Gray and white matter changes in patients with complex regional pain syndrome

A. V. APKARIAN[1], P. Y. GEHA[1], M. N. BALIKI[1], M. V. CENTENO[1], R. N. HARDEN[2], T. PARRISH[3], W. BAUER[4], D. R. CHIALVO[1]

1.Department of Physiology, Northwestern University 2. Physical Medicine & Rehabilitation, Rehabilitation Institute of Chicago, Chicago, IL

3.Department of Radiology, Northwestern University, Chicago, IL 60611 4. Neuroscience & Rehabilitation Medicine, Medical College Ohio, Toledo, OH

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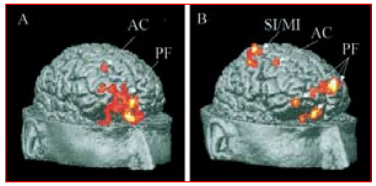
INTRODUCTION

Chronic pain is associated with cortical functional, neurochemical and morphological changes (Apkarian et al., 2001, Grachev et al., 2002, Apkarian et al., 2004). Furthermore, complex regional pain syndrome (CRPS) patients exhibit a specific deficit on an emotional decision making task, suggestive of damage to the medial prefrontal cortex (mPFC) (Apkarian et al., 2004). Here we hypothesize the occurrence of white and gray matter changes. Different measures of gray and white matter structure are compared between CRPS patients and matched healthy controls.

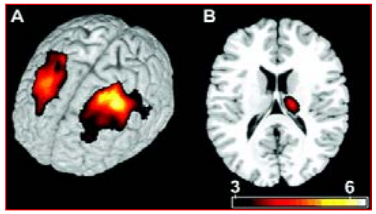
METHODS

- Twenty-three CRPS patients and 21 age and gender matched normal controls participated in this study.
- CRPS patients were diagnosed based on IASP criteria. Only patients who had a pain intensity of at least 3/10 on the VAS, and a history of at least 3 months of CRPS were recruited for this study.
- Subjects underwent whole brain diffusion tensor imaging (DTI) in a 3T magnet in two interleaved scans. Data was acquired with bvecs = 60 different directions, and vector strength of b = 1000 $s.mm^{-2}$, with a 1.7×1.7×2 voxel dimensions. T1 images were acquired using the MPRAGE protocol with 1 x 1 x 1 mm dimensions.
- Whole brain gray matter volume was determined using SIENAX from FSL toolbox (Smith et al., 2002)
- DTI was analyzed using the Diffusion Toolbox (FDT) of FSL (FMRIB, Oxford). (Behrens et al., 2003). Statistical analysis of FA maps was carried using TBSS) (Smith et al., 2006).
- VBM was done using SPM5

1 Chronic pain patients exhibit cortical reorganization

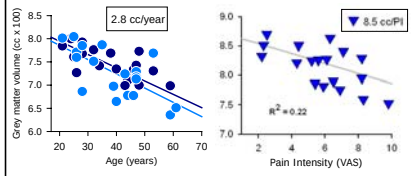


CRPS patients show cortical hyperactivity in the rostral prefrontal cortex (Apkarian et al., 2001).

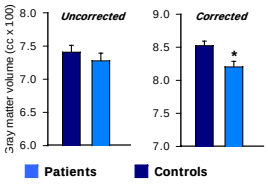


Chronic low-back pain patients have medial thalamic, as well as bilateral dorsal prefrontal gray matter atrophy (Apkarian et al., 2004b).

2 Whole brain gray matter volume

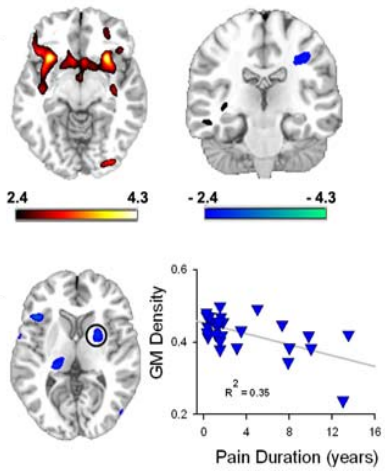


Regressing whole brain neocortical gray matter volume (WBCG) in patients against age, and against pain intensity (PI) after correcting for age. Pain intensity is a significant predictor of WBCG (P < 0.01)



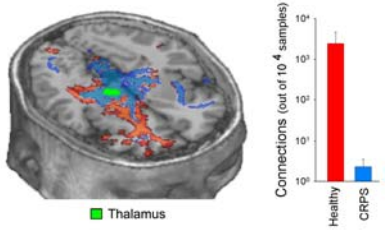
CRPS patients average WBCG is significantly decreased by ~ 6 % compared to normal controls after correcting for age.

3 Regional gray matter density



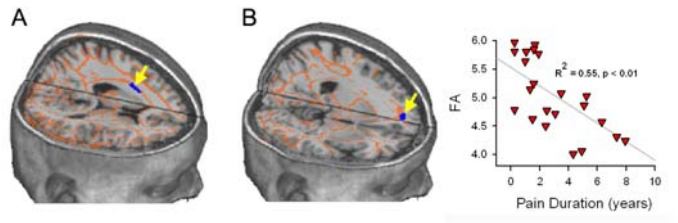
CRPS patients exhibit brain atrophy in bilateral ventral striatum, insula, inferior frontal gyrus, right ventrolateral – orbito-frontal cortex, right hippocampus, and right visual cortex. There is a significant increase in density in SI/MI. Pain duration has a negative effect on the left thalamus, right putamen, and left anterior insula (*VBM threshold p < 0.01, uncorrected, k> 500 voxels).*

4 Tractography



We have performed probabilistic diffusion tractography analysis on a subset of 3 patients and 3 matched healthy controls. We used two masks. The source mask shown in green lies in the left thalamus, defined by VBM result, an area exhibiting pain duration effect in panel 3. The target mask was the right prefrontal cortex. CRPS patients exhibit a prominent decrease in the probabilistic white matter connectivity between the posterior lateral thalamus and the prefrontal cortex;

5 Fractional anisotropy



Fractional anisotropy (FA), a measure of white matter integrity shows a significant decrease in CRPS patients compared to healthy matched controls in the white matter of the prefrontal cortex (**A**; n = 19 CRPS patients and 19 controls; p < 0.05 corrected for multiple comparisons). The effect of pain duration is seen on the same bundle of white matter only more rostral deep within the medial prefrontal cortex (mPFC) ; however the result did not reach significance after multiple comparisons (**B**; n =23 patients, P = 0.20). FA values were extracted from each subjects' voxels by projecting the area affected by duration shown in **B** back to the individual FA maps and then averaged. The scatter plot shows that pain duration has a significant negative effect on white matter integrity in the mPFC.

CONCLUSION

- Our results show that CRPS patients exhibit structural brain changes directly related to their number of years in pain.
- There are both whole brain effects on total cortical gray matter volume, and region specific decreases in gray matter density especially in areas involved in emotional and reward representation like the ventral striatum and mPFC.
- The changes observed in the white matter suggests that the atrophy may not be a reversible shrinkage in volume but rather a permanent loss of both gray and white matter.
- Those results confirm our previous findings in CBP patients and emphasize the importance of mapping both functional and structural changes in chronic pain since these can be used as markers of disease progression and treatment effect.
- Our result justify also the urgent need of early effective treatments of chronic pain in order to stop or reverse, at least in part, the extensive cortical changes and hence potentially avoid the cognitive deficits and co-morbidities observed in such patients.

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