Altered structural & functional connectivity to the ventrolateral PAG in in chronic migraine related to migraine frequency

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Background:
The neurophysiological mechanisms underlying migraine are not yet well understood. Accumulating evidence supports that numerous factors are involved including changes in brain structure, function and the neuro-vasculature. Most of the migraine studies to date have focused on episodic migraine. Consequently, little is known about what drives chronic migraine, which is defined as more than 15 headache days/month and is linked to significantly increased disability compared to episodic migraineurs.

The periaqueductal gray (PAG) is a brainstem region that plays a key role in the perception of pain and its dysfunction is linked to different chronic pain states. For example, it is implicated in migraine pathophysiology, and resting state functional magnetic resonance imaging (fMRI) studies have shown migraine-related allodynia is associated altered functional connectivity between the PAG and both cortical and subcortical pain regions.

Aim:
The aim of this study was to investigate if changes in PAG physiology are related to features of chronic migraine. We assessed this using a multi-modal imaging approach that included: measuring PAG glutamate concentrations with magnetic resonance spectroscopy (MRS) and assessing PAG structural and functional connectivity with DTI and BOLD-resting state FMRI, respectively. For each imaging modality, we investigated group group differences (CM versus controls) as well as relationships with patient's migraine frequency (MF).

Method:

FMRI data was acquired interictally from 12 female chronic migraineurs and 12 female healthy controls using a 3T Siemens Verio and standard fMRI analysis methods. We investigated changes in PAG: i) resting excitability as measured by magnetic resonance spectroscopy (MRS); ii) white-matter tract integrity with DTI/TBSS; and iii) resting-state functional connectivity with the whole brain. For all imaging modalities both simple and multiple regression analyses was performed to investigate group differences and relationships with MF.

Results:
i) MRS: We found no group differences between patients and chronic migraineurs in combined Glutamate/Glutamine concentrations (Glx) in the PAG nor a significant correlation between Glx of the PAG and migraine frequency. Ii) DTI: We also did not find significant changes in white matter structure between CM patients and controls. We found a significant negative correlation between migraine frequency and fractional anisotropy, a measure of white matter integrity, in the right saggital stratum ($t=5.49$, $p=0.016$) and the left anterior corona radiate ($t=4.11$, $p=0.024$) These effects were driven by a decrease in radial diffusivity. We also found a positive correlation between the concentration of Glx in

the PAG and fractional anisotropy in the right anterior corona radiate (t=3.74, p=0.048). We also found a significant positive relationship between migraine frequency and functional connectivity between the ventrolateral PAG and bilateral frontal pole, superior and middle frontal gyri. Two clusters were identified (z=3.876, p<0.01) and (z=

Conclusion:
Our results demonstrate a relationship between migraine frequency and altered structural connectivity in chronic migraine, showing a decrease in white matter structure in frontal cortical regions. Conversely, we found an increased functional connectivity between the vlPAG and multiple frontal and prefrontal regions. These regions have been implicated in higher order affective and cognitive pain processing. These results support the notion that increasing migraine frequency is related to altered connectivity between cortical regions and the vlPAG.