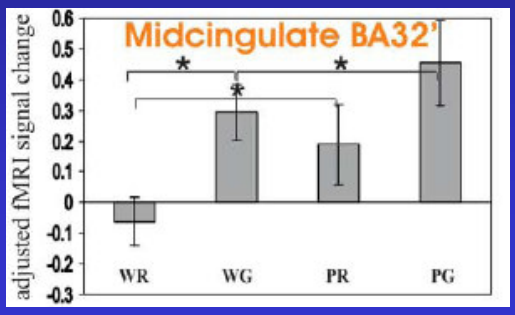




RESULTS: ATTENTION NETWORK

- Anterior Cingulate Gyrus
  - Involved in the cognitive task (attention component of the task)
  - Increased with pain
  - Part of a selective attention network (Peyron et al., 1999)

x = -8 mm P<0.01

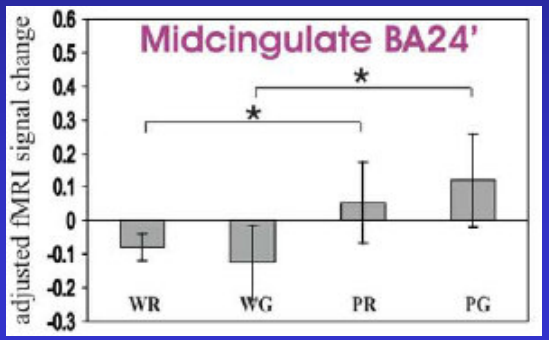


RESULTS: ATTENTION NETWORK

- Anterior Cingulate Gyrus BA24'
  - Pain-specific activity (Hutchison et al., 1999)
  - Reported in many neuroimaging studies on pain

x = -4 mm

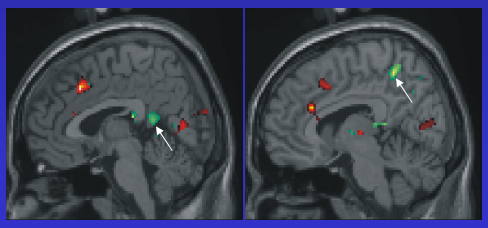
P<0.01



RESULTS: ATTENTION NETWORK

- Parietal cortex and Posterior Cingulate Gyrus
  - Recruited during pain conditions
  - Increased attentional load

x = +4 mm x = +8 mm

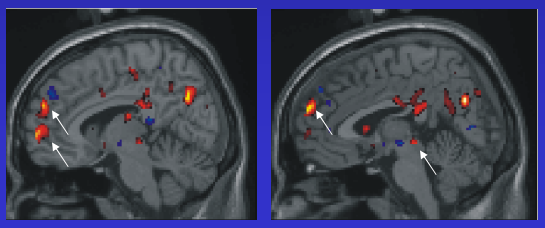


P<0.01

RESULTS: POSITIVE INTERACTION

- Medial prefrontal cortex
  - Involved in emotional tasks
  - Involved in high placebo responders during pain (Petrovic et al., 2002)
  - Projects to the periaqueductal gray, which is involved in analgesia
  - Recruitments of brain areas related to analgesia when cognition and pain tasks are presented simultaneously

x = +8 mm x = +4 mm



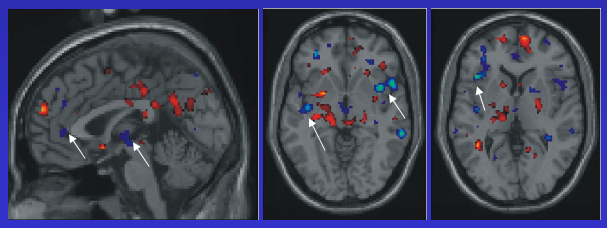
P < 0.05

RESULTS: NEGATIVE INTERACTION

- "Emotional" network (limbic system)
  - Bilateral insula
  - Perigenual cingulate
  - Medial thalamus

➡ Inhibition of emotional areas when cognition and pain tasks are presented simultaneously

x = 0 mm z = -4 mm z = +4 mm



P < 0.05

CONCLUSIONS: SEMANTIC TASK

- When a pain task is presented simultaneously with a cognitive task:
  - Cognition-related activity is increased
  - Attention-related activity is increased
  - Increase of activity in brain areas involved in analgesia
  - Inhibition of brain areas involved in emotional processing

MENTAL ARITHMETIC
Experimental design

4 scanning conditions:

(1) warm stimulation + simple arithmetic (WSA)
(2) warm stimulation + complex arithmetic (WCA)
(3) painful hot stimulation + simple arithmetic (PSA)
(4) painful hot stimulation + complex arithmetic (PCA)

Behavioral data

	WSA	PSA		WCA	PCA	
Pain Int	1.9±1.9	6.5±1.5	P<0.0001	2.0±2.3	6.3±1.3	P<0.0001
Unpl.	3.0±2.2	6.3±1.6	P<0.001	1.6±2.0	6.1±1.9	P<0.0001
Diff.	2.3±1.6	4.1±1.4	P<0.005	5.1±1.8	5.5±1.6	n.s.

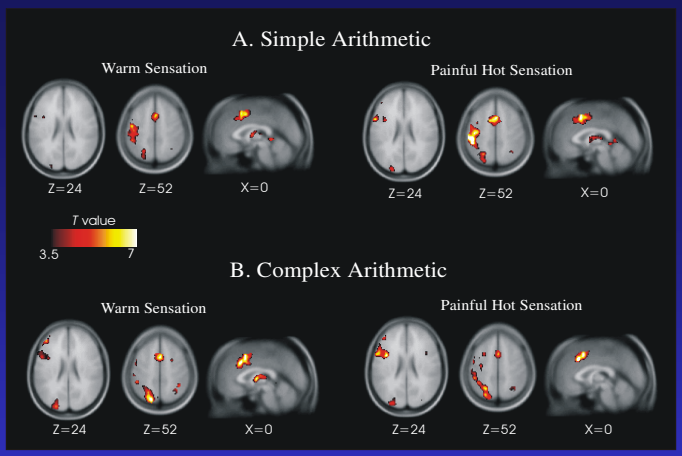
•Simple arithmetic task was perceived as significantly more difficult during pain

Behavioral data

Performance

	WSA	PSA		WCA	PCA	
Accuracy (%)	95.3±6.5	84.5±14.4	P<0.05	72.0±25.1	77.2±18.3	n.s.
RT	1.6±0.3	1.5±0.3	P<0.001	4.5±1.1	4.4±1.1	n.s.

Performance was significantly poorer during pain in SA, but was equivalent during pain and warm in CA



Group results for the simple effects (p<0.001 uncorr.)

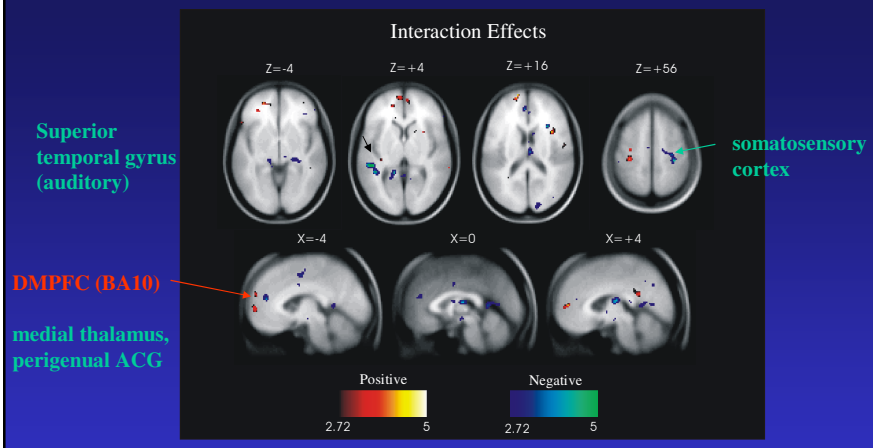
Areas (SA): supramarg. gyrus (BA40), sup. parietal lobule (BA7), MPFC (BA6/32 , L BA 44, R insula), med. Thal.

(CA):DLPFC (BA9), L occip-angular gyrus (BA39), L insula, L occip. cortex (BA18)

(Rémy et al., in prep)

Complex arithmetic

- Different influence of pain on the activity in distinct brain regions
- Increases: L prefrontal cortex (BA44, BA9), anterior insula
- Decrease: medial frontal cortex, SMA, and L posterior parietal lobe (BA7, BA39)
- Possible change of strategy when performing the complex task during pain exeprience



Positive and negative interactions between pain and arithmetic tasks (P<0.01)

Interaction analysis

Negative interactions

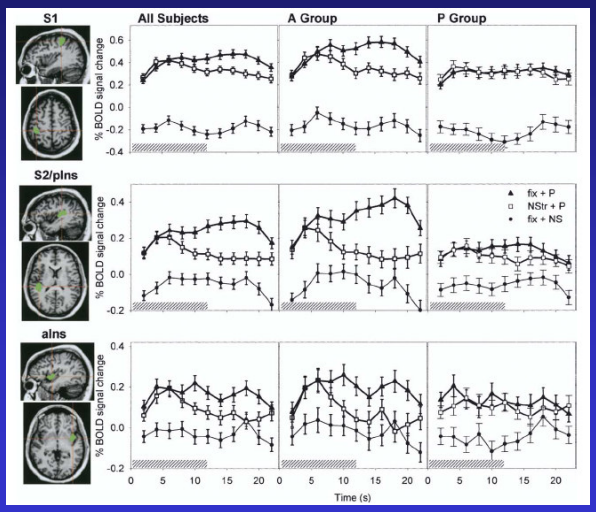
- left STG (BA22) and R somatosensory cortex (contra-lat.) → suppression of the task-irrelevant sensory input under increased attentional load
- medial thalamus, perigenual ACG - medial pain system, believed to be involved in the pain quality evaluation and affective aspects integration;

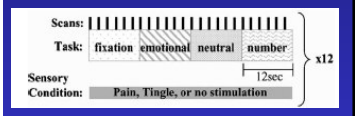
Interaction analysis

Positive interactions

- DMPFC (BA 10) - in pain studies DMPFC was related to analgesia during placebo (Petrovic P. et al, Science 2002)
- observed as well in interaction between pain and semantic generation task
- the increased activity in mental calculation during pain might be ascribed to the initiation of an analgesic response

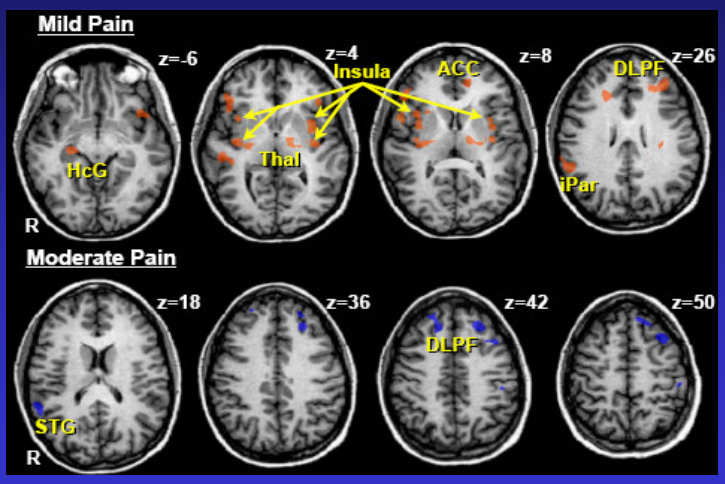
Cognitive modulation of pain-related activity depends on the strategy





(Seminowicz et al., 2004)

Pain catastrophyzing influences brain responses to pain



(Seminowicz and Davis, 2006)

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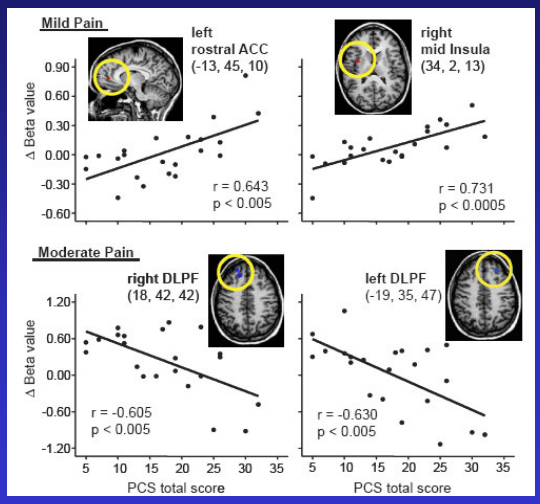

(Seminowicz and Davis, 2006)

Further research

Neural processing of pain in chronic pain patients:

- Impact of fear and threat in the context of pain catastrophyzing
- Effect (and efficiency) of CBT