

Summary

In this work, *Spectroscopy* has been used to measure changes in the chemical content of the human brain in depression. Inflammation is believed to cause a depressive mood and so the *Spectroscopy* results of a volunteer with psoriatic arthritis (a chronic skin disease causing joint inflammation) have been compared to that of a healthy volunteer. This comparison showed that inflammation does not only lead to depression but also increases the overall brain chemistry and water content.

Introduction

- *Proton-Magnetic Resonance Spectroscopy (¹H-MRS)*: a Nuclear Magnetic Resonance technique that measures body metabolites non-invasively and *in vivo*¹
- *Depression*: associated with under-activation of the forebrain structures (e.g. the anterior cingulate cortex, ACC) + over-activation of the limbic structures (e.g. the hippocampus) in brain imaging^{2, 3, 4}
- *Explanation*: depression is triggered by the action of pro-inflammatory cytokines that play a central role in the pathogenesis of inflammatory diseases.⁵

Study Aims:

- To evaluate relative and absolute metabolite and water concentration differences in the ACC and hippocampus between a normal subject and one patient diagnosed with (*but not yet treated for*) an inflammatory disease (*psoriatic arthritis, PsA*)
- To estimate the degree of change in the amounts of cerebral water and metabolites due to inflammation leading to depression.

Methods

Study Subjects

- 1 mild PsA male patient (38 years old) and 1 healthy male subject (37 years old) prospectively recruited after ethics approval and consent
- Both had no history of antidepressant intake in the previous 3 months, neurological disorders and DSM Axis I psychiatric disorder
- PsA patient scored for depression on the *Beck Depression Inventory (BDI)* scale by a trained psychiatrist

MRI/¹H-MRS Protocol

- Experiments on a GE Signa Excite 3.0 T MR scanner + 8 channel T/R head coil
- *MRI Acquisitions*: 3 plane localiser whole brain image, *T₁* FLAIR sagittal image (*TE/TR/TI* = 9/2686/920 ms), *T₂* FLAIR coronal image (*TR/TE/TI* = 9002/158/2250 ms) and *T₂* FSE/propeller axial image (*TR/TE* = 5000/110 ms); 240 x 240 mm² field-of-view with tilted slices along the hippocampal axis
- *Single voxel ¹H-MRS acquisition*: voxel sizes of 12 *SI* x 15 *LR* x 25 *AP* (= 4.5 mm³) and 25 *SI* x 20 *LR* x 10 *AP* (= 5.0 mm³) image-guided in a 3-plane view onto the left hippocampus (fig. 1) and ACC (fig. 2); *PRESS* sequence with (*TE/TR* = 144/1500 ms; 128 averages) and without (*TE/TR* = 23/15000 ms; 1 average) *CHESSE* water suppression and automatic shimming.
- *Total experimental time per subject*: ~15 minutes + blinding to patient's depression score

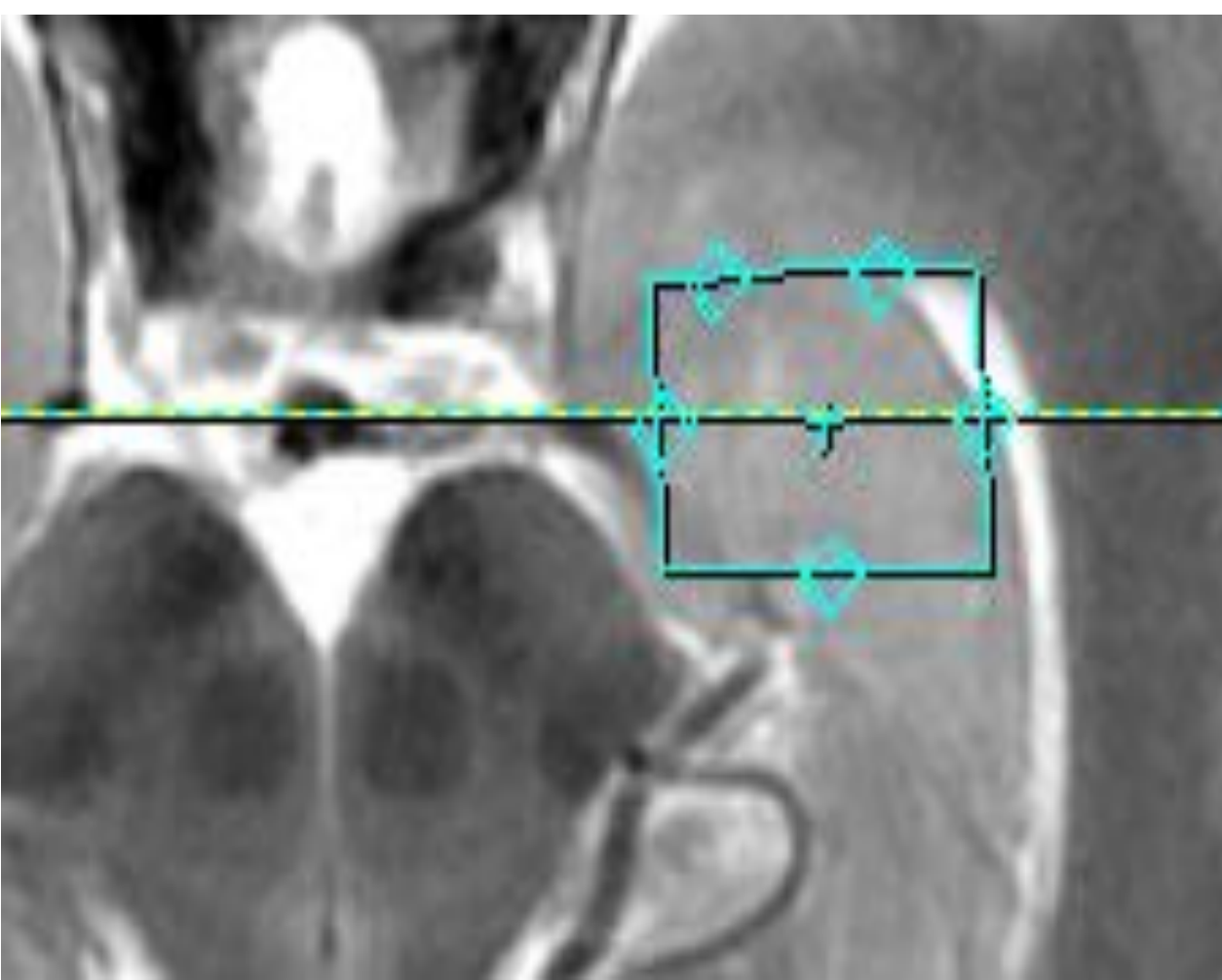


Fig. 1: VOI on the left hippocampus of the patient – axial view

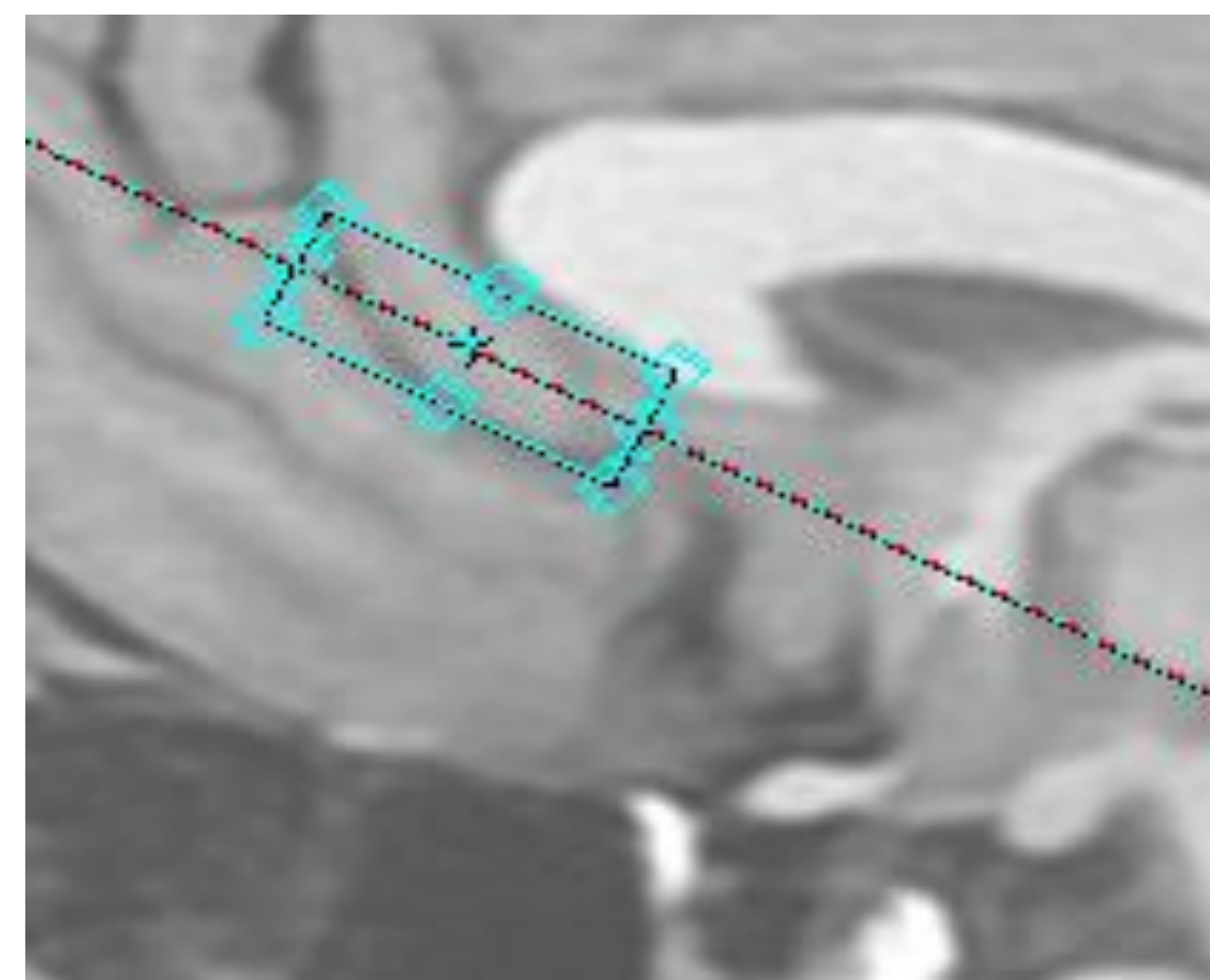


Fig. 2: VOI on the ACC of the patient – sagittal view



Fig 3: Metabolite peaks from the left hippocampus of the PsA patient (a) and healthy control subject (b)

Spectral Quantitation/Analysis

- *Relative concentrations*: *LC Model* curve-fitting algorithm used to normalise all concentrations to *tCr* in the suppressed water spectra
- *Water peaks*: *LC Model* basis set unable to read *unsuppressed water* files. So need for conversion to text files by in-house *C* program⁶ and the peak quantitated by *HLSVD* algorithm in *jMRUI*⁷ where the area under the water peak (or the initial amplitude of the water signal in the time domain) is proportional to the water content¹
- *Absolute concentrations*: product of the relative concentrations and the *LC Model* estimated *tCr* concentration *in vivo*.

Preliminary Results and Discussion

- *Table 1*: ¹H-MRS measures on the 2 subjects compared to previous absolute and relative measures with *STEAM*⁸ and *PRESS*⁹ pulse sequences respectively
- At the echo time (*TE*) of the measurements, only 3 metabolites with long *T₂* relaxation times could reliably be quantified (with standard deviations < 20%)
- *Table 2*: comparison of the absolute metabolite concentrations and water volumes in the two subjects.

Table 1: Absolute and Relative Cerebral Metabolite and Water Measures

Subject	Absolute measures (mM/kg)					Relative measures				
	Patient		Control		Literature ⁸	Patient		Control		Literature ⁹
TE (ms)	144		144		20	144		144		30
BR:VOI (mm ³)	ACC: 5.0	LH:4.5	ACC:5.0	LH:4.5	LFL: 8	ACC:5.0	LH:4.5	ACC:5.0	LH:4.5	ACC: 8
Metabolites:	Concentration ± Std deviation					Concentration ± Std deviation				
<i>t</i> NAA	37.40 ± 0.08	21.24 ± 0.13	8.54 ± 0.03	8.48 ± 0.07	7.68 ± 0.80	2.74 ± 0.42	1.12 ± 0.10	1.43 ± 0.01	1.56 ± 0.08	1.3 ± 0.11
<i>t</i> Cr	13.63 ± 0.19	19.04 ± 0.13	5.98 ± 0.03	5.44 ± 0.09	5.04 ± 0.65	1	1	1	1	1
<i>t</i> Cho	4.79 ± 0.19	6.35 ± 0.14	1.52 ± 0.04	1.21 ± 0.13	1.60 ± 0.32	0.35 ± 0.10	0.33 ± 0.11	0.25 ± 0.13	0.22 ± 0.14	0.21 ± 0.02
Water (A.U.)	232.77 ± 0.03	282.80 ± 0.004	210.8 ± 0.0001	272.36 ± 0.0004	-	-	-	-	-	-

BR = brain region; VOI = volume of interest; TE = echo time; ACC = anterior cingulate cortex; LH = left hippocampus; LFL = left frontal lobe;

*t*NAA = total N-acetyl aspartate; *t*Cr = total creatine; *t*Cho = total choline; A.U. = arbitrary units

Table 2: Metabolite ratios between the 2 subjects and percentage increase in water volume in the patient

Subject	PsA Patient : Healthy Control	
Brain region	ACC	LH
<i>t</i> NAA	4 : 1	3 : 1
<i>t</i> Cr	2 : 1	4 : 1
<i>t</i> Cho	3 : 1	5 : 1
Water (in patient)	+ 10%	+ 4%

- BDI score indicated a non-depressed mood
- ¹H-MRS results showed inflammation possibility: confirmed by 12% increase in cerebral water volume in MS¹⁰ + 3-fold increase in *Cr/Gly* ratio in psoriatic plaque extracts¹¹
- PsA is a non-CNS illness; so effects may remain at periphery and depression setting in by cytokine infiltration into brain depending on severity and duration
- Study power too low for a conclusion on findings

Conclusion and Future Directions

- Data uncorrected for PVEs in small VOIs but comparable to previous results
- Cerebral water fairly stable for internal referencing compared to *Cr*
- Protocol under test for optimisation and further measures on larger sample size
- Range of VOIs to fit brain sizes, with possibility of segmentation for PV correction before absolute quantitation

References

- [1] Jansen, J. F. et al (2006) *Radiol* 240(2): 318 – 332
- [2] Siegle, G. J. et al (2006) *Am J Psych* 163(4): 735 – U731
- [3] Ito, H. et al (1996) *J Nucl Med* 37(3): 410 – 414
- [4] Videbech, P. et al (2001) *Psychol Med* 31(7): 1147 – 1158
- [5] Raison, C. L. et al (2006) *Trends in Immun* 27(1): 24 – 31
- [6] Marshall, I. (2010) *Personal Communication*
- [7] Stefan, D. et al (2009) *Meas. Sci. Technol.* 20:9
- [8] Gruber, S. et al (2003) *Inv Radiol* 38(7): 403 – 408
- [9] Davanzo, P. A. et al (2001) *Proc. Intl Soc MRM* 1356
- [10] Helms, G. (2001) *Magn Reson Med* 46(2): 256 – 263
- [11] Kim, Y. H. Et al (1989) *J Inves Dermatol* 92: 210 – 216