

Single-voxel ¹H-MRS Study of the impact of Peripheral inflammation on Brain Metabolism and Mood

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Lay Summary

Tumor necrosis factor- α (TNF) is a protein involved in the regulation of inflammation and immunity. TNF is thought to play an important role in the development of psoriatic arthritis (PsA). PsA is associated with greater rates of major depression (MDD). MDD has been associated with abnormalities in the frontal and subcortical regions of the brain. Proton magnetic resonance spectroscopy (¹H-MRS) is a technique capable of non-invasively recording biochemical changes in the above regions. In this study, we used MRS to assess biochemical differences between healthy subjects and PsA patients in the frontal and subcortical regions of their brains. We also assessed the effect (on brain biochemistry) of administering TNF blockade agents (used in treating PsA). We estimated concentrations of the chemicals as ratios to creatine (Cr) which was assumed not to be affected by the disease. A reduction in frontal brain Choline/Cr ratio with TNF blockade was associated with an improvement in mood. Choline (Cho) is a marker of cell membrane breakdown and thus our data suggests that inflammation may play a role in cell membrane breakdown in the frontal brain of psoriasis patients.

Introduction

PsA is a chronic inflammatory condition that affects the skin and joints.^[1] Studies of animal models of chronic inflammation have reported that peripheral and cerebral immune systems communicate. Involvement of TNF in this interaction results in central neural changes and associated behavioural changes.^[2, 3] The condition usually develops between the ages of 30-50 years.

¹H-MRS is a sensitive MRI technique that records biochemical profiles (displayed as a spectrum of the metabolites; Figure 2) of a region of interest *non-invasively* and *in vivo*.^[4] ¹H-MRS has been previously used to explore the pathophysiology of MDD. Most studies have shown mixed patterns of biochemical changes in the frontal (e.g. anterior cingulate cortex, ACC) and subcortical (e.g. hippocampus) structures.

Very few ¹H-MRS studies have investigated the association between peripheral inflammation and depression in the hippocampal and ACC regions. One previous study in patients with rheumatoid arthritis^[2] showed an association between peripheral inflammation and Choline (Cho) – a marker of neuronal cell membrane breakdown – in the centrum semiovale. However, the study did not examine the relationship between the ¹H-MRS measures and mood. No previous studies have looked at this association in patients with PsA.

Aims of the Study

1. To compare baseline brain biochemistry of psoriasis patients with healthy subjects by single-voxel ¹H-MRS focusing on the ACC and left and right hippocampi.
2. To assess the treatment effect of TNF blockade on brain metabolism and its associated effect on mood

Methods

Participants

PsA patients and healthy controls (mean age \pm SD = 43.8 \pm 10.1 vs. 36.5 \pm 11.8 years; M/F = 9/7 in each group) underwent MRS examination. Patients underwent ¹H-MRS examination before and after 6-8 weeks of TNF blockade medication (Etanercept). Mood was assessed at baseline and follow up using the Beck Depression Inventory (BDI). Psychiatric symptoms were ruled out in controls using the 12-item General Health Questionnaire.

Data Acquisition

128 averages of CHES water-suppressed spectra were acquired from the ACC ($TE/TR = 35/2000$ ms; Figures 1a-b) and right and left hippocampi ($TE/TR = 144/2000$ ms; Figures 1c-d) of both patients and controls on a 3T GE scanner equipped with an 8-channel head coil.

Analysis

¹H-MRS data were post-processed and analysed with the **LCModel** software.

Statistical analyses were performed using **SPSS** version 18. Group difference in ¹H-MRS results between PsA (baseline) and controls was compared using *unpaired t-test*. Pre and post medication ¹H-MRS results and BDI scores in the PsA patients were compared using *paired t-test*. Correlations were explored by *Pearson's correlation*.

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No conflicts of interest to declare

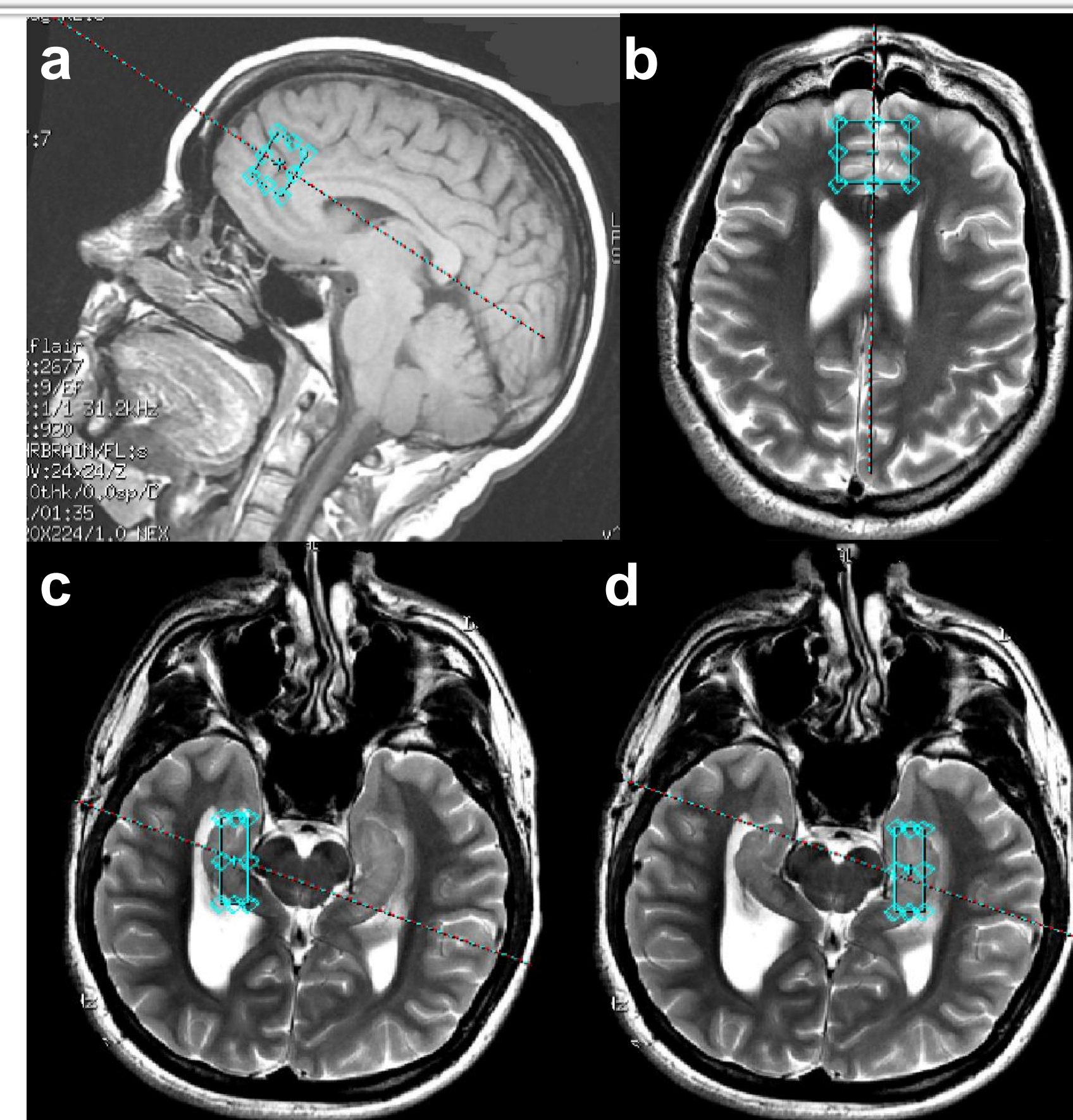


Figure 1: ¹H-MRS voxel placement in participants: ACC (a-b) and right (c) & left (d) hippocampi (VOI sizes: 7.1-11.5 mL)

Results & Discussion

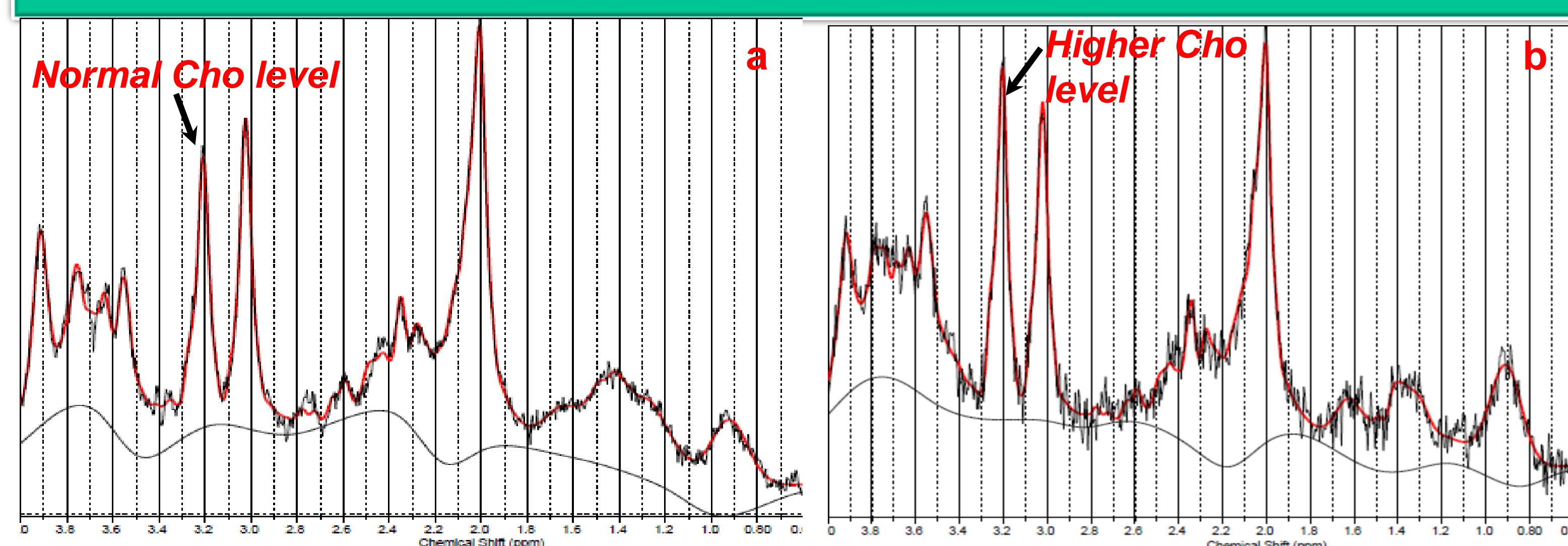


Figure 2: Representative spectra from the ACC of a healthy subject (a) & psoriasis patient (b)

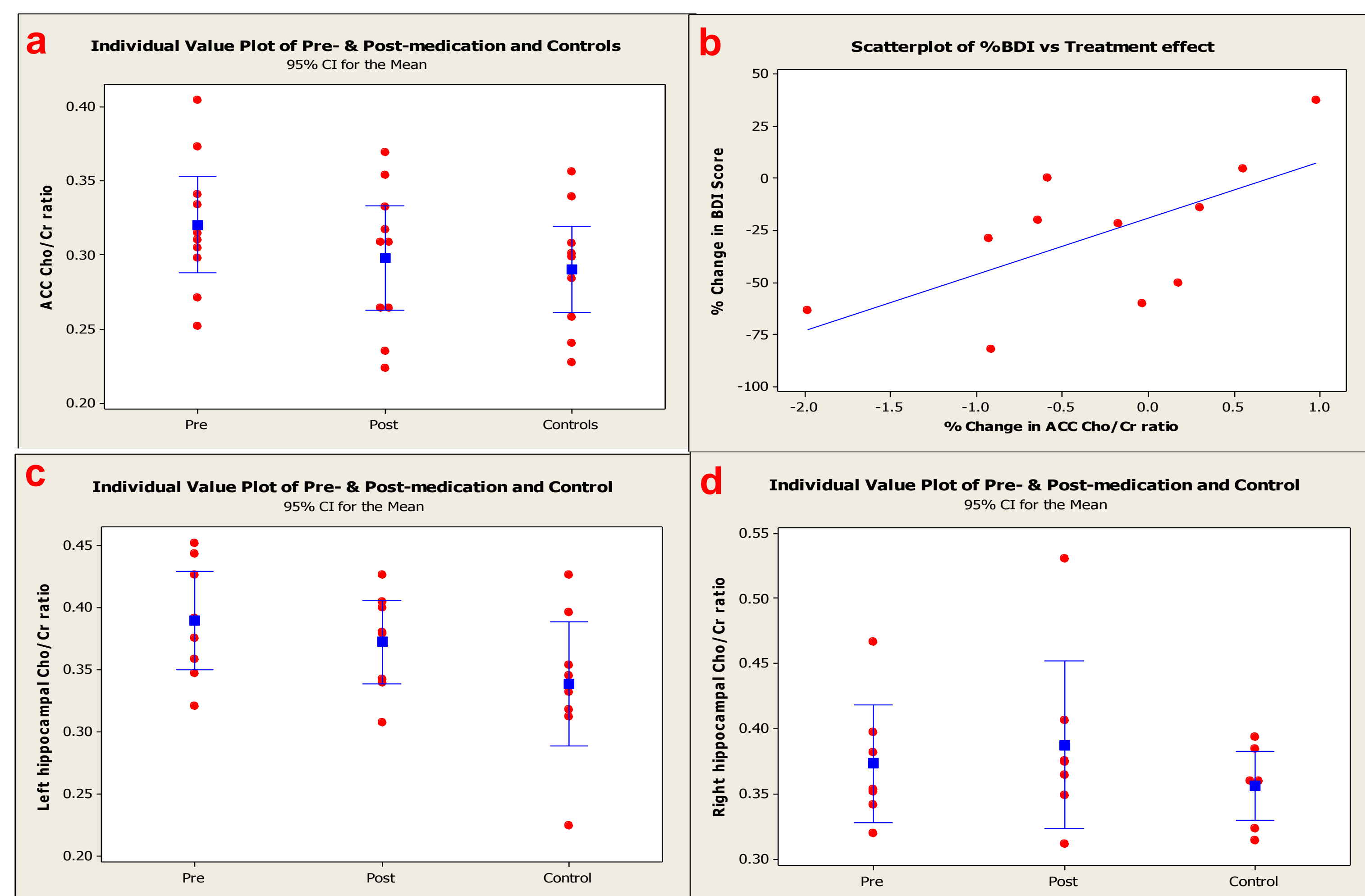


Figure 3: Effect of TNF blockade on Cho/Cr ratios in the ACC (a-b) and left (c) & right (d) hippocampi

- PsA patients had higher left hippocampal baseline Cho/Cr ratio than controls ($p = 0.114$)
- No significant difference in baseline Cho/Cr ratio in the ACC ($p = 0.853$) or right hippocampus ($p = 0.836$) between patients and controls
- Cho/Cr ratio did not change significantly in the ACC ($p = 0.148$) and right ($p = 0.357$) & left ($p = 0.334$) hippocampi of the PsA patients with the TNF blockade medication but...
- Percentage change in ACC Cho/Cr ratio was associated with percentage change in BDI scores ($r = 0.673$; $p = 0.023$)

Conclusions & Further Work

- ✓ This is the first ¹H-MRS study of the ACC & hippocampi implicating Cho/Cr ratio in PsA, similar to a previously reported higher Cho/Cr ratio in the centrum semiovale in rheumatoid arthritis^[2]
- ✓ The results of this study show that inflammation may be associated with a higher brain Cho/Cr ratio and low mood
- ✓ Future work will explore associations between ¹H-MRS results (ratios & absolute), mood and blood cytokine levels in PsA patients

References

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