INCREASED BRAIN ATROPHY IN CHRONIC BACK PAIN: PAIN HURTS THE BRAIN

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INTRODUCTION

• Ten percent of adults suffer from severe chronic pain. Back problems are the fifth most common reason for visits to the clinic; in 85% of such conditions no definitive diagnosis can be made. Although chronic pain greatly diminishes quality of life, and increases anxiety and depression, it is assumed that the cerebral cortex passively reflects spinal changes, and reverts to its normal state after cessation of chronic pain.

• Our studies show that chronic back pain (CBP, sustained for > 6 months after the healing process) is accompanied with abnormal brain chemistry, mainly a reduction in N-acetyl-aspartate/creatine ratio in the prefrontal cortex implying neuronal loss or dysfunction in this region, and reduced cognitive abilities on a task that implies abnormal prefrontal processing.

• Here we use automated whole-brain and regional morphometric analyses of structural MRI brain scan data to examine the association between CBP and brain atrophy.

METHODS

• We compared 26 CBP patients to 26 matched normal volunteers. Pairwise matching was done for gender, age (± 2 years, except in 2 subjects where match was within ± 5 years), and scan sequence. CBP patients were divided into neuropathic and non-neuropathic subtypes, based on symptoms of damage to the sciatic nerve, using standard criteria.

• We performed anatomic T1 weighted MRI brain scans using two slightly different 3D FLASH sequences, 'no-flow' and 'fast' paradigms, on a 1.5 T scanner. The 'fast' protocol uses interpolation in the slice direction, imaging parameters were TR = 15 ms, TE = 5.6 ms, flip angle = 20°, matrix 256 x 256 and a FOV of 240 mm, with 160 mm coverage in the slice direction. In 'no-flow' sequence slices are acquired at 1 mm slice thickness using a pre-saturation pulse to decrease ghosting artifacts in the temporal lobes, it has a TR = 22 ms.

• Total neocortical gray matter volumes were calculated after excluding the cerebellum, deep gray matter and brainstem. Normalized lateral ventricular volumes were also measured using a mask designed for this purpose. These measures were derived from SIENAX, which uses automated brain extraction and tissue segmentation software (www.fmrib.ox.ac.uk/fsl).

• Total gray matter volume was compared using a skull-based normalization (Sienax, FMRIB, Oxford, UK; Smith S. et al., 2002).

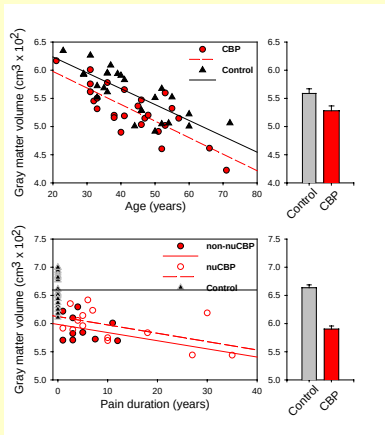
•Voxel-based morphometry (VBM) was performed with SPM99 in Matlab, using the optimized method of Good et al. (NeuroImage 2001), and a modified version of non-parametric testing SnPM.

RESULTS

1 Total brain gray matter volume is smaller in the chronic back pain patients & decreases by 1.3 cc/year of chronic pain

Neocortical gray matter volume was 528 ± 44 cm^3 (mean ± SD, n = 26) in the CBP brain and 559 ± 42 cm^3 (n = 26) in matched controls (top). The 30 cm^3 difference in gray matter volume, 5.4% decrease, was highly significant (paired *t*-test = 3.7, $P < 0.001$).

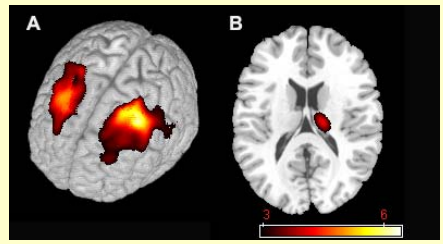
After correcting for age and gender confounds, pain duration had a beta = -0.33 ($P < 0.008$). This regression is significant in nuCBP with a slope of 1.3 cc/year of chronic pain (bottom).



Gray matter difference between CBP and controls increased to 11% after correcting for age and gender confounds (bottom right).

2 Decreased gray matter density is observed in bilateral DLPFC and right thalamus.

Non-parametric voxel-based morphometry: Dorsolateral prefrontal cortex (DLPFC), bilaterally, was the main region that showed decreased gray matter density in CBP (**A**). In the left the region contained two peaks [x, y, z coordinates (mm), -35, 4, 55; Pseudo-t_{max} = 6.38, P = 0.003, cluster size = 25.3 cm^3, P = 0.003; with a second peak at -24, 5, 59; Pseudo-t_{max} = 5.75, P = 0.006], and a single peak in the right [34, 18, 53; Pseudo-t_{max} = 5.1, P = 0.034, cluster size = 19.0 cm^3, P = 0.005].



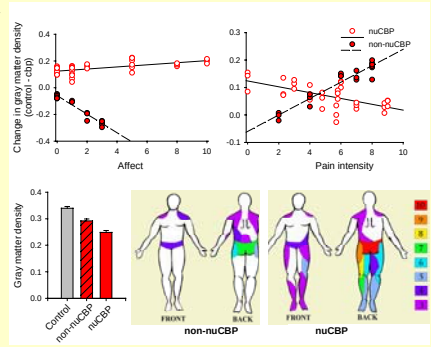
A separate non-parametric analysis was performed just for the thalami. Right anterior thalamus (**B**) showed a significant decrease in CBP [x, y, z, 14, -18, 16; Pseudo-t_{max} = 4.3, $P < 0.007$, cluster size = 2.3 cm^3, $P < 0.01$]

3 DLPFC gray matter density is related to CBP pain characteristics

Top: The change in gray matter density (control – CBP) in DLPFC depends on affective dimension of CBP and on pain intensity; neuropathic (nu) and non-neuropathic (non-nu) subtypes show opposite dependencies. Indicated r-values correspond to beta-s with $P < 0.001$.

Bottom: DLPFC gray matter density is highest in controls and lowest in neuropathic patients.

Somatotopy of pain is shown on the figurines on the right, for subtypes of CBP. Color-code is the number of subjects localizing pain to indicated body site.



RESULTS

• Total gray matter volume (fig 1 SIENAX results) and regional gray matter density (fig 2 VBM results) are reduced in chronic back pain patients, as compared to the matched controls.

• It seems that the presence of CLBP increases rate of atrophy due to normal ageing by about 50%.

CONCLUSIONS

• Using two independent morphometric approaches we observe significantly decreased global brain gray matter volume, and decreased regional brain matter density.

• Given that normal whole-brain gray matter atrophy is 0.5% per year of aging and atrophy due to CBP is 5-11%, the magnitude of brain gray matter atrophy due to CBP is equivalent to 10-20 years of aging.

• A large portion of the variance of atrophy in CBP cannot be accounted for by the measured pain characteristics, implying that there may be genetic and experiential predispositions contributing to the observed atrophy.

• These results suggest that the pattern of brain atrophy is directly related to the perceptual and behavioral properties of CBP, and it may explain the transition of acute to chronic pain by shifting brain activity related to pain affect away from anterior cingulate to orbitofrontal cortex.

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