

## Age Dependence of Brain Bioenergetics in Bipolar Disorder

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**Target Audience:** The work presented in this abstract is primarily of interest to clinicians and researchers studying bipolar disorder (BD) or, more generally, brain bioenergetics under normal and pathological conditions.

**Purpose:** Due to the poor spatial resolution inherent in <sup>31</sup>P MRS, previous studies of bipolar disorder (BD) have only investigated regions containing heterogeneous mixtures of gray (GM) and white matter (WM) tissue. To that effect, we employed tissue regression analysis of <sup>31</sup>P MRSI to estimate concentrations of phosphorus containing metabolites in homogenous cerebral GM and WM and compare the bioenergetic environments of these compartments between BD patients and healthy controls (HC).

**Methods:** Thirteen BD subjects (7M/6F, 33 yrs  $\pm$  8) and thirteen age-matched HC subjects (6M/7F, 29 yrs  $\pm$  8) were consented and participated in the study following the protocol approved by the institutional review board. BD subjects were scanned in euthymic state, defined as having scores of less than 10 on the Young Mania Rating Scale (YMRS) and the Montgomery-Asberg Depression Rating Scale (MADRS). HC subjects had no history of any Axis I psychiatric disorder in themselves or first-degree relatives. Spectroscopic and anatomic data were acquired at 4T using a one-pulse 3D MRSI sequence and a 3D MDEFT sequence, respectively. Resonance areas were quantified using jMRUI's AMARES algorithm and converted to concentrations (mM) via a phantom replacement method.<sup>1</sup> Tissue segmentation was performed using SPM5 on the MDEFT images. Tissue regression analyses were performed on metabolite concentrations and intracellular pH (pH<sub>i</sub>) to determine theoretical values in *pure* GM and WM. Separate one-way analysis of covariance (ANCOVA) tests with age as the covariate were employed to measure differences in the dependent variable (metabolite concentrations or pH<sub>i</sub>) between groups for GM or WM.

**Results:** ANCOVA testing found that dependence on age was significantly different in GM between BD and HC groups for concentrations of inorganic phosphate (Pi,  $p = 0.0032$ ), phosphocreatine (PCr,  $p = 0.0029$ ), and adenosine triphosphate (ATP,  $p = 0.0176$ ). These three metabolites were negatively correlated with age in GM of BD subjects while Pi and PCr were positively correlated with age in GM of HC subjects (ATP is constant in HC subjects). No significant differences were found in mean concentrations in GM or WM between groups for other dependent variables.

**Discussion:** This study confirms that mitochondrial dysfunction, and consequently abnormalities in cellular metabolism, are involved in the pathophysiology of BD.<sup>2</sup> These results suggest BD is physiologically progressive with alterations in brain bioenergetics occurring with age. We postulate that neuronal bioenergetic abnormality increases in severity with duration of illness, leading to progressive deficits in the high energy phosphate pool.

**Conclusion:** The data presented here is a cross-sectional sample of BD adults on various (or no) pharmacological and psychotherapeutic treatment regimen. It is, therefore, warranted to study a BD cohort longitudinally using these MRSI methods in order to draw more definitive conclusions about the progression of this disease.

**References:** 1. Dudley JA. *J Spectrosc Dyn*. 2012;2:16(1-6). 2. Stork C et al. *Mol Psychiatry* 2005; 10:900

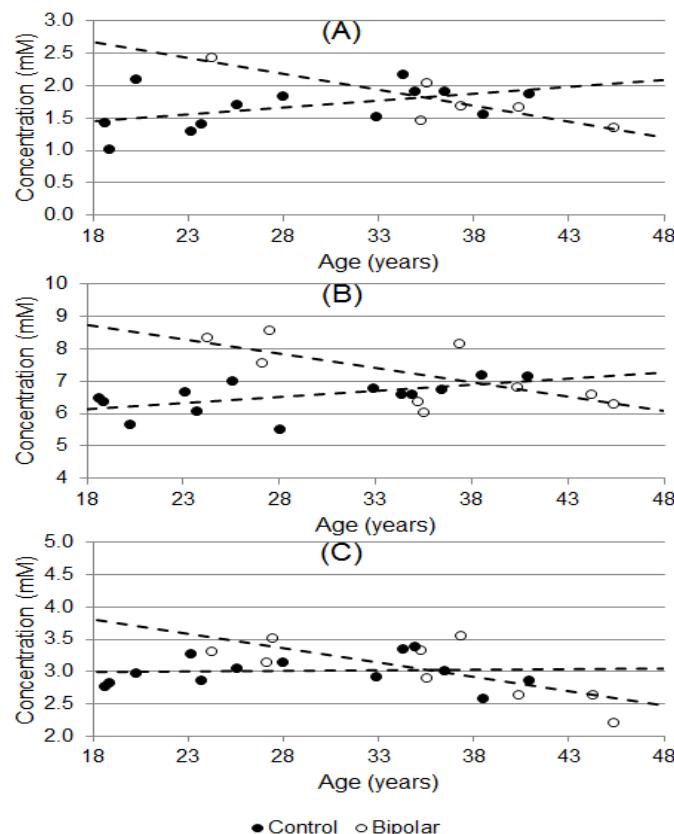


Figure 1: Dependence on age was significantly different for inorganic phosphate (A), phosphocreatine (B), and adenosine triphosphate (C) concentrations in gray matter between control and bipolar disorder subjects.