Central Sensitization of Mechanical Allodynia in Trigeminal System: Evidence from Cardiac Gated FMRI

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Background

A number of pain-related diseases affect the trigeminal system including migraine. It has been reported that 79% of migraine patients present either localized or extended allodynia, which is a painful sensation induced by innocuous stimulation such as brush (Burstein et al. 2000). Allodynia is generally thought to be associated with peripheral and/or central sensitization. In this study we applied an experimental model of neuropathic pain to the first ophthalmic division (V1) of the trigeminal nerve of healthy volunteers to investigate, using cardiac gated fMRI, whether experimental mechanical allodynia is associated with increased signal changes in spinal trigeminal nucleus, and possibly, in supraspinal structures as well.

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. In both visits, innocuous brush stimuli were given to the right V1, either untreated or treated with heat/capsaicin (Petersen 1999). 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 (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 epochs of brush (~1 Hz) were administered and each last 30 seconds, separated by 30 second intervals of rest (light touch but no brushing). In the capsaicin session, brush was given to two different areas: primary area where the capsaicin was applied, and the area surrounding it (secondary area). Immediately following the brush scans, subjects rated their pain using a 0 (no pain) to 10 (highest pain imaginable) scale.

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 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 (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.

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. In six subjects activation was located in the ipsilateral dorsal pons, two of them in the contralateral side and one bilaterally. Three out of 12 activated the dorsal medulla, two in ipsilateral and one in contralateral. During innocuous brush to the primary area 7 out of 12 subjects (58.3%) showed activation in the dorsal medulla, in six of them it was ipsilateral and in one bilateral. For the secondary area eight subjects (66.7%) activated the dorsal medulla, six ipsilaterally and two contralaterally. Statistical comparison of activation maps during brush stimulation to the primary and secondary area vs. the untreated right V1 showed that primary allodynia was significantly associated with increased activation in the ipsilateral dorsal medulla, contralateral periaqueductal grey (PAG) matter in midbrain, and contralateral thalamus. Contrarily, decreased activation in contralateral PAG and increased activation in contralateral caudate were shown during secondary allodynia, compared with normal brush (fig. 1). Figure 2 showed the inter-subject averaged time courses in medulla during primary and secondary allodynia.

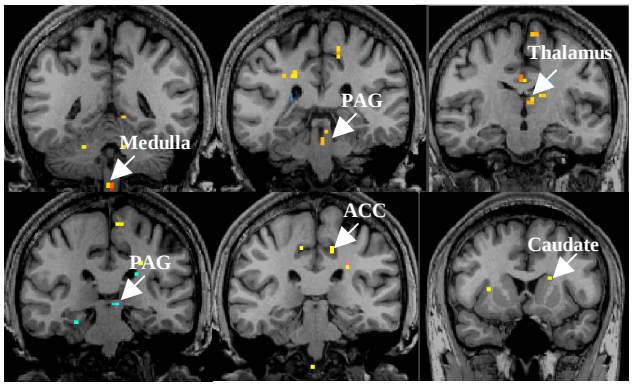

Fig.1. Statistical group maps (radiological convention) showing foci significantly activated during innocuous brush to the primary (upper row) and secondary (lower row) sensitized skin vs. the normal skin.

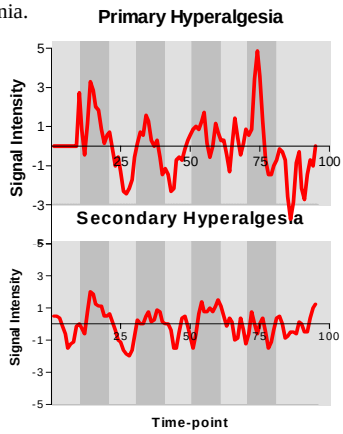

Fig. 2. Averaged time courses in dorsal medulla among all subjects who showed activation during primary and secondary allodynia.

Conclusion

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

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Acknowledgement

This work is supported by NIH P01NS35611.

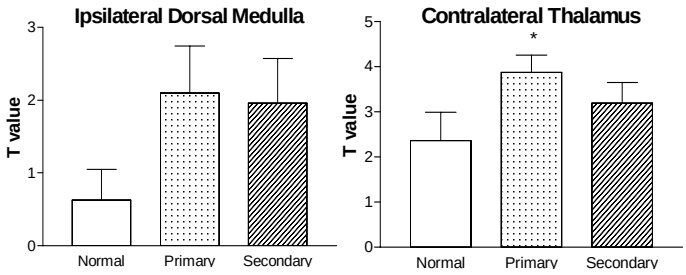

Fig. 3. Maximal *t*-values in twelve subjects under different conditions. * $p<0.05$.