Magnetic Resonance Spectroscopy (MRS) is a unique technique that can directly assess the concentration of various biochemical metabolites in the brain. Thus, it is used in the study of molecular pathophysiology of different neuropsychiatric disorders, such as, the major depressive disorder and has been an area of active research. We conducted a computer-based literature search using the Pubmed database with ‘magnetic resonance spectroscopy’, ‘MRS’, ‘depression’, and ‘major depressive disorder’ as the key words, supplemented by a manual search of bibliographic cross-referencing. Studies in depression report abnormalities in the frontal cortex, basal ganglia, hippocampus, anterior cingulate cortex, and the occipital cortex. These abnormalities improve after treatment with selective serotonin reuptake inhibitor, electroconvulsive therapy, and yoga, and thus, are possibly state-dependent. The findings are consistent with other morphometric and clinical studies and support the proposed pathophysiological theory of dysfunction in the neuronal circuits involving the frontal cortex, limbic cortex, and basal ganglia. Spectroscopy also has potential implications in predicting the response to treatment and formulating individualized pharmacotherapy.

**Key words:** Depression, gamma-aminobutyric acid, magnetic resonance spectroscopy, N-Acetyl Aspartate, neuroimaging, proton MRS

**INTRODUCTION**

Advances in neuroimaging techniques have helped to identify brain regions involved in psychiatric disorders. Among neuroimaging modalities, Magnetic Resonance Spectroscopy (MRS) is a unique technique that can directly assess the concentration of various biochemical metabolites in the brain. MRS in addition to being noninvasive has a high spatial resolution and requires neither radioactive tracers nor ionizing radiation — a distinct advantage over other imaging modalities. Thus, in the last two decades MRS has been used to study molecular pathophysiology of different neuropsychiatric disorders, including major depressive disorder (MDD). Among the several nuclei assessed in MRS, proton (\(^1\)H) MRS is the most commonly used. The goal of this article is to review literature on MRS in depression and the potential applications of this technique.

**Magnetic resonance spectroscopy – principle and procedure**

Magnetic resonance spectroscopy, similar to magnetic resonance imaging, is based on the principles of nuclear magnetic resonance. MRS requires a magnetic field and a radio frequency transmit pulse at a particular resonant frequency, to observe the signal of specific nuclei, like protons, in the sample of interest. Protons resonate at a particular frequency depending on the surrounding magnetic field. As different molecules surround protons in different compounds, they experience differing magnetic fields, and thus, resonate at different frequencies. These small differences in frequency are processed using Fourier transformation and plotted on a graph as the output. This output is called as the ‘MRS spectrum,’ with a frequency in parts per million along the X-axis and signal amplitude along the Y-axis. Specific nuclei contained in a metabolite give rise
to either a single peak or multiple peaks that are uniquely positioned along the frequency axis, and the peak position is known as the chemical shift. The area under the curve gives the tissue concentration of each metabolite. Thus, the MRS spectrum reflects the biochemical composition of the brain and each metabolite is identified accurately by its unique position.

A variety of factors determine the type of MRS used in a study. Important among them are the region of interest, nuclei of interest, and field strength of the magnet. MRS provides the selection of a particular region of the brain for analysis, known as the ‘region of interest’. The region of interest is determined by selecting the appropriate voxel – a volume element representing a value in three-dimensional space, analogous to a pixel in two-dimensional space. Depending on what biochemical information is to be assessed, the metabolite is chosen and is known as the ‘nuclei of interest’. Two kinds of spectroscopy are commonly used: 1H (proton) spectroscopy and 31P (Phosphorus) spectroscopy. 1H spectroscopy can assess the metabolite levels of N-acetylaspartate (NAA), glutamate (Glu), glutamine (Gln), glutamatergic compounds (Glx), g-aminobutyric acid (GABA), and myoinositol (MI). This gives information on the viability of neurons, the neuronal system, neurotransmission cycling, and the second messenger metabolism, respectively. Phosphorus spectroscopy can measure metabolite levels of adenosine tri phosphate, Phosphocreatine, and inorganic orthophosphate, which are associated with high-energy phosphate metabolism. The field strength of magnets used is important as higher field strength magnets offer better sensitivity, signal-to-noise ratio, and spatial resolution.

**MATERIALS AND METHODS**

We used a computer literature search of the National Library of Medicine, the Medline-Pubmed search, with ‘magnetic resonance spectroscopy’, ‘MRS’, ‘depression’, and ‘major depressive disorder’ as key words, supplemented by a manual search of bibliographic cross-referencing. *In vivo* MRS studies were included.

**Magnetic resonance spectroscopy correlates of depression – metabolites of interest**

### N-Acetyl Aspartate

Studies have examined NAA or NAA/Cr in the prefrontal cortex (PFC), anterior cingulate cortex (ACC), basal ganglia, hippocampus, and amygdala. Studies have given discrepant findings. Most of the studies have reported no significant difference in basal ganglia.[1,3] However, decreased NAA/Cr ratio in the thalamus[9,10] and decreased concentration of NAA in the caudate,[10] in comparison with healthy controls are also reported in a few studies. No difference in the NAA/Cr ratio in the PFC has been noted in most of the studies,[6,9] with a few exceptions.[10] Similarly, no difference is present in the ACC.[7,11-13] Studies in amygdala–hippocampus, have consistently reported the absence of a difference between patients and controls at baseline.[8,14] In one study, there was an increase in NAA after electroconvulsive therapy (ECT).[8] NAA studies in children and adolescents have consistently reported negative results: no difference between patient and controls in PFC, ACC, amygdala or basal ganglia.[15-20]

### Glutamate/Glutamine

Studies in ACC were consistent: Depressed patients had decreased Glu/Gln in ACC[11,13,16] and these abnormalities improved after ECT.[13] Similarly, decreased Glu/Gln was noted in PFC at the baseline, which improved after treatment with ECT.[8] However, there were negative reports.[6] Decreased concentration was also noted in amygdala–hippocampus.[8] In children and adolescents, increased Glx was seen in the basal ganglia,[20] while there was no difference in PFC.[16]

### g-Amino Butyric Acid

A number of MRS studies have reported reduced GABA concentration in the occipital cortex of depressed patients than healthy controls.[21-23] Reduction in GABA concentration was more (around 50%) in patients with melancholic depression than in those without melancholic depression (around 20%). However, these abnormalities in GABA concentration were found in the occipital cortex and not in the anterior brain regions, which were directly involved in the pathophysiology of mood disorder. Studies in the prefrontal cortex have not consistently replicated these findings. In earlier studies, there was no difference in the prefrontal GABA between the remitted patients and controls.[24] However, a recent study reported decreased GABA in the ACC.[25]

### Choline

Studies in basal ganglia have given conflicting findings. Some studies have reported increased choline/Cr ratio,[1,3] while others show a decreased ratio.[2,10] In a few, there was no significant difference.[1,26] On further analysis of subdivisions of the basal ganglia, increase in choline was seen in the putamen, but not in the caudate or thalamus.[3] Interestingly, an elevated choline concentration reversed after treatment with an antidepressant, similar to GABA abnormality reversal.[2] Studies have consistently reported no significant difference in PFC[9,13] and ACC.[7,11,12] Similar negative results were present in amygdala–hippocampus.[27] Similar to NAA, there was an increase in choline after treatment with ECT.[14] Inconsistent results were seen in children and adolescents, with few studies reporting no significant difference,[16] while others reported either increased or decreased choline levels.[15,17-20] In a recent study, adolescents with major depression had significantly elevated concentration of choline and creatine in left caudate.[28]

### Myoinositol

Most of the studies have reported negative findings in ACC[11,16] and basal ganglia.[3] In PFC, discrepancy has been
noted, with some reporting a decreased MI/Cr ratio,\textsuperscript{[7,10,29]} and other reporting an increased ratio.\textsuperscript{[12]} In one study, there was no difference.\textsuperscript{[6]} Similarly, an earlier study in children reported no significant difference.\textsuperscript{[20]} However, in a recent study there was an increased ratio in PFC.\textsuperscript{[15]}

A recent meta-analysis concluded the absence of difference in NAA/Cr and NAA in the basal ganglia, frontal lobes, and myoinositol in the frontal lobes, between patients and healthy controls. It also indicated significantly higher Cho/Cr levels in the basal ganglia and lower Glx values in the frontal lobes and occipital cortex of patients.\textsuperscript{[10]}

Regional correlation
Overall, MRS studies in depression report abnormalities in the frontal cortex, basal ganglia, hippocampus, anterior cingulate cortex, and occipital cortex. In PFC, significantly decreased Glu/Gln, but not choline is noted. Most of the studies in the basal ganglia have reported no difference in NAA and results are inconsistent with choline and glutamate. Consistent findings across studies are, decreased Glx and absence of difference in NAA in amygdala–hippocampus, decreased Glu/Gln and GABA in the ACC, and decreased GABA in the occipital cortex. These findings suggest an involvement of the cortical, subcortical, and limbic brain regions, in depression, in accordance with evidence from the clinical and morphometric studies.

Correlation with pathophysiology
N-Acetyl Aspartate functions in the brain as an acetyl donor for acetyl coenzyme A and takes part in lipid biosynthesis, including myelin.\textsuperscript{[31]} NAA is commonly considered to be a putative neuronal marker,\textsuperscript{[13]} as it is localized only in neurons, but not in glial cells or blood. Thus, NAA resonance measured by MRS is a marker of neuronal viability and function.\textsuperscript{[33]} Thus, reduction in NAA concentration possibly reflects an underlying neurodegenerative process in major depression.

Choline is an essential precursor of the neurotransmitter acetylcholine and membrane lipids, phosphatidylcholine and sphingomyelin.\textsuperscript{[17]} The Cho peak is considered as a potential biomarker for the status of membrane phospholipid metabolism,\textsuperscript{[31,34]} and an elevated Cho signal most likely reflects an increase in the membrane turnover.\textsuperscript{[14]} Alterations in the Cho signal may have an impact on signal transduction in MDD.\textsuperscript{[19]} Based on theories of cholinergic overactivity in phosphatidylcholine / membrane phospholipids metabolism and signal transduction systems in depression, the Cho peak in proton MRS has received considerable attention in MDD.

Inositol has a function in osmoregulation in brain glial cells.\textsuperscript{[29]} Glial cells store myoinositol and then gradually pass it on to the neurons, where it becomes a precursor of phosphoinositide.\textsuperscript{[29]} In the cerebrospinal fluid, markedly reduced levels of myoinositol have been reported in depressed patients with unipolar and bipolar affective disorder.\textsuperscript{[36]} and double blind trials have shown improvement in depression following inositol treatment.\textsuperscript{[37]}

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in central nervous system and is integral in managing brain excitability.\textsuperscript{[38]} GABA has an important function in cortical inhibition and in the pathophysiology of mood disorders, as evidenced by the decreased GABA levels in the plasma and cerebrospinal fluid, in acutely depressed patients.\textsuperscript{[39]}

Glutamate and N-methyl-d-aspartate (NMDA) receptors are implicated in the pathophysiology of depression.\textsuperscript{[13,40]} Although most studies in unipolar depression report decreased glutamate levels in the frontal lobe, a majority of studies on bipolar patients suggest higher glutamate / glutamine levels. Thus, the direction of change seems to be opposite in bipolar and unipolar affective disorders: a hyperglutamatergic state in the bipolar disorder and a hypoglutamatergic state in the unipolar disorder.

Treatment effect
It is not clear whether these abnormalities in depression are trait markers or state markers. A useful way to delineate trait/state markers is by assessing the brain metabolites before and after treatment. Although there are discrepant results in these longitudinal studies, most of them show that the abnormalities are reversible with treatment and possibly state-dependent.

Effect of electroconvulsive therapy and selective serotonin reuptake inhibitor
Decreased Glu/Gln in ACC and PFC were reported to improve after ECT.\textsuperscript{[8,13]} Similarly, there was an increase in occipital GABA\textsuperscript{[21]} and hippocampal choline after ECT.\textsuperscript{[14]} In addition, an increase in occipital GABA was noted after treatment with selective serotonin reuptake inhibitor (SSRI).\textsuperscript{[21,41]} These suggest that MRS abnormalities are more likely to be ‘state markers’.

However, this view is not universally accepted, as discrepant results are present in other studies. In one study, depressed patients had decreased occipital GABA levels even in the recovered phase, raising the possibility of trait vulnerability to mood disorder.\textsuperscript{[42]} In addition, an increase in occipital GABA is noted in healthy volunteers after SSRI (Citalopram) treatment.\textsuperscript{[33]} Thus, with the current reports, it is difficult to conclude whether the improvement noted after treatment is a reflection of change in the pathophysiology or a confounding effect of the medication.

Effect of Yoga
Streeter and colleagues\textsuperscript{[44]} assessed the effect of yoga on the brain GABA levels. They assessed GABA/creatinine ratio in yoga practitioners and non-practitioners before and after a 60-minute session of yoga. A reading task for 60 minutes was
given to non-practitioners. There was a 27% increase in the brain global GABA levels in yoga practitioners. The authors concluded that the practice of yoga should be explored for disorders with low GABA levels, such as depression.

**Therapeutic implications**

Renshaw and colleagues measured brain purine levels by proton spectroscopy and found approximately 30% decrease in female depressed patients who subsequently responded to fluoxetine, than in those who did not respond.[43] These preliminary findings suggest that MRS could possibly predict response to treatment.

Magnetic resonance spectroscopy is also useful in determining the pharmacokinetics of therapeutic compounds in brain. This is an important use to explore the dose-dependent therapeutic effect as well as the side effects following abrupt discontinuation. In a study comparing fluoxetine and paroxetine discontinuation, there was a significant decrease in the brain fluorine signal following paroxetine discontinuation, but not fluoxetine, reflecting the difference in their half-lives.[44] There was also a correlation between the clinical effects and the brain drug levels, suggesting a dose-dependent response.

**CONCLUSIONS AND FUTURE DIRECTIONS**

Proton MRS studies in depression have shown abnormalities in different metabolites like NAA/Cr, GABA, choline, and glutamate/glutamine in different regions of the brain. These findings are consistent with other morphometric and clinical studies and support the proposed pathophysiological theory of dysfunction in neuronal circuits involving the frontal cortex, limbic cortex, and basal ganglia.

As reviewed, studies in MRS have contrasting findings, possibly due to methodological issues, importantly, the confounding effect of psychotropic drugs and heterogeneous samples. Antidepressants have a significant effect on MRS findings, and thus, inclusion of psychotropic naive subjects is preferred in future studies. In addition, it is preferable to include a specific clinical subgroup such as familial depression or a subgroup based on age at onset, to decrease the heterogeneity in the sample. Use of higher strength magnets will help in a better delineation of individual metabolites.

Further studies are required to examine whether these changes seen in the symptomatic state are present in unaffected relatives, for elucidating the endophenotypes. Identifying the biochemical markers of treatment response will help to develop individualized pharmacological treatment.

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