Cerebral Blood Flow Changes Related to Pain Intensity in Chronic Knee Osteoarthritis

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Introduction

There is strong evidence for a common neural signature of experimentally induced pain[1,2]. Brain activation reflecting spontaneous pain in chronic pain patients (CPP) is less well understood. The lack of significant differences between activation likelihood estimates from experimental pain fMRI studies in CPP vs. HV highlights the limitation of experimental pain induction to study clinical pain[2]. Arterial spin labelling for CBF mapping is a promising new approach to study spontaneous pain as recently shown[3,4]. In this study we aimed to characterise the central processing of chronic knee osteoarthritis (OA) pain. To this end we investigated the interrelations between regional cerebral blood flow (CBF) and the level of experienced spontaneous OA pain severity in chronic knee OA pain patients

Methods

31 patients with Knee OA (M ± SD: 67.7yrs ± 7.6, 15 males, mean VAS 37.6 ± 21.8, average pain duration 9yrs) but no other co-morbidities and 21 healthy volunteers (60.2yrs ± 7.2, 8 males) were included in this study. All patients underwent questionnaire assessments looking at levels of pain and depression. Visual analogue scores (VAS) of pain (0 no pain and 100 being worst imaginable pain) were collected on the questionnaires and also shortly before each scanning session was carried out. All patients underwent multimodal MRI at 3T (Discovery MR750, GE Healthcare) including a 3D ASL[5] sequence (TE/TR=10.5/4632ms, slice thickness 4mm, voxel size 1.875x1.875mm, echo train length 1, field of view 240, number of excitations 3). Absolute CBF maps expressed in ml/100mg/min were generated using the proprietary software. For post processing, manual brain extraction was performed using NeuRoi and registration using FLIRT (FSL 5.0.4). Smoothing (8mm FWHM) and further analysis was performed within SPM8 as follows: Images were masked using a >20% grey matter probability mask and then a group comparison between OA and HC was performed followed by a within OA group correlation with VAS for those patients experiencing any pain (VAS 1 or higher, n=21) at the time of scanning controlling for age, sex and global mean CBF. In addition, regions of interest (ROI's) focusing on the known pain processing centres were defined *a priori* as implemented in a previous study[6] for small volume correction. Post hoc partial-correlation analyses were carried out in 2 ROI's (ACC and left posterior insula) previously implicated in the processing of pain intensity[7,8] using mean CBF values.

Results

Comparing patients and healthy controls revealed no significant differences in CBF at global or whole brain voxel-wise level. Within patient analysis however showed positive correlations between concurrent spontaneous pain severity (VAS scores) and local CBF within the anterior cingulate cortex, left hippocampus, left amygdala, left insula, left thalamus, left putamen, the subcallosal cortex and the brain stem (significant after small volume correction P<0.05)(figure 1). Partial-correlations of mean CBF in two *a priori* defined ROI's thought to be most consistently involved in nociceptive processing and VAS are shown in Fig.2 showing that 41% (insula, r=0.644, P=0.001) and 47% (anterior cingulate cortex (r=0.689, P=0.0004) of the regional CBF variance can be explained by the reported spontaneous pain.

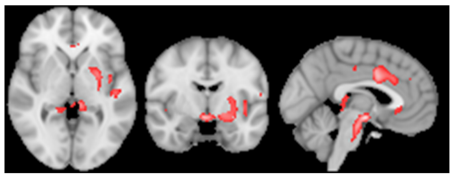

Figure 1. Whole-brain cerebral blood flow (CBF) maps correlated with VAS scores and controlled for age, sex and mean global CBF values. Results were thresholded at P<0.001 uncorrected.

Discussion

This study identified several brain regions where CBF as assessed with 3D ASL correlates with subjective pain measures in painful knee OA patients. Previous pain studies have reported these same areas as being involved in nociceptive processing[1,2,6].
A recent meta-analysis[9] presented a right hemisphere dominance in healthy subject pain processing which when compared to the left hemisphere dominant results within this study suggest that this may be a disease specific pattern of activity. Some areas reported within this analysis are also known to be involved in emotional processing (ACC, amygdala and putamen) which may suggest that chronic pain in OA could be modulated by emotional processes. This study however, is the first to look at between-subject variance during spontaneous pain. A separate study[4] performed a comparable ASL study in an OA cohort and also found significant correlations between subjective pain scores and CBF measures within the left amygdala and thalamus. Their subjects rated a similar level of pain during scanning but they measured session-wise variance in comparison to between-subject variance as we did. Focusing on the core nociceptive processing we found a substantial variance or regional CBF could be explained by reported pain intensity.

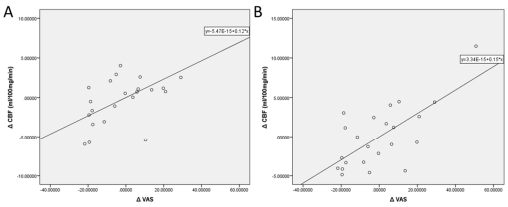

Figure 2. Partial-correlations of mean CBF values against VAS ratings (controlled for age sex and mean global CBF) in the left posterior insula (A) and the anterior cingulate cortex (B).

The limitations of this study include using a relatively small subjects sample and that the VAS score used as a covariate was taken shortly before the scan session for each participant rather than using ratings taken whilst in the scanner. Furthermore, the laterality of the osteoarthritic knee was not accounted for within the data analysis.

Conclusion

In conclusion, this study shows that ASL imaging allows us to map spontaneous OA pain involving known sensory and emotional pain processing areas.

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