

Developing a brain biomarker of pain in osteoarthritis using magnetic resonance spectroscopy

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Purpose: Osteoarthritis (OA) is the most prevalent arthritis worldwide. The chronic nature of OA often leads to long-term disability, with pain being a major symptom for which people seek care. During established OA disease, chronic pain due to cartilage, synovial and bone damage may be aggravated by the process of “central sensitisation”, whereby pain processing pathways in the central nervous system (CNS) become sensitised to peripheral nerve stimulation caused by degenerative and inflammatory disease processes. Our study aimed to establish if there are distinct brain regions activated during painful hand OA which could be used as a biomarker of OA pain.

Methods: We conducted a brain neuroimaging study using a Philips 3 Tesla (3T) magnetic resonance imaging (MRI) scanner. A total of 46 participants were enrolled into the study after obtaining full informed consent. We investigated whether biochemical changes in the brain detectable by 1H Magnetic Resonance Spectroscopy (MRS) are related to clinical measures of perceived pain and related symptoms. 1H MRS was performed in the anterior cingulate cortex and the insula cortex, which are brain regions involved in pain processing and implicated in central sensitisation identified from our previous work. LCModel™ was used to quantify metabolites and metabolite ratios were used to avoid the confound of variable CSF fraction in the voxel. Quantified metabolites included myo-Inositol (mI), an inflammatory biomarker and the neurotransmitters Glx (total of neurotransmitters glutamate and glutamine). Clinical scores were measured using the 100 mm visual analogue scale (VAS) for pain, the Australian and Canadian Hand Osteoarthritis Index (AUSCAN) and the Hospital Anxiety and Depression Scale (HADS).

Results: The age range of the recruited participants was 43 to 76 years, with all OA participants fulfilling ACR criteria for hand OA. Our study comprised n=32 participants with painful hand OA with a VAS scoring of at least 50 mm. Our control group (n=14) were age- and sex-matched participants with no history of hand OA or pain. Our MRS analysis demonstrated that there were no metabolite differences between controls and OA participants in the anterior cingulate gyrus, nor age related changes. In contrast, in the

insula cortex the myo-Inositol/glutamate/glutamine (ml/Glx) ratio correlated with age ($R^2 = 0.29$, $p = 0.0018$) and correlated with the VAS pain score ($R^2 = 0.52$, $p = 0.018$) after co-varying for age. In addition, principal component analysis (PCA) across all clinical scores relating to pain and depression indicated the VAS pain score and AUSCAN stiffness scores correlated to the ml/Glx ($p = 0.041$) with age as a covariate.

Conclusion: In conclusion, high ml/Glx in the insula cortex of hand OA participants is associated with high pain, and the age dependence of ml/Glx, suggests age dependent and/or duration dependent effects of OA on the brain. Our data show that distinct brain biomarkers are elevated specifically in the insula during chronic OA and could be useful in characterising OA pain.