ABSOLUTE QUANTITATIVE ^{1}H-MRS IN DEPRESSION

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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 (^{1}H-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) and1 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/^{1}H-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, T_1 FLAIR sagittal image (*TE/TR/TI* = 9/2686/920 ms), T_2 FLAIR coronal image (*TR/TE/TI* = 9002/158/2250 ms) and T_2 FSE/propeller axial image (*TR/TE* = 5000/110 ms); 240 x 240 mm^2 field-of-view with tilted slices along the hippocampal axis

- *Single voxel ^{1}H-MRS acquisition:* voxel sizes of 12 *SI* x 15 *LR* x 25 *AP* (= 4.5 mm^3) and 25 *SI* x 20 *LR* x 10 *AP* (= 5.0 mm^3) 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) *CHESS* water suppression and automatic shimming.

- *Total experimental time per subject:* ~15 minutes + blinding to patient's depression score

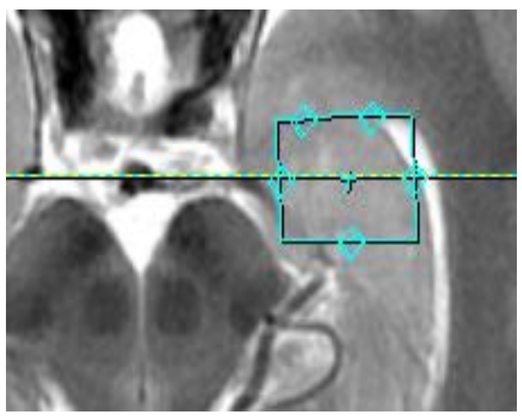

Fig. 1: VOI on the left hippocampus of the patient – axial view

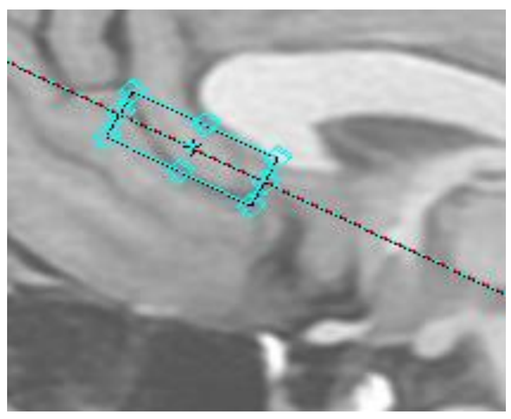

Fig. 2: VOI on the ACC of the patient – sagittal view

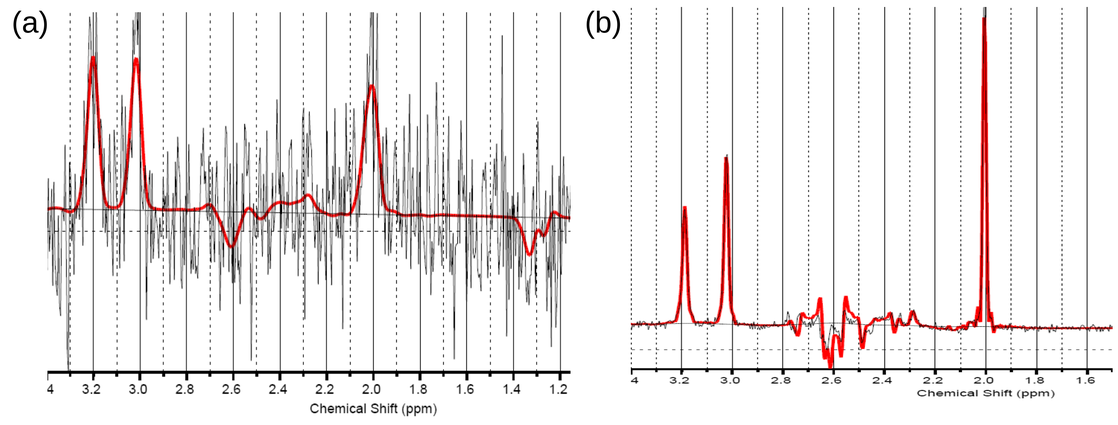

Fig 3: Metabolite peaks from the left hippocampus of the PsA patient (a) and healthy control subject (b)

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* program[6] 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 content[1]

- *Absolute concentrations:* product of the relative concentrations and the *LC Model* estimated *tCr* concentration *in vivo*.

Preliminary Results and Discussion

-*Table 1:* ^{1}H-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 T_2 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

	Absolute measures (mM/kg)					Relative measures				
Subject	***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*				
tNAA	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
tCr	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
tCho	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;

tNAA = total N-acetyl aspartate; tCr = total creatine; tCho = 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
tNAA	4 : 1	3 : 1
tCr	2 : 1	4 : 1
tCho	3 : 1	5 : 1
Water (in patient)	+ 10%	+ 4%

- BDI score indicated a non-depressed mood
- ^{1}H-MRS results showed inflammation possibility: confirmed by 12% increase in cerebral water volume in MS[10] + 3-fold increase in *Cr/Gly* ratio in psoriatic plaque extracts[11]
- 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

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