Social Modulation of Pain as Evidence for Empathy in Mice

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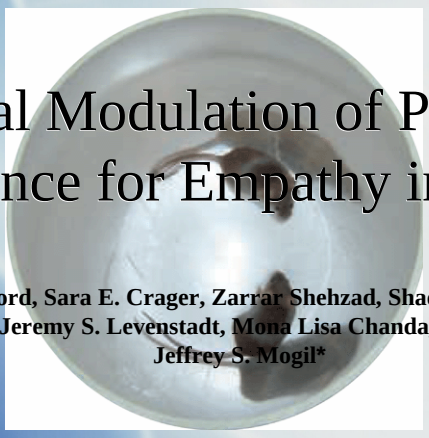

Journal Club

September 5th 2006

Introduction

- Empathy was studied in groups of mice by examining their responses to pain while they observed pain in another familiar individual.
- Definition of Empathy:
  - The capacity to share the feelings of others (Singer, Neurosci Biobehav Rev 2006, Cambridge Dictionaries)
  - Empathy is the recognition and understanding of the states of mind, including beliefs, desires and particularly emotions of others (Wikipedia).
  - The action of understanding, being aware of, being sensitive to, and vicariously experiencing the feelings, thoughts, and experience of another of either the past or present without having the feelings, thoughts, and experience fully communicated in an objectively explicit manner (Merriam Webster)

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Introduction

- There is little evidence for adult-adult empathy outside of primates.
- Evidence from rats and pigeons has shown that the pain-related distress in another individual can serve as a conditioning stimulus (Church, 1959; Watanabe and Ono, 1986).
- Operant responses can be produced in rats to terminate the distress of another (Rice and Gainer, 1962).

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Hypothesis

- If empathy does indeed exist in mice, the real-time observation of pain in one mouse might affect the responses to painful stimuli by another individual.

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Methods

- Subjects:
  - Pairs of same sex mice
  - Animals were placed in plexiglass cylinders
  - Pairs were either siblings, cagemates, or strangers
  - Compared to a control group tested in isolation

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Methods

- Nociceptive Assays:
- Abdominal constriction test (ACT) (Writhing)
  - 0.9% glacial acetic acid was injected intraperitoneally
  - Writhing: Characteristic lengthwise stretches of the torso with simultaneous concave arching of the back
  - Pairs: **Both Writhing (BW)**
  - One was injected and watched an uninjected mouse: **One Writhing (OW)**
- Formalin test (FT)
- Paw withdrawal test (PWT)

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Results: ACT

- Both Writhing mice displayed more pain behavior than isolated mice, but only when their counterparts were cagemates

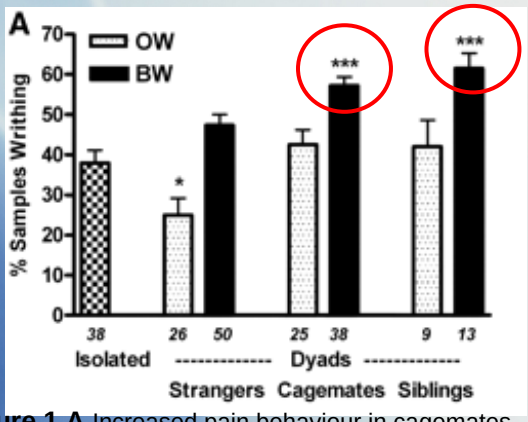

Figure 1 A Increased pain behaviour in cagemates [7]

Results: ACT

- Writhing behavior co-occurred in time at levels exceeding those expected by chance.
- Behaviour was higher in cagemate pairs than stranger pairs.

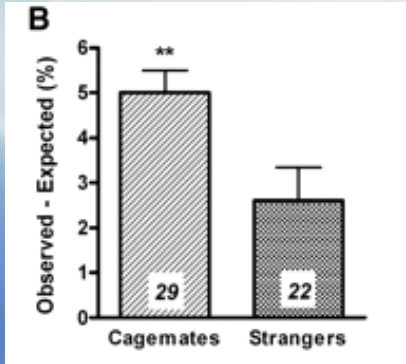

Figure 1B Pain related behaviour higher than chance in cagemates [8]

Results: ACT

- The hyperalgesia and behavior co-occurrence developed over 14 to 21 days of being housed together.

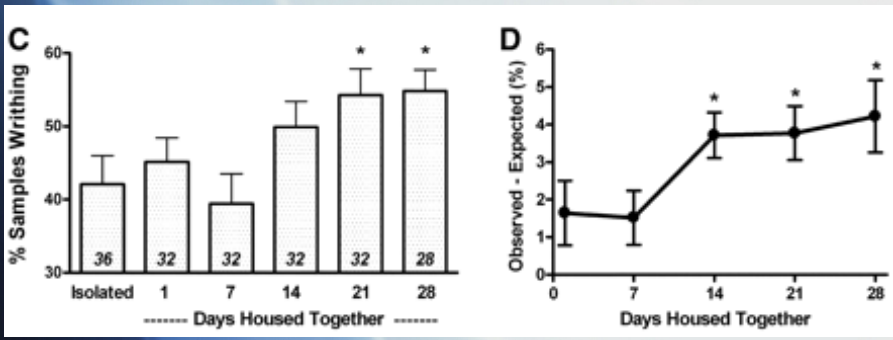

Figure 1C,D: Pain related behaviour increased as animals were housed together longer

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Results: ACT

- In general, observed behaviors other than writhing were similar across all conditions.
  - Locomotor behaviour
  - Physical contact
- There were higher levels of anxiety or stress in stranger pairs relative to cagemates
- Indicates that stress is not a likely mediator of pain behaviour because the observed effects were higher in cagemates.

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Results: ACT

- There was a significant decrease in writing behaviour in animals that were viewing an uninjected stranger animal.

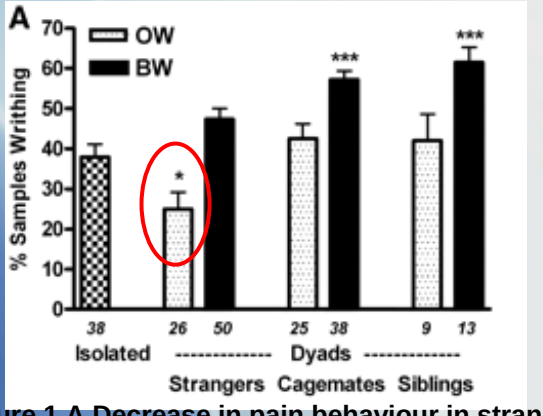

Figure 1 A Decrease in pain behaviour in strangers

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Results: ACT

- The inhibition was entirely specific to males and is likely due to distraction or social stress–induced analgesia.

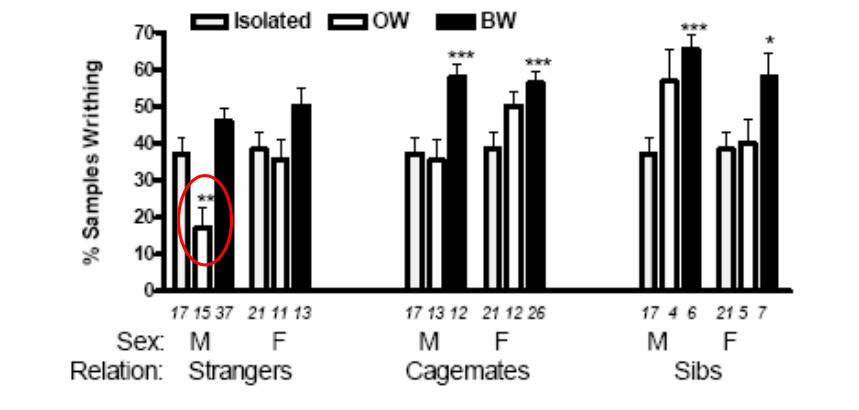

Figure S5 Decrease in pain behaviour in strangers was specific to males

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Modality of Communication

- The authors wanted to determine the modality of communication between the animals.
- Sensory inputs were blocked:
  - Visually and physically to prevent sight and touch using a barricade
  - Or by rendering the animals anosmic or deaf

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Results: ACT

- The only manipulation that significantly abolished the BW/OW hyperalgesia was a visual blockade using an opaque Plexiglas barrier

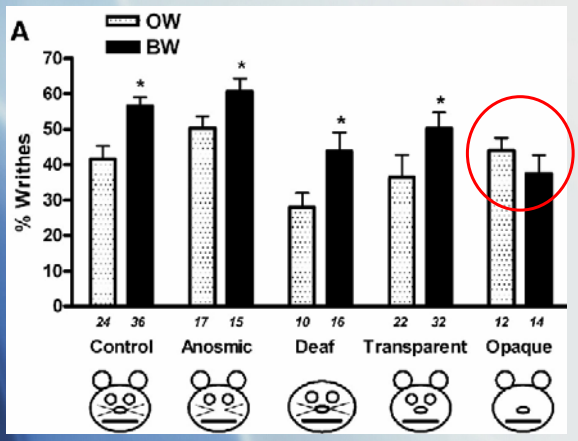

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Figure 2A: Visual and physical barrier significantly reduced hyperalgesia

Results: ACT

- The opaque barrier also blocked the co-occurrence of writhing behavior in the “Both Writhing” condition

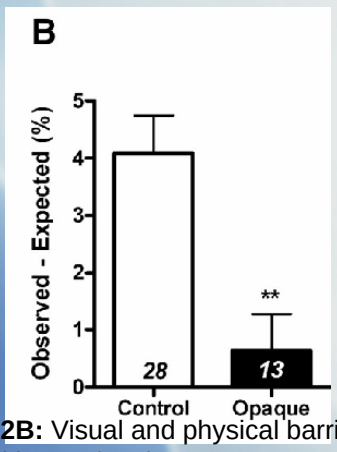

Figure 2B: Visual and physical barrier significantly reduced hyperalgesia

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Results: ACT

- Authors note that pheromonal communication may have been a factor
- Olfactory epithelium was destroyed but axonal transport from the vomeronasal organ to the accessory olfactory bulb was spared

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High Dose Formalin Test

- Results were independently verified using an existing data set
- 4 mice subjected to 5% formalin test
  - Formalin injected into hindpaw
- Mice were in individual cylinders but in full view of other mice
- Licking behaviour monitored

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Results: HDFT

- Licking behaviour was time-synchronized.
- They calculated possible correlations between time-courses of the licking behaviour and estimated the within-run synchronization as the average of those correlations (*R*).

The co-occurrence of pain behaviors in familiar individuals may itself be evidence of empathy.

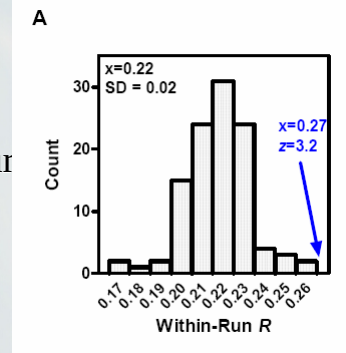

Figure S7: Frequency histogram of within run correlations of licking behaviour

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Results: HDFT

- Between-subject variance within a run was reduced
- Suggesting that subjects' pain behaviours were being influenced by their neighbours.

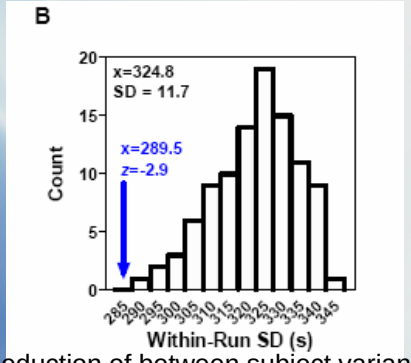

Figure S7 Reduction of between subject variance within a run

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High vs Low Dose Formalin Test

- Same pairs of mice in the ACT experiment underwent the formalin test
  - Formalin injected into hindpaw
- Pairs either received the SAME high dose (5%) or low dose of formalin (1%)
- Or DIFFERENT doses (1%, 5%)
- Licking behaviour monitored

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Results: HLDFT

- Licking times were *marginally* increased in mice receiving the low dose while observing a high dose injected cagemate.
- Licking times were reduced in mice receiving the high dose while observing a low dose injected cagemate.
- No significant effects were observed among strangers.

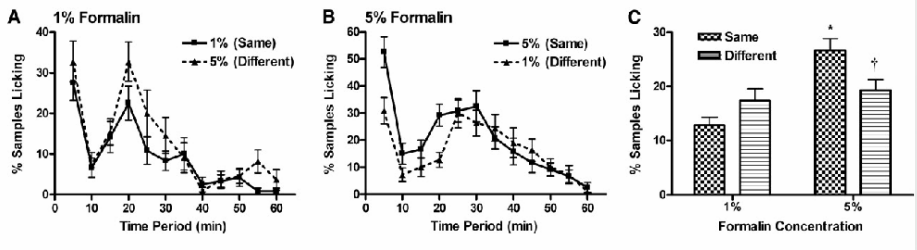

Figure 3 Pain behaviour significantly increased or decreased depending on state of cagemates

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Paw Withdrawal Test

- In order to determine if results were generalizable to another modality they tested the same group of mice on the paw withdrawal test (PWT).
- PWT measures the sensitivity to withdraw from a thermal heat stimulus.
- The stimulus was a high-intensity beam aimed at the plantar surface of the hindpaw.
- Measured withdrawal reflex before and at 5-min intervals after injection of acetic acid (or no injection).
- Withdrawal reflex measured in pairs of animals:
  - Both Writhing -BW
  - None Writhing - NW
  - One Writhing – one mouse received an acetic acid injection (OW-Inj.) and the other(OW-Uninj.) did not.

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Results: PWT

- Injection and observation of a cagemate's writhing behavior produced equivalent thermal hyperalgesia.
- Mice withdraw their feet from the heat more quickly--even if they'd received no injection themselves.

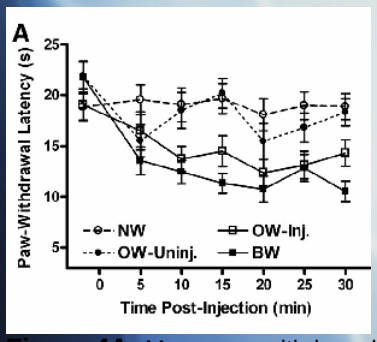

Figure 4A: Mean paw-withdrawal latencies

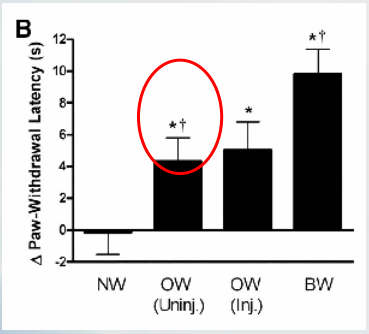

Figure 4B: Average change in paw-withdrawal latencies

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Results: PWT

- Concurrent thermal pain testing did not abolish the BW/OW increase in writhing behavior.
- Significant correlation was observed between the writhing behavior of one mouse in the dyad and the thermal hyperalgesia exhibited by the other.

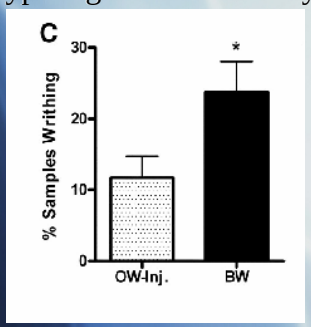

Figure 4C: BW behaviour increased in comparison to OW – Inj

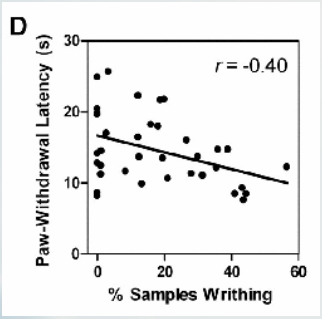

Figure 4D: Correlation between writhing behaviour and thermal hyperalgesia in conspecifics

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Conclusions

- Results indicate that the pain system can be sensitized in a generalized manner after viewing pain in a familiar counterpart.
- Socially mediated hyperalgesia can be elicited in the absence of imitation.
- Mechanisms underlying these phenomena are thus more likely to be found in the sensory/perceptual system than in the motor system.

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Is that empathy?

- Singer - "Philosophers would argue you can only have empathy if you have consciousness". "Psychologists would want to see evidence of altruistic behavior and altruistic motivation."
- Vierck – Modulation of reflex response. Writhing and paw licking are reflexive behaviors mediated by the spinal cord.
- Evidence for emotional contagion?

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