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Lower white matter fiber cross section and global structural brain network reorganization in chronic low back pain disorder

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ABSTRACT

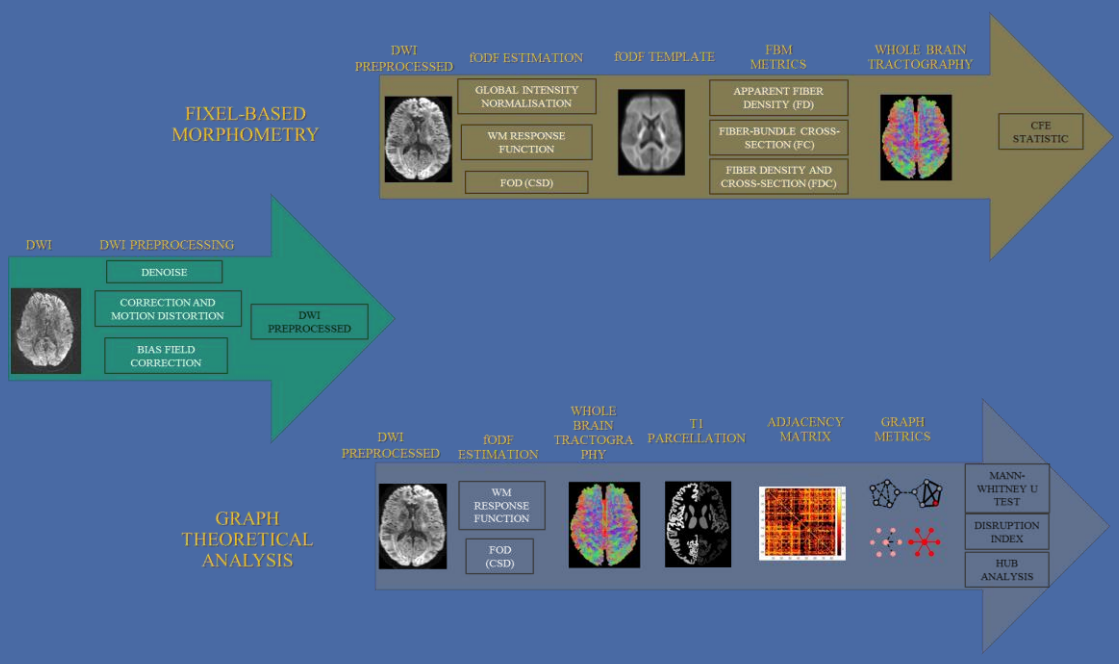
Chronic low back pain (CLBP) is a widespread public health issue, and its prevalence is enormous. Importantly, in most chronic pain conditions the correlation between pain and physical pathology at the site of referred pain (e.g., radiographs, physical examination, etc.) is typically weak. The decoupling between pain, disability levels and "peripheral" findings strongly suggests that alterations in the central nervous system may contribute to the establishment and/or maintenance of chronic pain. Using positron emission tomography (PET), we have previously shown that [11C]-PBR28 signal is elevated in the brain of CLBP patients. Because [11C]-PBR28 binds to the 18 kDa translocator protein (TSPO), a marker of glial activation, our results implicate neuroinflammation in the pathophysiology of CLBP patients. However, while PET imaging requires the injection of a radioactive ligand, the proximity of a cyclotron, diffusion weighted MRI (dMRI) can explore neuroinflammation-related microstructural alterations in a highly specific way. In this study, we employed constrained spherical deconvolution in high angular resolution DWI datasets to compare apparent fiber density (FD), fiber-bundle cross-section (FC) and fiber density and cross-section (FDC) as well as structural connectivity matrices and related graph-theoretic metrics in a population of 14 CLBP patients and 17 healthy controls. We found statistically significant group differences in FC in the right Anterior Thalamic Radiation (ATR) (p=0.04, effect size=0.941, HC>CLBP, Fig 1). Moreover, we found group-wise differences in global network disruption indices related to betweenness centrality (k=-0.187, p<0.001, Fig 1) and to local strength (k=0.183, p<0.001, Fig 1). Also, the right thalamus appeared to be network hub for HC (p=0.045) but not in the CLBP, while the right frontal pole (p=0.015) and the right caudal middle frontal gyrus (p=0.038) are hubs in CLBP but not in HC. Overall, our findings seem to imply a global, CLBP-related reorganization of the structural connectome, and specifically support a direct involvement of the thalamus in CLBP.

INTRODUCTION

Diffusion weighted image (DWI) it's a technique that employ the diffusive motion of water molecules to analyse white matter (WM) tissue micro-structure. Spherical deconvolution [1] is an advanced techniques that allows to estimate the distributions of fibers in each voxels. The recently proposed fixel-based morphometry (FBM) [2] allows to characterize changes in fiber pathways, also in fiber-crossing regions. This analysis is based on three measure: apparent fiber density (FD), fiber-bundle cross-section (FC) and the multiplication between the two aforementioned metrics (fiber density and cross-section, FDC) [2].
Structural connectivity DWI based enables to estimate indirectly the anatomical connection of WM pathway. It is based on tractography, a technique that allows to reconstruct the putative direction of axons based on the diffusive motion of water molecules. Probabilistic tractography in conjunction with CSD enable a more accurate reconstruction of the WM pathways [3] even in crossing-fiber regions. Graph theoretical analysis is a powerful test that enable to obtain information on the human brain networks. Several statistical analyses allow to infer possible modifications of the latter [4].
Chronical low back pain is one of the major cause of chronic pain disorder in the world. There is often a lack of peripheral cause in chronic pain and the central nervous system involvement is still not completely understood. In a recent research, PET imaging was used to highlight the possible role of [11C]-PBR28, radioligand that binds to the 18 kDa translocator protein (TSPO) [5], as a marker of glial activation, which is upregulated in neuroinflammatory responses, in CLBP patients [5], [6]. This finding suggests that neuroinflammation may play a role in the pathophysiology in human chronic pain.
The aim of our research is to study alterations in WM fiber pathways and in the structural connectome in CLBP subjects and to evaluate diffusion metrics for prediction of long-term pain and to study neuroinflammation in chronic pain.

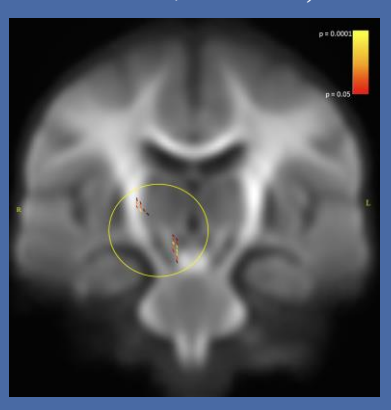
METHODS

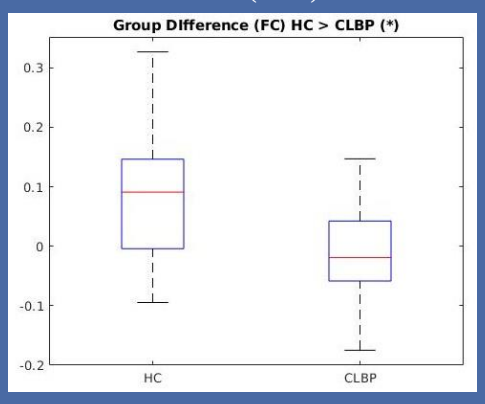
We recruited 14 chronical lower back pain (CLBP) patients and 17 healthy controls (HC). For each participants we acquired a multi-echo MPRAGE and a diffusion weighted image (SP-EPI single shot). We performed two set of analysis: FBM [2] and graph theoretical analysis.



RESULTS

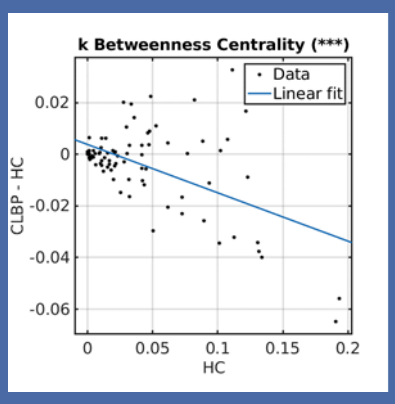
We fund statistically significant differences between CLBP patients and HC in FC (p=0.04, effect size=0.941, HC>CLBP) in the right anterior thalamus radiation (ATR).

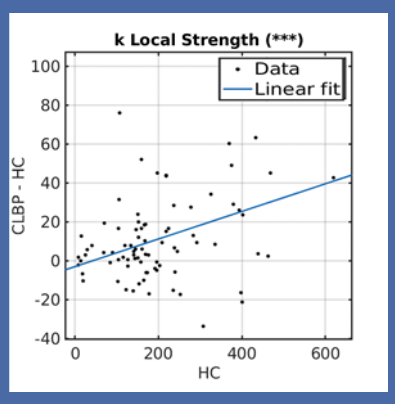




On the left fixels that show a statistically significant difference between HC and CLB (FDR <0.05) in the right ATR; On the right the effect size of the group difference between HC and CLBP. (*) p<0.05

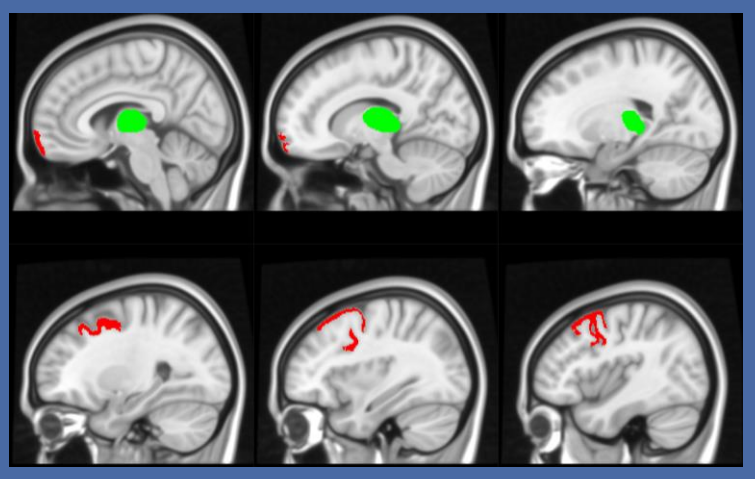
We also found a group-wise difference in betweenness centrality (k = -0.187, p<0.001) and local strength (k = 0.0673, p<0.001) in the disrupt index.





On the right alue<0.001the betweenness centrality group-wise disruption index; On the left the local group-wise disruption index. (***) p-value<0.001

Lastly, the hub analysis showed the presence of one hub in the HC and two hubs in the CLBP subjects. The right thalamus was a clustering coefficient hub for HC (p=0.045) but not in the CLBP, while the right frontal pole (p=0.015) and the right caudal middle frontal gyrus (p=0.038) are, respectively, local clustering coefficient and local efficiency hub in CLBP but not in HC.



Representation (in MNI space) of the brain regions that emerged as a hub healthy control but not in CLBP patients (in green) and in CLBP patients but not in health controls (in red).

CONCLUSION

The group-wise differences in the disruption index in conjunction with the appearance/disappearance of specific nodes as hub between the two groups seem to highlight a reorganization of the structural connectome. Moreover the statistically significant difference in FC between CLBP subjects and HC in the right ATR support the recent finding of involvement of the thalamus in the neuroinflammation in CLBP subjects [5], [6]

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