



Fractional Anisotropy of White Matter Tract Contrasted between Complex Regional Pain Syndrome and Normal Controls

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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/orbito-frontal cortex (Apkarian et al., 2004). Here we hypothesize the occurrence of white matter changes, reflecting their cognitive deficits, and the gray matter atrophy seen in back pain patients. White matter fractional anisotropy is compared between patients and matched control subjects.

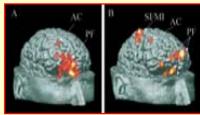
METHODS

11 CRPS patients and 10 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. The age of the participants ranged from 21 to 56 years. The patients' pain duration ranged from 6 months to 8 years. Subjects underwent whole brain diffusion tensor imaging (DTI) in a 3T magnet in two interleaved scans. Data was acquired with bvocs = 64 different directions, and vector strength of $b = 1000 \text{ s.mm}^{-2}$, with a $1.7 \times 1.7 \times 2$ voxel dimensions. DTI was analyzed using the Diffusion Toolbox (FDT) of FSL (FMRIB, Oxford). Data was eddy current corrected and then a diffusion tensor model was fit at each voxel (Behrens et al., 2003). Statistical analysis was carried using Tract Based Spatial Statistics (TBSS) (Smith et al., 2006).

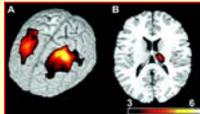
RESULTS

1 Chronic Pain Patients Exhibit Cortical Reorganization

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

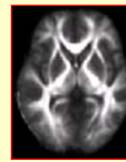


Chronic low-back pain patients have medial thalamic, as well as bilateral dorsal prefrontal gray matter atrophy (Apkarian et al., 2004).

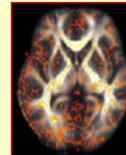


3 Group FA analysis

Axial section through the mean FA map derived from 10 patients and 10 control subjects. Brighter areas have higher FA values visualizing major white matter tracts such as the internal capsule.

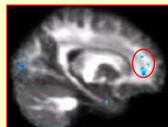
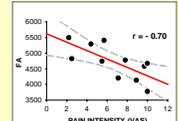


The mean FA skeleton for both groups is overlaid over the mean FA map (thresholded at $FA > 0.15$).

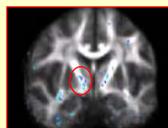
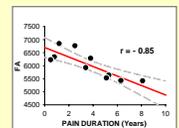


5 Impact of Chronic Pain on White Matter Volume

White matter volume as measured by FA is significantly smaller with higher pain intensities in the medial prefrontal tracts of patients with CRPS ($n = 11$).

The effect of pain duration is even stronger, but mostly in the internal capsule.

The DTI result overlaid on the mean FA map was corrected for age in both cases. A multiple regression analysis for both regions shows that age is not a significant confound.

2 Reconstruction of Diffusion Tensors

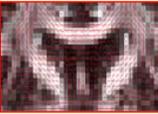
A diffusion tensor model, like the one shown on the right, is fit into the data at each voxel. Fractional anisotropy (FA) is then calculated.



Shown here is an example of an FA map from one subject.

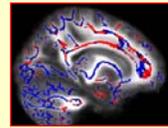


The principal diffusion direction is overlaid here on the FA map



4 Comparison between CRPS patients and normal controls

Areas in red show higher FA values in normal subjects compared to CRPS patients. Areas in blue show the opposite. (unthresholded map)



FA values are significantly ($t < -2.3$) decreased in CRPS patients in the medial prefrontal area, the dorso-lateral prefrontal cortex, and the corpus callosum.



A t-test was conducted comparing 10 CRPS patients to 10 normal age and sex matched controls using TBSS. A widespread white matter decrease is seen in CRPS patients compared to normal controls with significant clusters of decrease in the prefrontal areas and the corpus callosum. This result is consistent with the emotional decision making deficit exhibited by such patients.

CONCLUSION

- Our results show that CRPS patients exhibit a significant decrease in regional white matter volume compared to their age and sex matched normal controls, mainly in the prefrontal tracts and the corpus callosum.
- Pain intensity and pain duration are significant predictors of FA values:
- The higher the pain the smaller the FA value in the prefrontal tracts.
- The higher the pain duration the smaller the FA value in the internal capsule.
- These results are consistent with our earlier morphologic and functional studies showing reorganization in the brain of chronic pain patients.
- FA values reflect the state of integrity of white matter tracts. Therefore, reduced FA values indicate demyelination and, hence, neuronal loss. This leads to the conclusion that gray matter atrophy observed in earlier morphologic studies is most likely due to irreversible neuronal cell death rather than simple volume shrinkage.