Forebrain Mechanisms of Pain Modulation

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Topics of talk:
1. Involvement of the forebrain in pain perception
2. Descending pain control pathways from cortex
3. Attentional modulation of pain
4. Emotional modulation of pain
5. Empathy and pain
6. Placebo analgesia
7. Role of forebrain opiates and dopamine in analgesia

Multiple CNS pathways of pain signalling and pain modulation


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Cortical regions that receive direct nociceptive input from thalamus

Brain imaging used to visualize regions in the brain activated by pain

- Positron Emission Tomography (PET)
- Functional Magnetic Resonance Imaging (fMRI)

Brain imaging shows cortical network activated by pain
Pain is a complex sensory and emotional experience

Sensory-discriminative dimension
- Stimulus features: Location, quality, intensity

Affective-motivational dimension
- How unpleasant or upsetting is the pain?
- What will I do about the pain?

Pain activation in ACC and IC underlies the affective-motivational dimension of pain

Pain affect without “pain sensation” in patient with postcentral lesion

(Planer et al., 1999)

Some cortical regions are involved in descending pain modulation
Information from cortex ultimately received in spinal cord

What types of psychological conditions can alter pain?

Attentional state modulates pain
Shifting attention away from pain

Auditory stimulation

Thermal stimulation

Auditory task

Thermal task

Mean (+SE) VAS rating

P=0.01

P=0.09

Bushnell et al., 1999

Distraction from pain makes it weaker

Pain-evoked activity in somatosensory cortex reduced during distraction

Attention to pain

Attention to tones

Bushnell et al., 1999
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Attentional modulation in S1 and insular cortex

Commonly used distraction task: Stroops color/word task
Blue
Yellow
Red
Distracting, but also arousing, creates sympathetic autonomic response

Heat pain activation when attention to pain

Heat pain activation during distraction with Stroops task
Valet et al., 2004
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Cingulofrontal-PAG circuit activated during Stroops distraction

Is this extensive modulation related to attention or to changes in arousal or emotional state?

Blue
Yellow
Red

Emotional state alters pain

Studies to separate attention and emotions

Villemure et al., Pain 2003
Mood predicts pain unpleasantness

Mood alters pain-evoked activity in anterior cingulate cortex

Bad mood + Pain  Good mood + Pain

Villemure et al., in press
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Fronto-PAG circuit involved in emotional modulation of pain

Villemure et al., in press

Empathy and pain

Watching a loved-one in pain activates limbic pain areas in brain

Singer et al., 2004

Testing the effect of empathy on pain perception

Baseline testing: Subjects receive heat stimuli while watching the 'neutral' video

Empathy manipulation: Subjects watch either the 'AFF-' or 'AFF+' actor's interview

Experimental testing: Subjects receive heat stimuli while watching the 'testing session' video

Loggia, Mogil, Bushnell 2007

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High empathy = more pain

Temperature (°C)

∆ perceived intensity

Loggia, Mogil, Bushnell 2007

Placebo analgesia

The observed effect of an active drug is the combination of three parameters:

- Specific effect of the drug
- Natural course of the disease
- Placebo effect
Placebo effects have been documented for a number of disorders

- Pain relief
- Psychiatric disorders (anxiety, depression)
- Cardiovascular disease
- Parkinson’s disease

The placebo effect can be created in two ways

- Expectation
- Conditioning

Expectation-induced placebo analgesia is opiate mediated

Benedetti et al., 1999

Cold pain tolerance
Placebo reduced pain-evoked activity in ACC, insula and thalamus.

Wager et al., Science 2004

Placebo increased prefrontal and midbrain activity in anticipation of pain.

Wager et al., Science 2004

Forebrain involvement in opiate analgesia

Wager et al., Science 2004
Imaging of opiate analgesia

PET imaging of brain activation related to fentanyl administration
Which activations are related to analgesia and which are related to others effects of opiates?

Use of PET competitive binding techniques to determine which receptors are related to analgesia
- Administer radioactively labelled opiate agonist (\(^{11}C\)-Carfentanyl)
- Compare uptake with and without pain stimulus
- Brain regions in which endogenous opiates are released in response to pain will show less uptake of the radioactively labelled exogenous opiate

Pain-related opiate binding in cingulate cortex, thalamus, and nucleus accumbens

Zubieta et al., 2001

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Forebrain dopamine involved in pain modulation

Dopamine release in basal ganglia in response to muscle pain

Conclusions:
1. Cortical pain processing is distributed, including both sensory and limbic regions
2. Frontal and cingulate cortices are involved in descending pain modulation
3. Attentional state modulates perceived pain intensity and alters pain-evoked activations in somatosensory and insular cortices
4. Emotional state modulates pain unpleasantness and alters activity in limbic regions such as anterior cingulate cortex
5. Empathy enhances pain perception
6. Placebo analgesia involves descending modulation from frontal cortex
7. Forebrain opiates and dopamine are involved in pain modulation
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Thanks to:
Chantal Villemure
Marco Loggia
Petra Schweinhardt
David Seminowicz
Patrick Wood
for performing studies
AND
The audience

Funded by:

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