Brain iron accumulation in first episode of mania

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Target Audience: MR researchers, basic and clinical scientists, radiologists

Purpose: Bipolar disorder (BD) patients pass through a series of manic and depressive episodes. These episodes are associated with rapid mood changes, related to the functioning of the brain’s dopaminergic system. Dopamine is a neurotransmitter, which acts in the presence of iron as a neurotoxin due to the production of free radicals. An excessive amount of free radicals, which are not detoxified by antioxidants, is believed to increase oxidative stress levels, ultimately leading to damage of lipids, proteins or the DNA. Previous studies showed that decreasing dopamine transmission or increasing the level or antioxidants helps to reduce mood swings. Also, a dysregulation of the iron metabolism was suggested in patients with white matter lesions, as seen in BD. Here, we used magnetic resonance imaging to study brain iron levels in first episode mania patients. We hypothesize that changes in R2* or MR resonance frequency as markers for elevated levels of brain iron in the deep brain gray matter (DGM) might be detectable even at onset of the disease, preceding the onset of symptoms or to develop rapidly at disease onset.

Methods: 18 first episode mania patients (age: [14-30], 11 male, 7 female) and 15 age and gender matched healthy controls (age: [17-35]) received baseline MRI scans. Patients were selected based on structured clinical interview for DSM-IV. Healthy controls were chosen with no history of psychiatric disorders or previous brain injuries. A multi-gradient echo (GRE) scan was performed in addition to conventional, structural sequences (5 echoes, TR/TE/ΔTE = 46/13/7ms; reconstructed voxelsize= 0.42x0.41x1mm3; FOV = 220x150x96mm3). The GRE magnitude information was used to calculate R2* maps by voxelwise fitting of an exponential decay curve over all echoes. The phase was homodyne filtered, converted into maps of frequency shifts and averaged. DGM regions were extracted from the Harvard-Oxford MNI space atlas, regions of interest (ROI) in the ventral striatum were defined manually. Image registration between 3D T1 and T2*weighted images was performed using FSL’s FLIRT tool. The MNI atlas regions were registered to the frequency image using FNIRT and FLIRT via the T1 weighted scan. All ROI’s were eroded by 1 voxel and the mean and standard deviation were calculated. The non-parametric Kruskal-Wallis test was used to determine statistical group differences.

Results: 10 age and gender matched couples (mean age: 22.3yrs, maximum age difference 1 year, 4 male/6 female) were analyzed to exclude iron changes due to aging. The results for 4 regions are shown in Fig. 1. R2* (left) did not show any differences between patients and healthy controls for any of the regions. Frequency shifts, on the other hand, (right) were significantly increased in the caudate (34.8%, p=0.01) and globus pallidus (34.9%, p=0.0005) and a non-significant increase in the putamen (51.4%, p=0.38) was observed. In contrast, the ventral striatum showed lower frequency shifts in patients compared to healthy controls (87.4%, p=0.003). No gender differences (p>0.2) or differences between the left and right hemisphere (p>0.1) were observed.

Discussion: Various studies suggest a role of the striatum in mood disorders. The striatum includes the nucleus accumbens, ventral caudate and ventral putamen. Earlier studies showed that subcortical lesions in the basal ganglia may result in mood modulations or bipolar disorder. Some studies reported manic episodes with deep brain stimulation targeting the globus pallidus or after pallidotomy. The observed increase in MR frequency could be explained with increased iron levels in these areas. However, the lack of R2* differences between patients and controls indicates changes other than the accumulation of paramagnetic iron. Another possible explanation for this finding is the reduced signal-to-noise ratio of R2 maps compared to frequency maps. Also, the reduced frequency in the ventral striatum in subjects with bipolar disorder seems to conflict the hypothesis of iron accumulation and warrants further investigation.

Conclusion: MR frequency shift imaging is sensitive to early changes in the deep gray matter in first episode mania patients. However the observed changes may be associated to factors other than the accumulation of iron.