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A Structural Magnetization Transfer Imaging In Schizophrenia Patients with Major Depressive Disorder

***Raju Anitha*[1] *A. Amruthavalli*[2] *P.SivaKrishna*[3]**
[1]Associate Professor
[2,3]Assistant Professor
[12]Department of Computer Science & Engineering
[3]Department of Electrical and Electronics Engineering
[123]Pace Institute of Technology & Sciences, Ongole

Abstract-Schizophrenia is a chronic and serious mental disorder that affects how a person thinks, feels, behaves and acts. People with schizophrenia may seem like they have lost touch with reality. Contrary to public perception, schizophrenia is not split personality or multiple personality. The vast majority of people with schizophrenia are not violent and do not pose a danger to others. However it is not caused by childhood experiences, poor parenting or lack of willpower, nor is the symptoms identical for each person. The people with this disorder may have difficulty expressing normal emotions in social situations. The window on the brain provided by structural imaging has transformed our view of schizophrenia to one that views the very structure of the brain as altered. A technique that is particularly interesting in this context is magnetic transfer imaging (MTI). MTI creates a contrast between tissues by exploiting the phenomenon of magnetization exchange between the spins of free water and water bound to macromolecules. The efficiency of these exchange phenomena is measured by the magnetization transfer ratio (MTR), which depends on both the amount and states of macromolecules. MTI is highly sensitive to white matter abnormalities like depression and multiple sclerosis (MS) even when conventional MRI is negative. Lower MTR in gray matter is believed to be associated with abnormalities of cell membrane proteins and phospholipids. In the present work MTI is using to explore and characterize further the neuropath logical abnormalities in vivo in MDD patients with history of Schizophrenia brain disorders and healthy controls.

***Index Terms*:-MTR, Schizophrenia, Gray mater, MDD etc.,**

I. INTRODUCTION

Schizophrenia is a major health problem throughout the world. The disorder typically strikes young people at the very time they are establishing their independence and can result in lifelong disability and stigma. In terms of personal and economic costs, schizophrenia has been described as among the worst disorders afflicting humankind. It is a mental disorder characterized by loss of contact with reality (psychosis), hallucinations (usually, hearing voices), firmly held false beliefs (delusions), abnormal thinking and behavior, reduced expression of emotions, diminished motivation, a decline in mental function (cognition), and problems in daily functioning, including work, social relationships, and self-care. The disease is probably caused by hereditary and environmental factors. The People with Schizophrenia may have a variety of symptoms, ranging from bizarre behavior and rambling, disorganized speech to loss of emotions and little or no speech to inability to concentrate and remember. Doctors diagnose schizophrenia based on symptoms after they do tests to rule out other possible causes. Treatment involves antipsychotic drugs, training programs and community support activities, psychotherapy, and family education.

It is more common than Alzheimer disease and multiple sclerosis. Determining when schizophrenia begins (onset) is often difficult because unfamiliarity with symptoms may delay medical care for several years. The average age at onset is the early to mid-20s for men and slightly later for women. Onset during childhood is rare. But schizophrenia may begin during adolescence or late in life. Deterioration in social functioning can lead to substance abuse, poverty, and homelessness. People with untreated schizophrenia may lose contact with their families and friends and often find themselves living on the streets of large cities. The following figure shows the Schizophrenia disease patients and normal control subject.

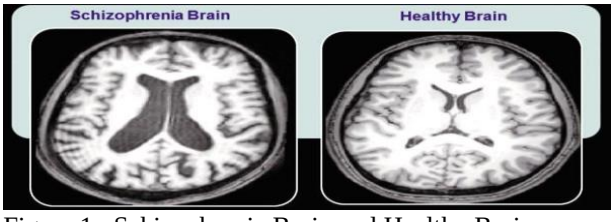


Figure 1: Schizophrenia Brain and Healthy Brain

It has recently been suggested that new imaging methods such as magnetization transfer imaging (MTI) may play an

important role in detecting subtle gray- and white-matter abnormalities in schizophrenia. The aim of the study was to investigate whether MTI, analyzed on a voxel-by-voxel basis, could identify areas of abnormal magnetization transfer ratio (MTR) in patients with schizophrenia.

Magnetization Transfer Imaging

Magnetization transfer imaging (MTI) is a technique by which radiofrequency (RF) energy is applied exclusively to the bound pool using specially designed MT pulse(s). Some of this energy is then transferred to the free water pool primarily via dipole-dipole interactions. Depending on the degree of coupling between these pools, the free water pool becomes partially saturated. If the free water pool is subsequently imaged using routine RF pulses and gradients, its signal will be reduced secondary to the MT effect. The magnitude of this MT effect can be quantified by obtaining two sets of images (one with an MT pulse and one without it) and then digitally subtracting them. The magnetization transfer ratio (MTR) for a given voxel may then be defined and computed as:

$$MTR = (So - SMT)/So$$

Where So is the magnitude of tissue signal before the MT pulse and SMT is the signal after the MT pulse has been applied. The relative difference in signal between two adjacent tissues (A and B) is known as magnetization transfer contrast (MTC). It should be noted that MTR measurements are not absolute, are susceptible to motion-related errors, and vary significantly as a function of the shape, bandwidth, and frequency offset of the MT pulse. The following figure shows the brain images before and after MT saturation.

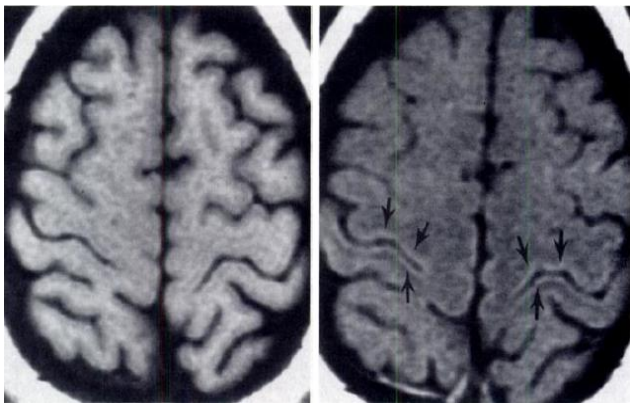


Figure 2: Normal brain before (left) and after (right) MT saturation. Note the central sulcus (arrows) has different MT contrast than the other sulci.

The main limitation of this approach is the difficulty in defining region of- interest boundaries to avoid any bias in placing ROIs and to minimize partial volume effects. Only three schizophrenia studies published to date have investigated MTR using a voxel-based analysis approach. This method can be applied without a priori hypotheses; it reduces observer bias, and allows whole-brain analysis.

II MATERIAL AND METHODS

A) Data Acquisition

Twenty schizophrenic patients (13 men, 7 women, mean age: 35.5±6.3 years, range: 23 to 45 years, right-handed) who fulfilled the DSM-IV criteria for schizophrenia Expertly collected, well-curated data sets consisting of comprehensive clinical characterization and raw structural, functional and diffusion-weighted DICOM images in schizophrenia patients and sex and age-matched controls are now accessible to the scientific community through an on-line data repository (coins.mrn.org). The Mental Illness and Neuroscience Discovery Institute, now the Mind Research Network (MRN, www.mrn.org), comprised of investigators at the University of New Mexico, the University of Minnesota, Massachusetts General Hospital, and the University of Iowa, conducted a cross-sectional study to identify quantitative neuro imaging biomarkers of schizophrenia. All participants underwent conventional MR imaging and MTI on a 3-tesla scanner (Intera, Philips Medical System, Best, the Netherlands) with a SENSE-head coil. Total scanning time (including sequences not reported herein) was about 50 minutes. Anatomical images were acquired using a 3D T1-weighted TFE sequence generating 68 contiguous, 2-mm axial slices (TE=2.5 ms; TR=5.4 ms; FOV=20 cm2, image matrix 128×128, FA=8°). MTIs were acquired using a 3D FFE MTI sequence (TE=3.6 ms; TR=146 ms; FOV=22.4 cm2, 224×224 pixel image matrix; 60 contiguous 4-mm axial slices) with and without saturation pulse (an off-resonance RF pulse centered 1.1 kHz below the water frequency, with a Gaussian envelope of duration of 15 ms, a bandwidth of 363 Hz, angle=620°, and a B1 of 14 μT).

B) Image Processing and Statistical Analysis

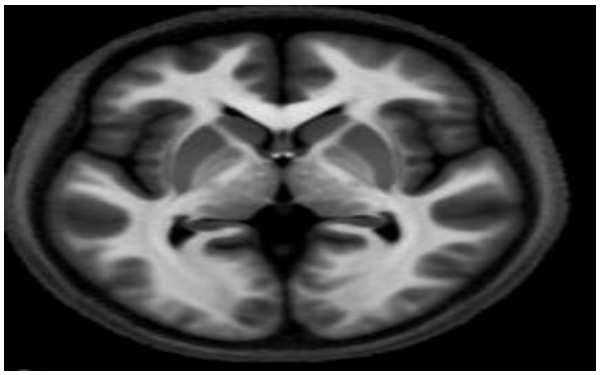
Image Processing

MR images from all the subjects were first reviewed by a neuroradiologist to ensure that there were no structural abnormalities or data quality flaws. Data processing and analysis were carried out using the statistical parametric mapping software SPM8 (Welcome Trust Centre for Neuroimaging). For each subject, the MT-weighted and non-MT-weighted images were first co-registered using a mutual information registration algorithm. MTR was then calculated on a voxel-by-voxel basis as follows: MTR = $(M_0\text{-}M_s)/M_0 \times 100$, where M_0 and M_s are the signal intensities without and with the saturation pulse applied.

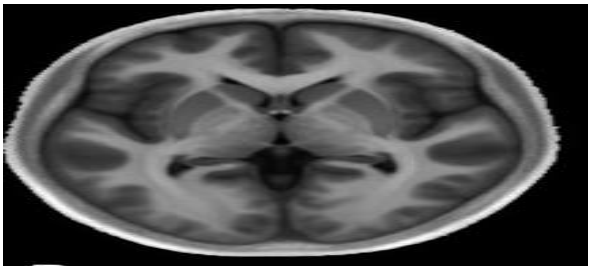
Because the non-MT images are partially T1-weighted, we directly normalized them to the MNI T1W template and then used the transformation parameters to normalize the co-registered MTR map. The normalized non-MT images were skull-stripped using the brain extraction tool (BET, http://www.fmrib.ox.ac.uk/fsl/bet/) and were then used as masks to remove non-brain tissues on the normalized MTR maps. Finally, MTR maps were smoothed with a Gaussian kernel of 6-mm full-width half-maximum.

Voxel-Based Analysis

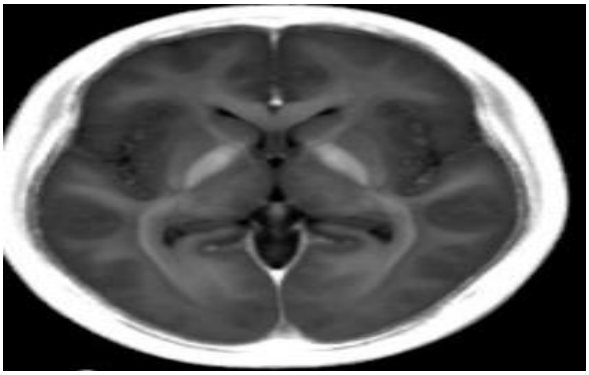
MTR maps were compared among the three groups using analysis of covariance (ANCOVA) with age and sex as covariates. Correction for multiple comparisons was determined by Monte Carlo simulations (with the following parameters: individual voxel p value = 0.005, 1,000 simulations, FWHM = 6 mm), applied with the Resting-State fMRI Data Analysis Toolkit (REST) of the Alpha Sim program[50], to determine a corrected significance level of $p < 0.05$ for a minimum cluster size of 86 voxels. For clusters identified in the ANCOVA, we performed follow-up between-group voxel-wise t tests in regions with overall group differences to identify pair-wise group differences using the same thresholding method. Montreal Neurological Institute coordinates were transformed to Talairach coordinates using MNI2tal (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/). To quantify changes in the affected regions, MTR values were extracted using a volume-of-interest approach in SPM. We conducted correlation analyses between the average regional values in these regions with HAM-D score and illness duration.



(a)



(b)



(c)

Figure 3: Example parameter maps used for voxel-based quantification analyses: magnetization transfer, MT (a); longitudinal relaxation rate, R_1 (b); and transverse relaxation rate, R_2* (c).

Region-of-Interest Analysis

In a secondary analysis, ITK-SNAP was used to obtain bilateral measures of the head of the caudate nucleus. This was done based on a previous MT study reporting focal biophysical abnormalities in this region in depression. The slice displaying the most anterior margin of genu of the corpus callosum (Montreal Neurological Institute (MNI) coordinates: was chosen as the reference slice for placing the ROI, since this landmark could be easily and consistently identified across subjects. We used constant volumes 72 mm^3 for the head of caudate nucleus in the MTR maps of all subjects and the MTR values were extracted bilaterally and compared across groups using univariate analysis of covariance controlling for age and sex.

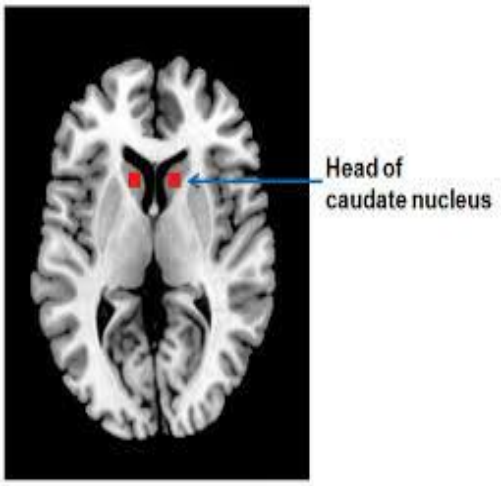


Fig 4: Regions of interest (head of bilateral caudate nucleus) for magnetization transfer ratio analysis.

III DISCUSSION

This MTI study is to compare untreated adult patients with major depressive disorder using a voxel-based analysis. The main findings are that the MT signal is largely dependent on the macromolecular density of cell membranes and phospholipids, and grey matter MTR reductions in the parietal lobe in the patients we observed likely reflect decreases in the size and number of neurons and dendritic density. One possible mechanism for these effects is that stress-induced hyperactivity of the hypothalamic–pituitary–adrenal axis may lead to cell damage through glucocorticoid-mediated glutamatergic neurotoxicity and decreased astrocytic activation, with reduced uptake of glucose and altered neuronal metabolism resulting in reduced neuronal volume and dendritic barbarization.

IV CONCLUSION

A study using repetitive transcranial magnetic stimulation reported that the inhibition of cerebella function resulted in mood deregulation and increased negative moods in healthy subjects. This is consistent with a body of literature showing a role of cerebellum in emotion modulation. The abnormality in MTR of the left cerebellum is consistent with a previous report of reduced GM volume in the cerebellum in MDD patients..

ROI analysis revealed no significant group differences in the head of the caudate nucleus, failing to replicate a prior report that a biophysical abnormality in the caudate nucleus is related to behavior or depression. However, a voxel based mormphometrey is to quantify changes in the affected regions, MTR values were extracted using a volume-of-interest approach in SPM..

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