Metabolic Changes in Medication-free Patients with Bipolar and Unipolar Disorder

U. Dydak[1,2], J. M. Nixon[1], M. Dzemidzic[3], H. S. Karne[4], and A. Anand[4]
[1]School of Health Sciences, Purdue University, West Lafayette, IN, United States, [2]Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, United States, [3]Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, United States, [4]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, United States

Introduction

Bipolar Disorder is a major mental illness characterized by devastating cycles of periods of depression and mania. Despite significant advances made in neuroscience in the last fifty years, the neurobiological causes underlying bipolar disorder remain unclear. Converging findings from animal and human studies point to the anterior cingulate-striatal-pallidial-thalamic-amygdalar regions as a putative mood regulating circuit (MRC), which may be dysfunctional in mood disorders [1]. As part of a larger study, which looks at the relationship between neurochemical changes in cortical mood regulating areas and alterations in activation and connectivity measures using fMRI, we present the comparison of metabolite levels at baseline in medication-free patients with bipolar disorder to those in medication-free patients with unipolar disorder and matched healthy controls.

Materials and Methods

A group of 19 bipolar disorder (BD) patients either in the manic or depressed phase and medication-free for at least two weeks at the time of the exam, as well as a group of 15 unipolar depressed patients (UD), also medication-free for at least two weeks at the time of the exam, were recruited for this study. These two groups were compared to a matched control group of 13 healthy volunteers (HV) with no history of psychiatric illness of themselves or a first degree relative. All subjects underwent a 2D MR spectroscopic imaging (MRSI) exam of the brain in addition to anatomical and fMRI exams, which are part of the larger study. All participants gave written informed consent prior to participating in this study.

MRSI data were acquired on a 3T Tim Trio (Siemens Healthcare) MRI scanner equipped with a standard 12-channel head coil array. A 15 mm axial slice was placed along the AC-PC line in a way to cover anterior cingulate cortex (ACC), thalamus as well as posterior cingulate cortex (PCC) (Fig.1). MRSI data were acquired from this slice with a nominal voxel size of 2.8 ml (13.75 x 13.75 x 15 mm^3), TR = 1500 ms and TE = 30 ms. For each subject a single MRSI voxel was manually chosen on that subjects' T2-weighted image to represent each of the following brain areas, known to be involved into the mood regulating circuit: right ACC (ACC-R), left ACC (ACC-L), right thalamus (Thal-R), left thalamus (Thal-L), right PCC (PCC-R) and left PCC (PCC-L). Typical voxels chosen for these areas are shown in Figure 1. Spectra from these six areas were quantified using LCModel. Results are given as ratios to total creatine (tCr) and were only used for statistical analysis if the Cramer-Rao lower bound of the fit was ≤ 15%. The resulting metabolite ratios for N-Acetylaspartate (NAA), choline (Cho), myo-inositol (mI), glutamate (Glu), glutamate + glutamine (Glx), and lactate (Lac) were compared between the different groups by a student's t-test for significant differences in metabolic concentrations within each of the six different brain regions.

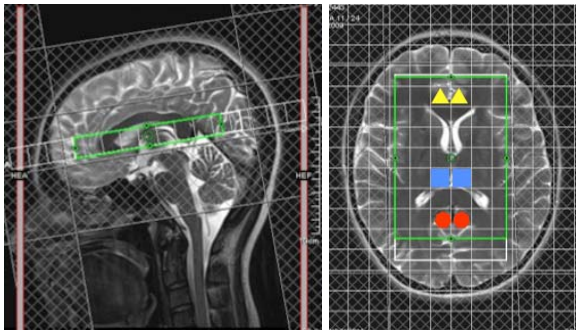

Figure 1: Placement of the MRSI slice and typical voxel choice for the region of interest analysis: triangle – ACC, square – thalamus, circle – PCC.

Results

Spectral data quality achieved in the different brain regions studied was high enough to include over 75% of the fitting results for NAA, tCr, Cho and mI and over 50% of the fitting results for Glx into the statistical analysis even in the ACC area, which is the most difficult area to shim. Significant changes in baseline metabolism between the three groups are summarized in Table 1: The main finding was decreased NAA/tCr of the bipolar patients compared to healthy controls both in right thalamus and right ACC. Bipolar patients also showed decreased Cho/tCr primarily in the right thalamus compared to the unipolar group. In addition, decreased Glu/tCr in the right thalamus was found when the unipolar group was compared to HV. No significant changes between groups were found in the PCC, nor were any significant changes of tCr found in any region between any groups.

region	metabolite	groups compared	difference (%)	p-value
Thal-R	NAA/tCr	BD versus HV	-14.2 %	0.008*
Thal-R	Cho/tCr	BD versus UD	-14.4 %	0.01*
Thal-L	Cho/tCr	BD versus UD	- 10.1%	0.08
Thal-R	Glu/tCr	UD versus HV	-25.4 %	0.02*
ACC-R	NAA/tCr	BD versus HV	-32.3 %	0.008*

Table 1: Significant metabolic changes found between groups: p-values < 0.05 were considered significant.

Discussion

This is the first MRS study, to our knowledge, which has concurrently investigated unmedicated unipolar depressed and bipolar patients as well as closely matched healthy control subjects. Differences seen between unipolar and bipolar patients are important to understanding the etiology of these similar but at the same time very different mood disorders. Moreover, using the unipolar subjects as an additional psychiatric control group makes it easier to interpret disease specific MRS abnormalities in bipolar disorder. Contrary to Port et al. [2], who investigated similar brain regions in patients with BD, we found significant changes in the right thalamus and right ACC region. The decrease in NAA in the Thalamus is consistent with the findings by Frye et al. [3], who also found decreased NAA/tCr in right basal ganglia. The increase in Lac and Glx reported by Dager et al. [4] could not be reproduced, which might be due to difference in type of patient populations as well as differences in MRS methodology. An interesting finding in our study, which is similar to the findings by others [2,3], is that most of the significant metabolic alterations in bipolar disorder are found in the right hemisphere, which needs further investigation. A clear limitation of this study is the lack of water reference data to be used as internal reference, since conflicting reports exist about possible changes in tCr in BD [2,5,6]. However our data does not suggest any group differences in tCr in any of the brain areas studied. A correction of the metabolite values for CSF content is in progress.

References:

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