Mapping heat allodynia in the trigeminal system using cardiac gated fMRI

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Background

Pain to innocuous heat and/or mechanical stimuli (allodynia) is common in diseases that affect the trigeminal system including neuropathic pain and migraine. Animal data suggest that allodynia reflects peripheral and/or central sensitization in second-order neurons (spinal trigeminal nucleus, spV), and possibly higher order neurons. We used cardiac gated fMRI and applied an experimental model of neuropathic pain to the first ophthalmic division (V1) of the trigeminal nerve of healthy volunteers to: 1) map heat allodynia in the spV in the dorsal medulla, and in higher-order structures; 2) map differences between the sensitized area and the surrounding area vs the untreated skin; 3) investigate the relation between behavioral and functional data.

Methods

Twelve healthy male right handed subjects (mean±SD age of 26.6±6.7 years) underwent two randomly ordered fMRI studies, separated by an interval of at least a week, one following innocuous heat to the right V1 after heat/capsaicin-induced allodynia [1], and one during the same stimulus to the untreated right V1. To eliminate the effects of pulsatile brainstem motion, we synchronized fMRI acquisition to a particular time in the subject's cardiac cycle. Seventeen sagittal slices (3mm thick, 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 thermal stimuli of normally innocuous 42°C lasting 30 seconds each, separated by 30 second intervals at 32°C, were administered using a 1.6 cm^2 Peltier thermode (Medoc, Haifa, Israel). During the capsaicin session thermal stimuli were given to the area treated with capsaicin (primary area), and to the surrounding area (secondary area). After each thermal scan, subjects rated their pain using a 0 (no pain) to 10 (highest pain imaginable) scale. The EPI data were first motion-corrected using 3dvolreg from AFNI [2]. T1 correction was necessary to correct changes in signal intensity due to different residual longitudinal magnetization following variability in TR [3]. The T1-corrected data were then despiked, 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 to calculate regression coefficients 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 and secondary area) were compared with two-way ANOVA with different conditions as a fixed factor and subjects as a random factor.

Results

Pain ratings after thermal stimulation to the right V1 in the primary area (6.3±1.4) were significantly higher (p<.000 by Anova) than those in the secondary (3.4±2.2) and untreated area (1.1±1.5). Pain ratings after stimulation of the secondary area were significantly higher than those in the untreated right V1 (p<.05 by t-test). fMRI individual analysis showed that eight out of 12 subjects (66.7%) activated the spV during innocuous heat to the untreated right V1 (Fig. 1). In five subjects activation was in the ipsilateral dorsal medulla, in two of them in the contralateral side and in one bilaterally. During innocuous heat to the primary area 10 out of 12 subjects (83.3%) showed activation in the dorsal medulla (four ipsilaterally, four contralaterally, and two bilaterally). For the secondary area six subjects (50%) activated the dorsal medulla, either ipsilaterally (2 subjects), contralaterally (3 subiects), or bilaterally (1 subject). Statistical comparison of activation maps during thermal stimulation to the primary area vs the untreated right V1 showed that primary heat allodynia was significantly associated with increased activation in the ipsilateral spV and insula, contralateral thalamus, caudate and anterior cingulate (Fig. 2). There was no increased activation in the spV during heat stimulation to the secondary area compared to the untreated area, however, we found an increased activity in the contralateral midbrain, ipsilateral thalamus, and bilateral anterior cingulate. We found a positive correlation (p.03 by linear regression) between the pain scores obtained after thermal stimulation to the primary area and the corresponding maximal T values in the contralateral thalamus (Fig. 3). There was no significant relation between behavioral and functional data in the dorsal medulla and thalamus for the secondary area.

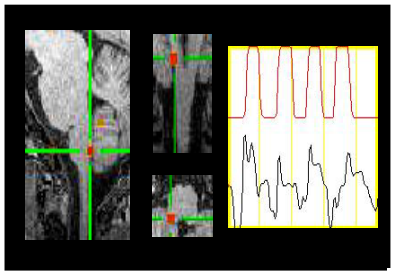

Fig. 1. Innocuous heat-induced activation in the ipsilateral dorsal medulla displayed on the sagittal, coronal and axial planes, and the corresponding time course following the heat stimulus.

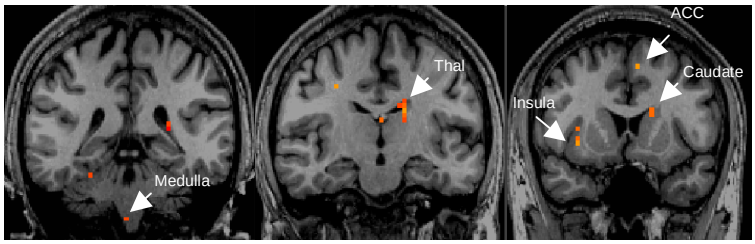

Fig 2. Statistical group maps (radiological convention) showing foci signicantly activated during innocuous heat to the right ophthalmic division of the trigeminal nerve on the primary sensitized area vs the normal skin.

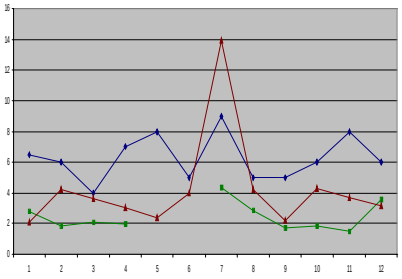

Fig. 3. Diagram showing for each subject the relation between pain scores (blue), maximal T value in the contralateral thalamus (red) and dorsal medulla (green) during primary heat allodynia (x axis= subject).

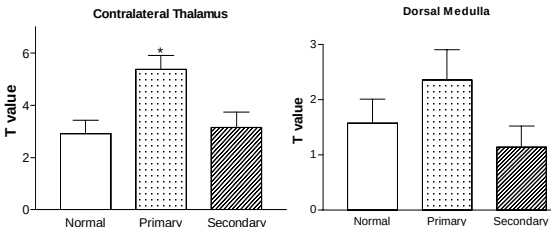

Fig. 4. Average maximal T value in the contralateral thalamus and dorsal medulla in 12 healthy male subjects during innocuous thermal stimulation to the right ophthalmic division of the trigeminal nerve on the normal and sensitized skin (*p<0.05 by Anova).

Conclusion

Primary heat allodynia is associated with increased activity in the second-order neurons in the ipsilateral spV, and in other brain structures known to be part of pain circuitries, including the thalamus. The perception of allodynic pain is correlated to the activity of the thalamus where the pain sensation starts to be conveyed to consciousness. The absence of significant differences in the second-order neurons between the secondary and the untreated area is consistent with previous behavioral data showing that capsaicin-induced heat allodynia is typically restricted to the primary area. The increased activity in the cingulate during thermal stimulation to the secondary area suggests an involvement of the emotional pain pathway. These data provide in vivo evidence of a role of second-order neurons in peripheral/central sensitization.

References

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Acknowledgments

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