Elevated lactate levels and impaired neural circuit in manic bipolar disorder I

W-J. Chu[1], M. M. Norris[2], J-H. Lee[1,2], K. B. Jarvis[1], X. Wang[2], M-J. Kim[1], M. P. DelBello[1], S. M. Strakowski[1,2], and C. Adler[1]

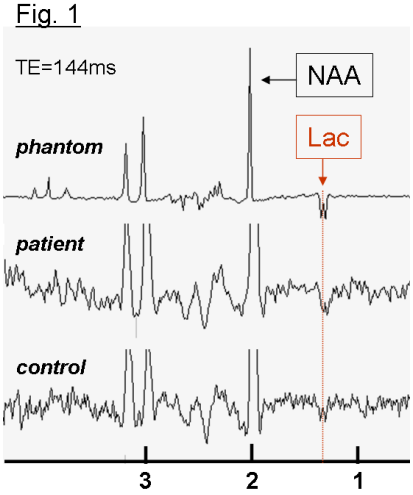
[1]Psychiatry, University of Cincinnati, Cincinnati, Ohio, United States, [2]Biomedical Engineering, University of Cincinnati, Cincinnati, Ohio, United States

INTRODUCTION: Recent studies have suggested that bipolar disorder (BD) is associated with mitochondria dysfunction, characterized by the presence of neuronal lactate (Lac).[1] Unlike studies of ischemic tissue such as stroke, Lac signals in BD were reported to be weak and difficult to identify. The goals of our present work were to investigate the abnormalities of Lac and the regions in which Lac signals were most commonly exhibited in bipolar brains using the 2-D ^{1}H MRSI on a 4T MR system.

METHODS: Twelve manic, BD I patients (M3/F9; age: 25.1±6.3 years) and 7 healthy volunteers (M4/F3; age: 21.7±2.3 years) were studied. All MRSI and MR scout images were acquired with a 4T Varian INOVA system using a TEM volume head coil. Spectra were localized to a 10x80x100 mm^3 voxel angulated along the anterior, posterior commissure line using a 3D localized adiabatic LASER sequence with 2D phase encoding. Shimming was optimized by automatic B_0 mapping.[2] Water suppression was performed with an initial broad-band semi-selective excitation pulse and a frequency selective DANTE pulse applied to the water resonance. To detect Lac signals, data were acquired using TR 2000ms, TE 144 ms (TE_1/TE_2/TE_3/TE_4=36/28/38/42 ms), FOV 192x192mm^2 with 24x24 encodes. The spectroscopic imaging data were processed with a Gaussian filter of 2 Hz line broadening, co-registered with scout image, and displayed using the house-written software in MATLAB. Typical spectra showing Lac signals with inverted doublet methyl protons resonance at 1.33 ppm and the J-coupling constant (7.36 Hz) in patient, and control groups were selected (Fig. 1) for further analysis using LCModel. Metabolite data are presented in terms of lactate/N-acetyl aspartate ratio (Lac/NAA).

RESULTS: Figure 1 displays the localized spectra of Lac from phantom solution, patient, and healthy control subjects. Both *in vivo* spectra were selected from voxels in the caudate region. Twenty spectra exhibiting Lac signal were identified in 9 patients and 6 Lac spectra were found in 3 healthy control subjects. Regions exhibiting Lac signals within the brain, and the averaged Lac/NAA ratio are summarized in Table 1 and Fig. 2. Lactate signals were most common in the anterior cingulate cortex (ACC) and caudate of bipolar patients. The highest Lac/NAA ratio, 0.26, was found in the caudate region of bipolar patients. The highest Lac/NAA ratio in the corresponding region of healthy controls was 0.08. In the ACC, the highest bipolar Lac/NAA ratio is 0.11. No Lac was found in the ACC of healthy control subjects. The overall Lac/NAA average across voxels in bipolar patients is 0.18±0.14; significantly higher than the average Lac/NAA ratio of 0.07±0.08 in healthy controls (Table 1).

Fig. 1



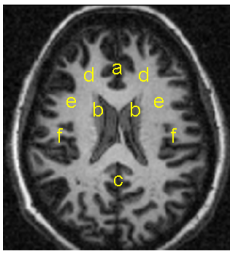
DISCUSSION AND CONCLUSION: 1) The frontal-subcortical network has been implicated in modulating affective symptomatology in BD.[3] The dysfunction of critical subcortical structures (e.g. amygdala and caudate) that constitute this frontal-subcortical brain network may lead to a loss of modulatory input into the prefrontal cortex. The elevated Lac/NAA ratio in patients' ACC and caudate, components of the frontal-subcortical network, suggests that affective dysregulation may be related to metabolic abnormalities in these regions. 2) Only 75% of bipolar patients in this study exhibit Lac signals, which may be related to patients' illness and treatment history. 3) The finding of Lac/NAA in the healthy control group is consistent with previously published data from a 1.5T study,[1] 4) Lac signals detected in healthy control subjects of this work are somewhat more prominent may be due to the higher signal-to-noise ratio provided by the higher field, 4T MR system.

Table 1. Brain regions and the numbers of MRSI voxel exhibiting lactate signals in patient and healthy control groups.

	anterior cingulate (a)	caudate (b)	posterior cingulate (c)	frontal (d)	parietal (e)	insula (f)	Lac/NAA ratio
Control	0	2	0	3	1	0	0.07±0.08
Patient	7	7	1	2	2	1	0.18±0.14*

*significantly different from healthy control value, p=0.03.

Fig. 2



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