Measurement of Creatine-Kinase Reaction Rate Constant in Human Brain using ^{31}P Magnetization Transfer Image Selected In-vivo Spectroscopy (MT-ISIS): a Preliminary Application to Bipolar Disorder

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INTRODUCTION: Synthesis and regeneration of high energy phosphates such as phosphocreatine (PCr) and adenosine triphosphate (ATP) play an important role in supporting neuronal activity. PCr serves as an energy reservoir in skeletal muscle and brain, while ATP is a direct energy source for metabolic processes. Alternations in PCr and ATP concentrations have been observed in the brain of individuals with bipolar disorder (BD). It has been recently reported that BD is associated with mitochondrial dysfunction [1-3]. 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). Change in the CK reaction rate constant implies the variation of both PCr and ATP concentrations and thus may be important in better understanding the pathophysiology of BD. By employing a recently updated phosphorus magnetization transfer (MT), image selected in-vivo spectroscopy (^{31}P MT-ISIS) technique [4], estimates of the CK reaction rate constant (k_f) of PCr in human brain for healthy volunteers and bipolar patients are presented.

METHOD: The longitudinal magnetization $M_z(t)$ of PCr in the CK reaction with γ-ATP suppression can be described by the modified Bloch equation as, $\frac{dM_z(t)}{dt} = \frac{M_0 - M_z(t)}{T_1} - k_f M_z(t) - \varepsilon M_z(t)$, where M_0, T_1, k_f *and* ε represent the steady state magnetization, the spin-lattice relaxation time, the CK reaction rate constant and the RF bleedover effect of PCr, respectively [2]. The solution of this differential equation can be expressed as $k_f = \frac{1}{T_1'}\left[1 - \frac{M_z(\infty)}{M_0'}\right]$, where $1/T_1'$ ($=\frac{1}{T_1} + k_f + \varepsilon$) is apparent relaxation time, $M_z(\infty)$ the steady state longitudinal magnetization of PCr (0 ppm) with the saturation on γ-ATP (-2.5 ppm) and M_0' thermal equilibrium magnetization with control MT irradiation at +2.5 ppm. $1/T_1'$ can be measured by fitting the signal intensity of PCr acquired with different MT saturation duration t_{sat} Figs.1(a,~c) show pulse sequence diagram (MT-ISIS), a stacked plot of ^{31}P MR spectra with respect to MT saturation time, and the positions of the voxel and outer-volume-suppression bands, respectively. Fig.1d displays the typical fitting of PCr signal to an exponential recovery function $A + Be^{-\frac{t_{sat}}{T_1'}}$ with respect to the MT saturation duration t_{sat}, of which coefficient A corresponds to $M_z(\infty)$. M_0' is derived from ^{31}P spectra acquired by setting MT saturation RF pulse centered at +2.5 ppm with TR 20 s. All studies were performed on a 3 T clinical MRI system (Trio-Tim, Siemens Medical Solutions, Erlangen, Germany) with Avanto gradients (40 mT/m strength and 150 T/m/s slew rate) using a ^{31}P/^{1}H double-tuned volume head coil (Clinical MR Solutions, LLC, Brookfield, WI, USA). ^{31}P spectra are acquired using MT-ISIS pulse sequence with FOV 11x8x3 cm^3, receiver bandwidth 2.5 kHz, and vector size 1024. All spectra are preprocessed by home-made matlab program. Each spectrum was apodized with 10 Hz Gaussian line broadening before zerofilling 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 [5]. Study protocol was approved by the Institutional Review Board, University of Utah and informed consent was obtained from all 15 normal volunteers (7 Females: mean age 26.1±4.4 years and 8 Males: mean age 26.0±6.3 years) and 4 bipolar patients (2 Females: mean age 34±1.4 years and 2 Males: 30.5±2.1 years).

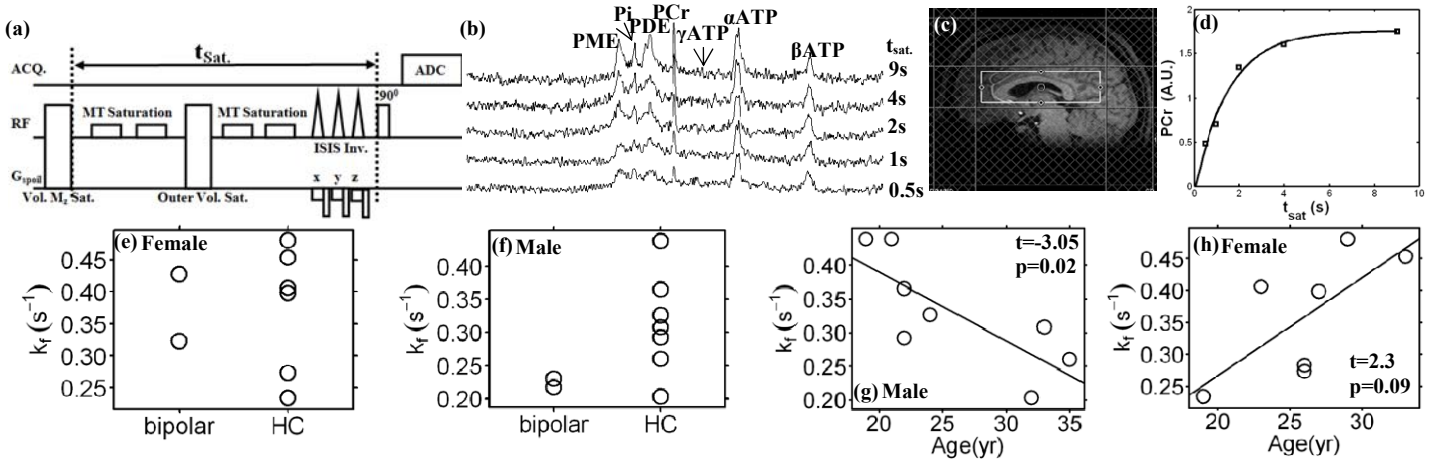

Figure 1: (a) Schematic MT-ISIS pulse sequence diagram. Volume M_z saturation, ISIS inversion and outer volume saturation (OVS) are labeled as Vol. M_z Sat., ISIS Inv. and Outer Vol. Sat., respectively. (b) Plot of ^{31}P signal intensity with respect to MT saturation duration. (c) Location of voxel and OVS bands. (d) PCr signal curve fitting. (e,f) k_f comparison between healthy controls (HC) and bipolar patients (bipolar) for male and female subjects, respectively. (g,h) The k_f scatter plots with respect to age for male and female healthy subjects, respectively. Linear model is applied to fit k_f and the t value and p value is added on the plot.

RESULT & DISCUSSION: The mean k_f values of female/male bipolar patient and female/male healthy volunteer are 0.38±0.07/0.224±0.009 s^{-1} and 0.36±0.10/0.32±0.08 s^{-1}, respectively (see Fig. 1e and 1f). These sex differences are consistent with the differential effect on mood that is observed in male and female rats following creatine supplementation [6]. In healthy male subjects, a decreasing trend was observed while the k_f in female controls increases with increasing ages, as shown in Figs. 1g and 1h, respectively. Mitochondrial function is thought to decrease with age, but strong gender effects have not been consistency observed [7]. Because the sample size does not reach statistical significance for a comparison of subjects with bipolar disorder and healthy volunteers, an increased sample size will be necessary to confirm possible differences in k_f, as well as their correlation with clinical symptoms (e.g. depression mania).

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