Differentiating Pain-Intensity from Stimulus Encoding in Brain Activation in Neuropathic Pain

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Introduction: Chronic pain is a condition that affects millions of patients and costs billions of dollars a year. One of the difficulties in treating chronic pain is the lack of knowledge of the effects of the disease on the central nervous system. We studied neuropathic pain patients with pain to one side of the face. We sought to determine brain structures that encoded pain intensity regardless of stimulated side; brain substrates that encoded sensation regardless of the perception of the stimulus (painful or not); and brain structures whose activation significantly differed between the affected and unaffected side but that do not encode pain intensity. Thermal (heat and cold) and mechanical (brush) stimuli were used to evoke pain.

Methods: Patients (N=6) with facial allodynia to the maxillary area (V2) were recruited for this study. Subjects underwent 2 imaging sessions in which brush, cold and heat were applied to the maxillary and mandibular areas of the face on both the affected and unaffected side (4 areas total). Brush stimulation was applied with a soft velcro. Thermal stimuli were applied to a set temperature 1 °C beyond pain threshold in the affected area. A 3.0 T Siemens Trio scanner with a phase-array coil was used. Functional scans consisted of 128 volumes with each volume of 41 slices of isotropic resolution (3.5 mm) acquired with a GE EPI (TR/TE=2.5s/30ms) sequence. Data was analyzed using fsl (www.fmrib.oxford.ac.uk/fsl); briefly, data was motion-corrected, spatially smoothed (5mm) and high-pass filtered, a GLM approach was used for individual statistical analysis based on the temporal profile of the stimuli. Images from stimulating the unaffected side were flipped (left-right) to compare directly with the affected side. Group results were generated in 3 ways: (i) testing for stimuli producing same level of activation regardless of side of the face stimulated; (ii) using average individual pain intensity scores for affected and unaffected sides as covariates of interest; and (iii) comparing affected vs. unaffected and eliminating what encoded pain intensity. The analysis yielded 3 types of maps: stimulus encoding, intensity encoding, and non-intensity encoding.

Results: Brush Stimulation (Figure 1): Stimulus encoding areas (TOP) included superior/inf. Frontal gyrus (S/IFG), anterior cingulate gyrus (ACG), Caudate Nucleus (CN), Putamen (Pu), PAG. and others; minimal intensity encoding activation was found. Non-intensity encoding structures (BOTTOM) included ACG, Insula (Ins), S1, thalamus (Th), hippocampus (Hip). Cold Stimulation (Figure 2-TOP): Only intensity encoding areas were found and included MFG, ACG, S1, Th, Pons. Heat Stimulation (Figure 2-BOTTOM): Most of the activation was found in the intensity encoding analysis in the following structures: IFG, Orbital Gyrus (GOb), ACG, Ins, NC, ParaHip, PAG, Ventral Tegmentum (VT).

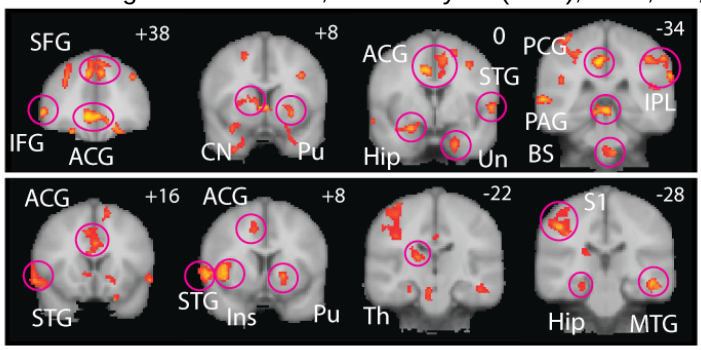

Figure 1: Brush Activation in response to stimulus (TOP) and non-intensity-encoding (BOTTOM)

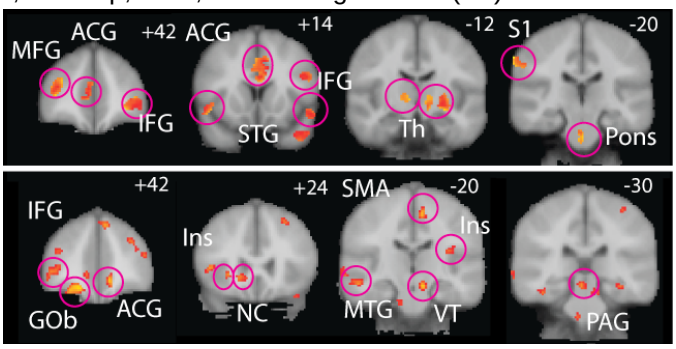

Figure 2 : Cold (TOP) and Heat (BOTTOM) intensity encoding activation

Discussion: Activation following thermal stimulation of affected and unaffected areas indicated that the brain responded according to the intensity perceived regardless of the side of the face stimulated. Mechanical stimulation, however, resulted in dissociation of pain intensities from brain activation; i.e., affected and unaffected brain responses did not correlate with pain intensity scores. Furthermore, mechanical stimulation also produced activation of the same level in the affected and unaffected side (stimulus encoding) that included structures processing pain suggesting that even the unaffected side did not have a normal (just sensory) response. These two observations might be a reflection of central processes taking place.

Conclusions: These results seem to indicate that mechanical allodynia is processed differently than thermal allodynia in chronic neuropathic pain patients. The data suggests that the thermal response is interpretable in terms of the correlation of pain intensity scores and brain activation. Mechanical stimulation seems to have a complex response in which the unaffected side activation appears to reflect processing of pain when an innocuous stimulus is applied and the affected side response is dissociated from the observed pain scores.

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