Distinct cerebral metabolic patterns related to trigeminal sensory profiles in migraine patients and healthy volunteers

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Objectives: Episodic migraine patients are thought to be overall hypersensitive to various stimuli between (Ambrosini 2006) and allodynic during (Burstein et al. 2000) attacks, while chronic migraine patients may be permanently allodynic (Bigal et al. 2008). However, there is great variability within patients groups in all studies. It seems thus of interest to identify subgroups of patients with different pain sensitivities and to investigate whether this reflects in distinct brain activity patterns. We decided to analyse thermal perception and pain thresholds in the 1st division of the trigeminal nerve in large cohorts of healthy volunteers (HV), episodic migraine patients between attacks (EM) and chronic migraine patients (CM), and to search for correlations with brain metabolism assessed with FDG-PET.

Methods: A total of 173 subjects (mean age: 35 ± 14 years) underwent quantitative sensory testing (QST): 54 HV (70% fem); 69 EM patients (83% fem), and 50 CM patients (86% fem). Sensory and pain thresholds to cold and warm stimuli were determined using a 1.5x1.5cm thermode (Advanced Thermal Stimulator-Medoc.) placed on the right forehead during three consecutive runs. Additionally, fifty-five subjects underwent an 18-FDG-PET scan (Philips Medical Systems): 20 HV, 21 EM without aura and 14 CM.

Results: QST (n = 173). No significant difference was found between subject groups for Cold Sensory Threshold (CST), Heat Sensory Threshold (HST), Cold Pain Threshold (CPT) or Heat Pain Threshold (HPT). A K-means cluster analysis however (Freeman et al. 2014), revealed the existence of 2 distinct sensory profiles within the global population (namely ‘hyper-’ and ‘hyposensitive’), which significantly differed in all QST variables (CST, p < 0.001; HST, p < 0.001; CPT, p < 0.001; HPT, p < 0.001, Fig. 1). Based on k-means cluster pain profiles, both heat and cold pain thresholds were significantly reduced in ‘hypersensitive’ CM compared with ‘hyposensitive’ HV (CPT: p = 0.05; HPT: p = 0.02), indicating that CM patients are hypersensitive to pain.

FDG-PET (n = 55). In EM, compared to HV, FDG uptake was reduced in left visual cortex, left medial frontal gyrus and bilaterally in the insular, somatosensory and motor cortices. CM had also a reduced metabolism in the orbitofrontal (OFC) and rostral anterior cingulate cortices (rACC). Cerebral metabolism differed between hyper- and hyposensitive individuals with a distinct pattern in each subgroup (Fig. 2). Compared to hyposensitive, hypersensitivity was associated with reduced metabolism in the brainstem in EM, the thalamus in CM and the somatosensory and anterior cingulate cortices in HV. In addition, SPM-ANOVA contrast modeling the potential gradual effect on brain activity of increasing differences in pain sensitivity between groups showed significant metabolic changes in bilateral thalamus.

Conclusion: Overall, we found no difference in trigeminal perception or pain thresholds for cold or warm stimuli between episodic or chronic migraine patients and healthy subjects. Collectively, cluster analysis of QST results disclosed ‘hypersensitive’ and ‘hyposensitive’ subgroups. When compared to their counterparts, ‘hypersensitive’ subjects had decreased metabolism in key pain processing regions of the CNS, but these regions differed between migraine patients (brainstem, thalamus) and healthy volunteers (somatosensory and cingulate cortices). This suggests that individual pain sensitivity is controlled by cortical pain matrix areas in healthy subjects, but that this control shifts to subcortical structures in episodic and chronic migraine patients. Acknowledgements: This work was supported by the EUROHEADPAIN project, FP7-602633