Altered functional connectivity in the pain modulatory system of migraineurs

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Introduction. Migraine is a neurological disorder that affects up to a fifth of the population. While it is usually accepted as a frequently disabling disease, the concept that it is also associated with progressive symptoms is becoming recognized. Recent studies, including our preliminary data, have shown persistent anatomical changes in the white and in the gray matter of migraineurs, located in regions involved in pain processing and modulation including the somatosensory cortex, thalamus, and periaqueductal gray matter (PAG) (1-3). Whether these anatomical changes are associated with functional changes is not known. We used functional connectivity during rest in migraineurs and healthy controls and compared the amount of connectivity in the pain modulatory system between the two groups.

Methods. Seven migraineurs (four with migraine without aura, and three with migraine with aura; mean±SD age: 34.7±7.8 years; mean±SD disease duration: 20.7±9.9 years) and seven age-matched controls underwent anatomical and functional scanning on a 3Tesla Tim Trio scanner (Siemens, Erlangen) with a 32-channel Siemens head-coil. Single-shot EPI images (47, 3×3×3mm³ slices, TR=300, TE=30ms, flip angle 90°, 160 volumes) were acquired for functional resting state analysis. Anatomical data consisted of a high-resolution structural 3D scan with a magnetization-prepared rapid acquisition with multiple gradient echoes (MEMPR) sequence resolution (0.9 x 0.9 x 0.9 mm, TI=1200 ms, TR=2530 ms, flip angle=7°, TE=1.7+n×1.88 ms where n=0, ..., 3, FoV=230 mm, bandwidth=651 Hz/px). Images were processed using FMRIB software library (FSL, www.fmrib.ox.ac.uk). Data were motion corrected and spatially smoothed with 6mm FWHM. Temporal filtering was applied with a high-pass filter cutoff 100.0s and a low-pass filter (sigma=2.8s.) to remove low and high frequency artifacts respectively. Independent Component Analysis (ICA) using MELODIC was run to remove structured noise from the data. Registration of functional and anatomical data was performed using FLIRT. Nonlinear registration using FNIRT was applied between the subject's structural and the standard space (the MNI_2mm brain). Seeds were manually selected based on the Harvard-Oxford cortical and subcortical structural atlases included with FSL. The PAG was selected as the region of interest. Time course was extracted from this seed, and used as a regressor using GLM. Group comparison of correlation effect size was performed using an unpaired t-test on seven controls and seven subjects.

Results. We found that migraineurs had stronger correlation between the PAG and other elements of the pain system, in particular with the somatosensory cortex, with a region of the medial anterior brainstem consistent with the location of the rostral ventromedial medulla (RVM), and with the prefrontal cortex (Fig. 1). Previous studies have demonstrated activation of the PAG during migraine attacks (4). In addition, anatomical changes consisting of iron deposition correlated with disease duration (1), and of fractional anisotropy (2) have been described in the PAG. Previous work has also reported changes of cortical thickness in the somatosensory cortex of migraineurs (3). Both the RVM and the prefrontal cortex have been involved in pain modulation (5,6).

Conclusion. While still preliminary, our results show that functional connectivity is stronger within the pain modulatory system of migraineurs compared with controls. It needs to be clarified whether these findings reflect a disease-specific process or are the consequence of repetitive episodes of pain and thus might be observed in other chronic pain conditions.

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References.