

# CENTRAL SENSITIZATION OF MECHANICAL ALLODYNIA IN TRIGEMINAL SYSTEM: EVIDENCE FROM CARDIAC GATED FMRI

Wei-Ting Zhang, MD, PhD; Caterina Mainero, MD, PhD; Ashok Kumar, PhD; A. Gregory Sorensen, MD  
 Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School,  
 Charlestown, MA, United States

## BACKGROUND

Pain to innocuous stimuli (allodynia) is a hallmark of a number of pain-related diseases that affect the trigeminal system. Allodynia reflects altered central processing of sensory information in the second-order neurons in the dorsal horn and possibly higher order structures. The involvement of higher order structures (thalamus, somatosensory cortex) during allodynia in humans has been shown by previous neuroimaging studies. Animal data have also outlined a substantial contribution, at the supraspinal level, of the pain modulatory system to the development and maintenance of allodynia (Figure 1).

## AIM OF THE STUDY

In the present study, using cardiac gated fMRI, we mapped activity in the second-order neurons and brainstem nuclei of the pain modulatory system putatively involved in the allodynic process that changes an innocuous stimulation of the skin in a painful perception following application of an experimental model of neuropathic pain to the trigeminal territory of 12 healthy subjects.

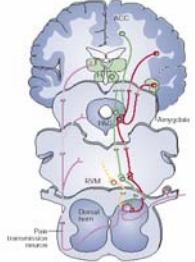


Figure 1 (Fields H. 2004). Descending pain modulation System. ACC: anterior cingulate; H: hypothalamus; PAG: periaqueductal gray; RVM: rostral-ventromedial medulla; T: thalamus. This pathway can exert both inhibitory (green) and facilitatory (red) control. Yellow: serotonergic.

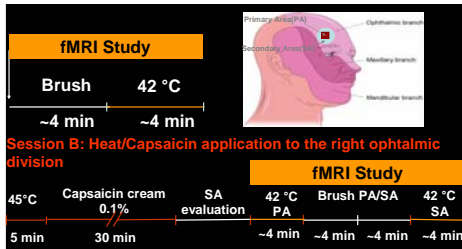


Figure 2. Study Design. Each fMRI scan last 4.5 min including four "on" blocks and five "off" blocks. PA: primary area; SA: secondary area. **Results of the heat hyperalgia will be presented on Wednesday by C. Mainero (#0438, Room B 118-122, 2:10pm)**

## SUBJECTS AND METHODS

**Subjects and model:** Twelve healthy male subjects (mean  $\pm$  SD age of  $26.6 \pm 6.7$  years) underwent two randomly ordered fMRI studies (Figure 2), separated by an interval of at least a week. Five minutes 45 degrees heat stimuli and 30 minutes topical capsaicin (0.1%) application can successfully induce hyperalgnesia and allodynia (Petersen 1999).

**Data acquisition:** To eliminate the effects of pulsatile brainstem motion, we synchronized fMRI acquisition to a particular time in the subject's cardiac cycle. During the functional scan 17 sagittal slices ( $3^{\circ}3^{\circ}3^{\circ}$ mm<sup>3</sup>, gap 20%) were acquired every three heartbeats (TR=3 s) on a 3T system (Siemens Trio, Germany) with a gradient EPI sequence and an eight-channel head coil. Four epochs of brush (-1 Hz) were administered and each last 30 seconds, separated by 30 second intervals of rest. In the capsaicin session, brush was given to two different areas: primary area (PA) where the capsaicin was applied, and the area surrounding it (secondary area, SA). Immediately following the brush scans, subjects rated their pain using a 0 (no pain) to 10 (highest pain imaginable) scale.

**Data analysis:** The EPI data were first motion-corrected using the algorithm from 3dvolreg in AFNI package (Cox, 1996). T1 correction was necessary to correct changes in signal intensity due to different residual longitudinal magnetization following variability in TR (Guimaraes et al. 1998). The T1-corrected data were then de-spiked, spatially smoothed (fwhm = 4mm), and low- and high-pass filtered. Stimulus input for statistical analysis was modeled reflecting different TRs between time-points. Regression analysis was performed with 3dDeconvolve in AFNI (Cox, 1996) to calculate regression coefficient and corresponding *t* statistics. *T* threshold was set to 2.88 ( $p < 0.005$ , uncorrected) to determine individual subject's activation maps. For group analysis, those statistical maps were transformed into Talairach space. Regression coefficients of the same stimuli but in different conditions (normal skin, primary area, and secondary area) were compared with two-way ANOVA with different conditions as a fixed factor and subjects as a random factor. There were 5 output contrasts: 1) brush to untreated skin, 2) to PA and 3) SA, 4) brush to PA vs. untreated skin, 5) brush to SA vs. untreated skin. ( $p < 0.05$ , corrected)

## RESULTS

Skin redness was observed in and around the area capsaicin was applied. Pain to brush was successfully induced in both primary and secondary areas. fMRI individual analysis showed that nine out of 12 subjects (75%) activated the dorsal pons during innocuous brush to the untreated right V1. During innocuous brush to the primary area, 7 out of 12 subjects (58.3%) showed activation in the dorsal medulla, which is consistent with group averaged maps (Figure 3). For the secondary area eight subjects (66.7%) activated the dorsal medulla. However, activation in dorsal medulla during brush to the secondary area was not detected in the group averaged maps.

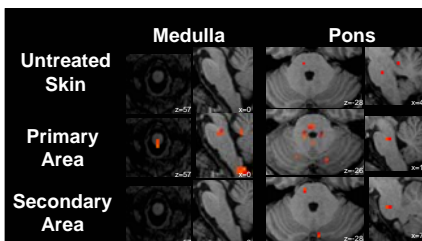


Figure 3. Group *t* statistical maps overlaid on high-resolution anatomical images ( $p < 0.05$ , corrected) showing brainstem results.

Group statistical maps of brush to three different conditions are shown in Figure 4. Ipsilateral putamen, insula, contralateral caudate and anterior cingulate (ACC) are activated by brush to the untreated skin. More extensive activation are seen during brush to the primary area including bilateral thalamus (both medial and lateral), ipsilateral putamen, globus pallidus, contralateral caudate, bilateral ACC, and contralateral posterior cingulate (PCC). For brush to the secondary area, ipsilateral insula, bilateral putamen, contralateral caudate, and contralateral ACC are activated.

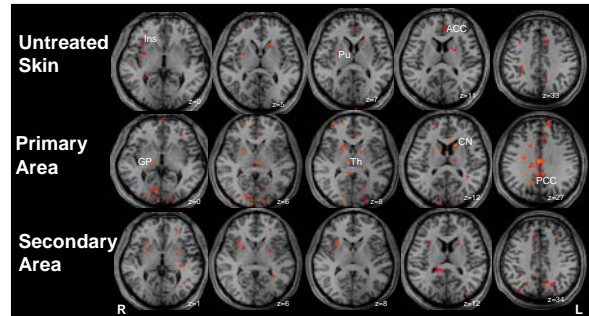


Figure 4. Group *t* statistical maps in cortex. ACC: anterior cingulate; CN: caudate nucleus, GP: globus pallidus; Ins: insula; PCC: posterior cingulate; Pu: putamen; Th: thalamus. ( $p < 0.05$ , corrected)

Results more specific to allodynia revealed by comparison maps indicate that both primary and secondary mechanical allodynia activated dorsal medulla/spinal cord (Figure 5). However, their effect in periaqueductal gray (PAG) of midbrain is opposite.

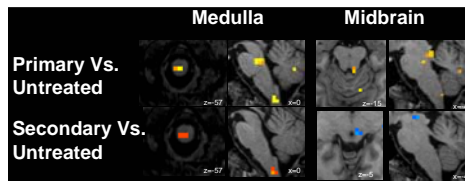


Figure 5. Brainstem *t* statistical maps of comparison between two different conditions. ( $p < 0.05$ , corrected). Note that in PAG there is opposite effect in primary and secondary mechanical allodynia.

Comparison results in cortex (Figure 6) show that activity in contralateral amygdala, thalamus, ipsilateral caudate, and bilateral ACC during brush to the primary area is enhanced compared to that during brush to the untreated skin. While activity in ipsilateral amygdala, insula, contralateral ACC, ipsilateral supplementary motor area (SMA) and superior parietal lobule (SPL) is increased during brush to the secondary area.

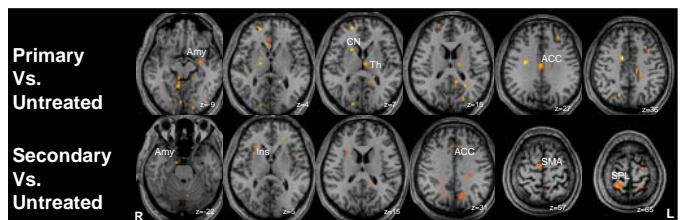


Figure 6. Cortex *t* statistical maps of comparison between two different conditions. ACC: anterior cingulate; CN: caudate nucleus, Ins: insula; SMA: supplementary motor area; SPL: superior parietal lobule; Th: thalamus. ( $p < 0.05$ , corrected)

## CONCLUSIONS

Central sensitization happened both in primary and secondary mechanical allodynia, however, in different foci. PAG, as a key in descending antinociceptive system, plays a different role in primary and secondary mechanical allodynia. The ability to detect activation within the trigeminal nuclei in the brainstem and to discriminate between noxious and non-noxious stimuli may prove useful in clinical conditions and in the evaluation of pain.

## REFERENCES

- [1] Cox RW. Comput Biomed Res. 1996; 29(3): 162-73
- [2] Fields H. Nature Review Neurosci. 2004; 5:565-575
- [3] Guimaraes AR et al. Hum Brain Mapp. 1998; 6 (1): 33-41.
- [4] Petersen KL et al. Neuroreport. 1999 May 14;10(7):1511-6

## ACKNOWLEDGEMENT

This work is supported by NIH P01NS35611.