White Matter Abnormality in Adolescents with Bipolar Disorder

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

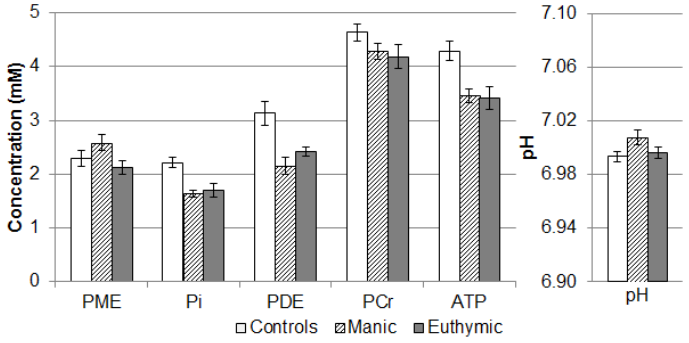
Purpose: Disruption of the anterior limbic network has been implicated in the pathophysiology of BD by a number of DTI studies reporting decreased fractional anisotropy in prefrontal-subcortical white matter (WM) in adolescents with BD.[1] However, there is a paucity of complementary information (e.g. biochemical) with which to draw conclusions about the nature of these abnormalities. To that end, the purpose of this work was to investigate the metabolic environment of gray matter (GM) and WM in adolescent BD patients using tissue regression analysis of ^{31}P MRSI data.

Methods: Nineteen manic state BD subjects (9M/10F, 15 yrs ± 2), thirteen euthymic state BD subjects (5M/8F, 16 yrs ± 2), and twenty healthy control subjects (10M/10F, 15 yrs ± 3) were consented and participated in the study following IRB guidelines. Manic and euthymic states were defined as scores of over 20 or under 12 on the young mania rating scale, respectively. All subjects were medication free for at least 72 hours prior to scanning. 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.[2] GM, WM, and cerebrospinal fluid contents corresponding to each ^{31}P voxel were obtained by SPM5 segmentation of the MDEFT images. Lobular probabilistic atlases were used to define three regions of interest (ROI): frontal lobe, parietal lobe, and the entire cerebrum. MDEFT images were warped to the ICBM 452 template; resulting transformation matrices were used to assign each spectrum to a ROI. Tissue regression analyses were performed on metabolite concentrations and intracellular pH (pH_i) to determine theoretical values in homogeneous GM and WM in each ROI. One-way MANOVAs with pairwise group contrast tested group differences due to metabolic variables grouped into bioenergetically relevant measures (adenosine triphosphate (ATP), phosphocreatine (PCr), inorganic phosphate (Pi), pH_i) and phospholipid measures (phosphomonoesters (PME) and phosphodiesters (PDE)).

Wilks' lambda probabilities for one-way MANOVAs testing group differences from bioenergetic (BE) or phospholipid (PL) measures. Contrasts were examined for comparisons between control (C), manic (M), and euthymic (E) groups.

		Cerebrum		Frontal Lobe		Parietal Lobe	
		WM	GM	WM	GM	WM	GM
BE	C v M	0.0005	0.0050	0.0003	0.0276	0.0162	0.0002
	C v E	0.0024	0.0594	0.0005	0.1331	0.1448	0.0025
PL	C v M	0.0249	0.0691	0.0321	0.7146	0.9668	0.8908
	C v E	0.0247	0.3469	0.1796	0.3466	0.5409	0.6522

Results: The Table summarizes the results of the findings. Bioenergetically relevant measures caused significant group differences in the cerebrum as well as the frontal and parietal lobes in GM and WM tissues. Phospholipid measures caused significant group differences in WM in the cerebrum between control and manic as well as euthymic groups and in the frontal lobe between control and manic. No differences between groups were found for phospholipids in GM for any ROI. The Figure illustrates ^{31}P MRSI measures in WM for the entire cerebrum.



Mean and standard error for metabolite concentrations and pH estimated in WM for the entire cerebrum

Discussion: The results show that differences of bioenergetic and phospholipid measures were generally widespread in the brain. Interestingly, significant bioenergetic measures were occurring in GM and WM in both frontal and parietal lobes, while phospholipids were constrained to WM in the frontal lobe only. This suggests abnormal energy metabolism (i.e. mitochondrial dysfunction) is present throughout the brain while altered membrane metabolism is limited primarily to prefrontal-subcortical WM, possibly in association with ALN disruption.

Conclusion: The preliminary study shows that altered energy metabolism in brain generally agrees with previous findings[3] and altered phospholipid metabolism exhibits in WM was also in agreement with the previous finding of decreased fractional anisotropy in DTI studies.[1]

References: 1. Adler CM, et al. Bipolar Disord, 2004; 6: 197. 2. Dudley JA. et al. *J Spectrosc Dyn*. 2012; 2:16. 3. Stork C et al. Mol Psychiatry 2005; 10:900