Brain Bioenergics in Bipolar Depression: A Preliminary Phosphorus-31 Magnetization Transfer MR Spectroscopy Study

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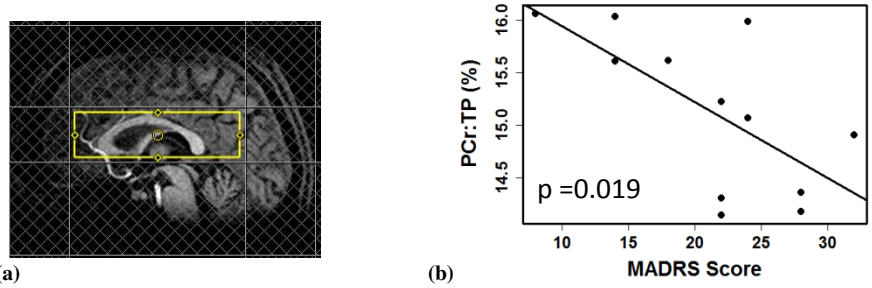
INTRODUCTION: Synthesis and regeneration of high energy phosphates such as phosphocreatine (PCr) and nucleoside triphosphate (NTP) play an important role in supporting neuronal activity. PCr serves as an energy reservoir in skeletal muscle and brain, while NTP (which is primarily adenosine triphosphate (ATP) in brain) is a direct energy source for metabolic processes. It has been recently reported that bipolar disorder (BD) is associated with mitochondrial dysfunction [1] and alterations in brain PCr and ATP concentrations have been observed in individuals with BD [2]. Creatine kinase (CK) is an enzyme that catalyzes the conversion between PCr and ATP and this reaction is described by the following equation: $PCr^{2-} + ADP^{-} + H^{+} \overset{CK}{\Leftrightarrow} ATP^{2-} + Cr$ (1). ATP may be hydrolyzed to release adenosine diphophate (ADP), inorganic phosphate (Pi) and energy that supports brain metabolic activities. Change in the CK reaction rate constant implies variation of both PCr and NTP concentrations and thus may be important in better understanding the pathophysiology of BD. For example, it has been reported that measured CK k_f in rat brain [3] is linearly correlated with total EEG power. In addition, studies with enzymatic assays have noted that both acute and chronic electroconvulsive shock resulted in brain tissue increases in CK activity [4]. Recently, postmortem studies in hippocampus and cortex [5] of BD decedents noted decreased CK activity. MacDonald et al. [6] have also reported that levels of CK mRNA are decreased in BD patients. By employing a recently updated phosphorus magnetization transfer (MT), image selected in-vivo spectroscopy (^{31}P MT-ISIS) technique [7], evaluation of all 31P-containing metabolites and CK reaction rates (k_f) in human brain for bipolar disorder patients with depression were assessed. Correlations between energetic parameters (PCr, β-NTP, k_f) and Montgomery-Asberg Depression Rating Scores (MADRS) [8] are also reported, where MADRS scores increase with the severity of depression.

METHOD: The Field of View is a defined 264 cm^3 voxel around frontal lobe, corpus callosum and occipital lobe regions shown in Fig. 1a. Studies were performed on a 3 T clinical MRI system using a ^{31}P/^{1}H double-tuned volume head coil. ^{31}P spectra were acquired using an MT-ISIS pulse sequence with FOV 11x8x3 cm^3, receiver bandwidth 2.5 kHz, and vector size 1024. To effectively saturate unnecessary fat signal from scalp, six outer volume ^{31}P saturation bands were placed in the scalp and skull regions. All spectra were preprocessed using matlab-based programs. Each spectrum was apodized with 10 Hz Gaussian line broadening before zero-filling and FFT. The zero- and first-order phase corrections are performed in all spectra. The signal intensity of each metabolite was obtained using advance magnetic resonance (AMARES) fitting algorithm within jMRUI [9]. The study protocol was approved by the Institutional Review Board of the University of Utah and informed consent was obtained from 9 normal volunteers and 12 bipolar disorder patients. Table 1 includes phosphate-containing metabolite and subject demographic information.

Table 1: Metabolites' peak area ratio, k_f, and intracellular pH measured by ^{31}P-MRS in whole brain in patients with depression and healthy control subjects.

	Healthy			Depression		
	Subject#	Mean	SD	Subject#	Mean	SD
Age (years)	9	27.8	6.2	12	34	7.4
Gender	F4/M5			F7/M5		
PCr	9	15.17%	1.53%	12	15.12%	0.75%
α-NTP	9	11.24%	1.32%	12	12.21%	1.18%
β-NTP	9	8.92%	1.09%	12	8.27%	1.48%
γ-NTP	9	12.63%	0.66%	12	12.15%	0.69%
Pi	9	5.92%	1.16%	12	5.74%	1.28%
PDE	9	26.92%	2.87%	12	28.81%	3.24%
PME	9	15.95%	1.07%	12	15.32%	1.39%
PME/PDE	9	59.76%	6.64%	12	53.96%	8.91%
k_f (s^{-1})	9	0.349	0.130	12	0.339	0.101
pH	9	7.04	0.01	12	7.04	0.02
[Mg^{2+}] mM	9	0.152	0.020	12	0.153	0.020

Pi, inorganic phosphate; PDE, Phosphodiester; PME, Phosphomonoester; F, Female; M, Male.



(a) (b)

Figure 1: (a) Region of Interest. (b) Plot demonstrates the correlation between PCr and Montgomery-Asberg depression rating score.

RESULT & DISCUSSION: In Fig. 1b**,** there is a significant negative correlation between PCr level and MADRS score (p=0.019). This result is consistent with a prior report [2] which noted decreased PCr levels from the frontal lobe in bipolar depressed patients. In addition, our findings of a negative correlation for PCr levels with MADRS scores are consistent with an earlier study [10] that found decreased white matter total creatine in bipolar depressed subjects from a similar region of interest. Reduced PCr levels may affect high demand energy states and have potential impact on the course of illness. Therefore creatine as a treatment supplement for depressed patients has been investigated and found to increase PCr levels in adolescent subjects [11]. Creatine also provided beneficial effects in adult women with unipolar depression [12]. Among the comparison of metabolites between healthy control and depressed bipolar disorder patients, no significant differences were observed as indicated in Table 1. However, k_f demonstrates a slight downward trend (-2.9%) in bipolar patients with depression compared to control subjects. This small reduction of k_f in depressed subjects is consistent with the findings in the previous study [13] which measured k_f from a central brain region and found a 5% reduction in bipolar depressed subjects. Further study of a larger sample of bipolar disorder patients with depression will be needed to clarify these analysis results.

REFERENCES [1] Stork and P F Renshaw. Mol. Psychiatry 2005 (10): 900-919. [2] Kato. J. Affect Disord. 1994 31(2): 125-133. [3] Sauter et al. J. Biol. Chem. 1993 268(18): 13166-71. [4] Erakovic et al. Epilepsia 2001 42(2): 181-189. [5] Sun X. et al. JPN 2006 31(3): 189-196. [6] Macdonald et al. Bipolar Disorder 2006 8(3): 255-264. [7] Jeong EK et al. NMR in Biomedicine 2011 24(7): 765-770. [8] Montgomery and Asberg. Br J Psychiatry. 1979 134(4): 362-389. [9] The MRUI software package. [10] Dager et al. Arch. Gen. Psychiatry. 2004 61(5): 450-458. [11] Kondo et al. J. Affect. Disord. 2011 135(1-3): 354-361. [12] Roitman et al. Bipolar Disorder. 2007 9(7): 754-758. [13] Forester et al. J Geriatr Psychiatry Neurol. 2012 25(2): 43-50