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REVIEWS

Selective Review of Proton Magnetic Resonance Spectroscopy in Schizophrenia

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Abstract | Magnetic Resonance Spectroscopy (MRS) offers a unique opportunity to measure brain metabolites in-vivo, and in doing so enables one to understand the brain function and cellular processes implicated in the pathophysiology of psychiatric disorders. MRS, in addition to being non-invasive, is devoid of radioactive tracers and ionizing radiation, a distinct advantage over other imaging modalities like positron emission tomography and single photon emission computed tomography. With advances in MRS technique it is now possible to quantify concentrations of relevant compounds like neurotransmitters, neuronal viability markers and pharmacological compounds. Majority of the MRS studies have examined the neurometabolites in schizophrenia, a common and debilitating psychiatric disorder. Abnormalities in N Acetyl aspartate and Glutamate are consistently reported while the reports regarding the myoinsoitol and choline are inconsistent. These abnormalities are not changed across the illness stages and despite treatment. However, multiple technical challenges have limited the widespread use of MRS in psychiatric disorders. Guidelines for uniform acquisition and preprocessing are need of the hour, which would increase the replicability and validity of MRS measures in psychiatry. Finally long term, prospective, longitudinal studies are required in different psychiatric disorders for potential clinical applications.

1 Introduction

Magnetic Resonance Spectroscopy (MRS) is a non-invasive, non-radioactive procedure that allows quantification of several metabolites in specific regions of the human brain. MRS provides unique opportunity to examine different neuro-metabolites in-vivo, and helps in examination of molecular pathophysiology of different neuropsychiatric disorders. MRS, in addition to being non-invasive, is devoid of radioactive tracers and ionizing radiation, a distinct advantage over other imaging modalities like Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT). Hence, in the last two decades a significant number of studies have employed MRS to study the molecular pathophysiology of different neuropsychiatric disorders like schizophrenia, bipolar disorder, depression.[1] Majority of the MRS studies have examined the neurometabolites in schizophrenia, a common and debilitating psychiatric disorder. In this selective review I will outline the major MRS findings in schizophrenia and discuss the potential applications. For the benefit of readers of this journal a brief outline of schizophrenia is presented initially, followed by a review of the previous MRS studies.

2 Schizophrenia

Schizophrenia is a common psychiatric disorder with debilitating course affecting roughly 1% of population.[2] Worldwide, schizophrenia accounts

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for 2.6% of total disability adjusted life years, and 4.9% of years lived with disability,[3] making it one among the top ten causes of disability. Schizophrenia is increasingly recognized as a complex syndrome with heterogeneous clinical symptoms. Features of schizophrenia differ between patients as well as within the same patient over the course of illness. The symptoms of schizophrenia comprise positive symptoms (delusions, hallucinations), negative symptoms (apathy, amotivation, flat affect, decreased socialization etc.), and cognitive symptoms (impairments in memory, attention, executive functions etc.). A multi factorial etiological model with an interaction between genetic and environmental risk factors has been proposed.[4] Currently, the treatment is primarily pharmacological with dopamine blocking compounds which have proven efficacy in treating positive symptoms, but only modest efficacy in treating cognitive deficits and negative symptoms.

Schizophrenia has onset in adolescence and early adulthood and runs a chronic course with varied outcome. A majority of individuals with schizophrenia have debilitating course with poor social and occupational functioning even after remission of their psychotic symptoms like delusions and hallucinations. Only a minor proportion has complete recovery from the symptoms, but even they continue to be at high risk for relapse and often require indefinite prophylactic treatment. Among the neurotransmitter theories, dopamine hypothesis is the most widely accepted heuristic model of schizophrenia with treatment implications. Based on antipsychotic effect[5–8] and stimulant induced psychotic symptoms,[9] the original hypothesis suggested schizophrenia to be a disorder of general dopaminergic hyperactivity.[10,11] However, this hypothesis could not explain the negative and cognitive symptoms though it could explain the *antipsychotic* action of available agents.[12] Consequently, a modified dopamine hypothesis premised on regional dopamine differences[13] was proposed. This second version proposed subcortical hyperdopaminergia and cortical hypodopaminergia as underlying the symptoms of schizophrenia based on the finding that Prefrontal Cortex (PFC) dopamine neuron lesions result in increased dopamine levels, dopamine D_2 receptor density in striatum[14] and neuroimaging finding of lower metabolic activity of PFC termed as 'hypofrontality'.[15,16] A third version of the dopamine hypothesis, which positions dopamine dysregulation as the final common pathway to psychosis in schizophrenia,[17] is also proposed.

3 Magnetic Resonance Spectroscopy in Neuropsychiatry—Principle and Procedure

The principle of MRS is outlined elsewhere[1] and in other articles of this issue. MRS 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 proton 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 field, and thus resonate at different frequencies. These small differences in frequency are processed using Fourier transformation and plotted on a graph as output. This output is called as 'MRS spectrum', and has a frequency in parts per million along X-axis and signal amplitude along Y-axis. Specific nuclei contained in a metabolite give rise to either a single peak or multiple peaks that are uniquely positioned along frequency axis, and the peak position is known as chemical shift. Area under curve gives the tissue concentration of each metabolite. Thus, MRS spectrum reflects the biochemical composition of brain and each metabolite is identified by its unique position. A variety of factors determine the type of MRS used in a study; important among them are region of interest, nuclei of interest and field strength of magnet. MRS provides selection of a particular region of brain for analysis known as 'region of interest'. Region of interest is determined by selecting appropriate voxel—a volume element representing a value in 3-dimensional space, analogous to a pixel in 2-dimensional space. One needs to remember that the metabolites of interest occur in gray and white matter of brain, but not the cerebrospinal fluid. So, the placement of voxel is critical; if the voxel (the area from where the spectrum is acquired) contains more CSF then the measured concentrations will be less than the actual concentration. The field strength of magnets used is important as higher filed strength magnets offer better sensitivity, signal to noise ratio and spatial resolution. Generally different studies have looked at the metabolites of interest in schizophrenia patients in comparison with healthy controls. Few studies have examined the relation between the stage of illness and effect of treatment on these metabolites.

3.1 *Compounds relevant to MRS in psychiatry*

A number of isotopes namely proton [1H], carbon [13C], phosphorus [31P], lithium [7Li],

fluorine [19F] and sodium [23Na] are used in MRS in psychiatry. While each isotope has its own application, proton [1H] and phosphorus [31P] are widely used in psychiatric clinical research due to their abundance, and as they allow examination of metabolites important in the brain metabolism. However, other isotopes like lithium [7Li] and fluorine [19F], which are absent in physiological systems, are sometimes used to examine the pharmacological properties of medications like lithium, fluoxetine and fluvoxamine. Though hydrogen atom is present in most of the molecules in brain, only those metabolites that are sufficiently small and mobile are able to generate clinically detectable MR spectra, and those present in sufficiently high concentration can be detected using the typical proton spectra. Using a typical proton spectrum N-acetyl aspartate, choline, combined creatine and phosphocreatine, glutamate, myoinositol, and lactate can be measured. Phosphorus [31P] spectroscopy is predominantly used for assessing membrane phospholipids and high-energy metabolism as it quantifies the resonances of phosphomonoesters (PMEs), phosphodiesters (PDEs), inorganic orthophosphate (Pi), phosphocreatine (PCr) and the nucleoside adenosine triphosphate (ATP).

4 Important MRS Findings in Schizophrenia

4.1 *N Acetyl Aspartate (NAA)*

NAA functions in the brain as an acetyl donor for acetyl coenzyme A and takes part in lipid biosynthesis including myelin.[18] NAA is considered as a putative neuronal marker as it is localized only in neurons but not in glial cells or blood.[19] Thus, NAA concentration measured by MRS is considered as a marker of neuronal viability and function.[20] A reduction in NAA concentration possibly reflects an underlying neuronal loss. Studies examined NAA or NAA/Cr in frontal lobes, temporal lobes, thalamus, corpus callosum, basal ganglia, hippocampus and cerebellum and consistently reported decreased NAA in schizophrenia compared to controls in frontal lobes, temporal lobes, thalamus, corpus callosum and cerebellum. In contrast, no significant reduction in basal ganglia is reported.[21,22]

4.2 *Glutamate/Glutamine*

Glutamate is the major excitatory amino acid in brain, and glutamatergic abnormality has been well documented in schizophrenia. Abnormality in glutamate receptor, in particular N-methyl-D-Aspartate (NMDA) receptor dysfunction, has been the focus of several investigations. Drugs like ketamine and phencyclidine (PCP), which are NMDA-receptor antagonists, produce symptoms that resemble psychosis as seen in schizophrenia[23–25] providing further credentials. Hence, studies have measured the concentration of glutamate in schizophrenia using MRS. However, measurement of glutamate concentration in-vivo is challenging as glutamate is present in both active and inactive forms. After being released by presynaptic neurons, Glutamate (Glu) is taken up into glial cells and rapidly converted to Glutamine (Gln). Gln is subsequently transported back to neurons and reconverted to Glu. Both the physiologically active forms, Glu and inactive form Gln, are measured together (Glx) using lower strength magnets and separately using higher magnet strength. Moreover, glutamate levels decrease with age in healthy individuals, making interpretations difficult.[26] The reports from individual studies are inconsistent. A meta-analysis of 24 studies examining glutamatergic abnormality in schizophrenia reported lower glutamate, higher glutamine in frontal lobes of patients. Interestingly, there was no difference in the Glx between patients and healthy controls. No differences in Glu between patients and controls were observed in hippocampus and thalamus. In addition, the same meta-analysis also reported Glu and Gln levels to decrease progressively with age in the frontal region of patients with schizophrenia, suggesting a possible progressive loss of synaptic activity.[27]

4.3 *Choline*

Choline is an essential precursor of the neurotransmitter acetylcholine and membrane lipids, phosphatidylcholine and sphingomyelin.[28] The Cho peak is considered a potential biomarker for the status of membrane phospholipid metabolism,[18,29] and an elevated Cho signal most likely reflects an increase in membrane turnover.[30] Studies in schizophrenia have reported conflicting results with respect to choline; both increased and decreased levels of choline are reported in the basal ganglia, hippocampus and dorsolateral prefrontal cortex (DLPFC) in schizophrenia.[31–36]

4.4 *Gamma Amino Butyric Acid (GABA)*

Postmortem studies have consistently demonstrated a decrease in the GABAergic potential of specific interneurons in the frontal cortex and hippocampus of schizophrenia patients (Maddock et al. 2012). Reduction in GABA concentration was reported in the visual cortex of schizophrenia patients, however other studies reported absence of difference.[37–39]

4.5 *Myoinositol*

Inositol has a function in osmoregulation in brain glial cells. Glial cells store myoinositol and then gradually pass on to neurons, where it becomes a precursor of phosphoinositide.[40] Myoinsoitol is also the precursor for the regeneration of phosphatidylinositol in the inositol phosphate second messenger system. Findings from studies examining myoinsoitol are not consistent and have reported differing findings.[22,41,42]

5 Correlation with Stage of Illness

While the NAA abnormalities in schizophrenia compared to healthy controls are established, it is not clear whether regional brain NAA changes vary according to illness stage. Most of the studies are cross sectional in nature, and hence it is difficult to draw definitive conclusions. One meta-analysis examined the influence of stage of illness on MRS measures; authors compared MRS measures in people who are at risk of developing schizophrenia, first episode schizophrenia and chronic schizophrenia patients. There was no difference between first episode schizophrenia and chronic schizophrenia, since both groups had significant reductions in NAA levels in frontal lobe, temporal lobe, and thalamus, indicating a lack of progression. Those at high risk of schizophrenia had NAA reduction only in thalamus but not in the frontal lobe.[43] However, as the group of individuals at risk of developing schizophrenia is a heterogeneous with only 20% converting to schizophrenia, findings indicate NAA reduction in thalamus to be a trait marker of schizophrenia risk or, alternatively, might be the first regions to be affected by the illness.

6 Effect of Antipsychotic Treatment

Compared to numerous cross-sectional studies comparing schizophrenia patients and controls, very few studies have examined the effect of treatment on MRS measures. The results from studies examining the change in NAA after antipsychotic treatment are inconsistent. Majority of the studies have reported absence of change in NAA.[32,44–47] However, few other studies have reported normalization of abnormal NAA levels in DLPFC[48] and temporal cortex[49] following treatment. These clinical observations are supported by animal studies, which also suggest the absence of effect of different antipsychotic medications on NAA levels.[50–52] In contrary to NAA studies, MRS studies examining Glx have reported decrease in Glx in prefrontal cortex, thalamus and caudate following treatment.[44,47,53]

7 Challenges for Clinical Applications

Despite being available for nearly two decades, MRS has been an underutilized imaging utility in psychiatry. One major concern is the validation/replication of MRS findings, which is relatively low in comparison to other neuroimaging methods; absence of uniform methods for MRS acquisition and post-processing procedures may account for the differing results. There is an immediate need for guidelines to report MRS

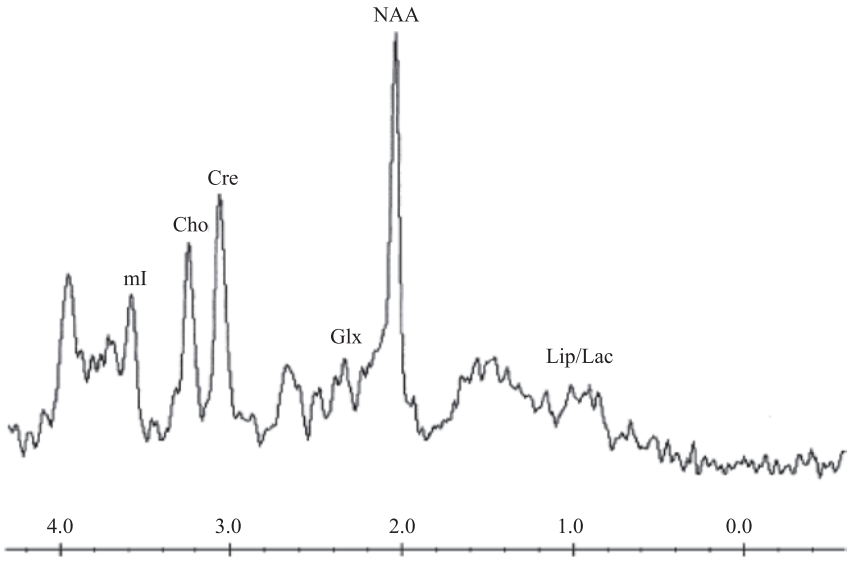

Figure 1: [1H] MRS spectrum of healthy brain from anterior cingulate cortex (Cho-choline; Cre-creatine; NAA-N-acetyl-aspartate; Lip-lipids; Lac-lactate; Glx-glutamate and glutamine; mI-myo-inositol).

findings so that the findings could be replicated. Some of the other reasons for underutilization of MRS are, relatively low signal to noise ratio in comparison with structural and functional magnetic resonance imaging; requirement of specialized hardware and sequences and requirement of higher strength magnet for separating individual metabolites in the spectrum. Another major limitation is the poor spatial resolution; MRS quantifies the metabolite of interest in the parenchyma and not specific to synaptic abnormalities.[54] Need for a skilled personnel to properly place the voxel on the region of interest is another challenge for replication of findings. Currently available methods allow us MRS measurements only in few voxels of interest limiting the simultaneous measurements across multiple brain regions. Introduction of whole brain MRS may overcome this limitation. In terms of study designs prospective, longitudinal, treatment guided studies are required in comparison to the current practice of cross sectional studies. Moreover, very few studies have compared the utility of MRS measurements as diagnostic biomarker.

8 Conclusions and Future Directions

MRS offers a unique opportunity to measure brain metabolites in-vivo, and in doing so enables one to understand the brain function and cellular processes implicated in the pathophysiology of psychiatric disorders. With advances in MRS technique concentrations of relevant compounds, namely neurotransmitters, neuronal viability markers and pharmacological compounds can be quantified. However, multiple technical challenges have limited the widespread use of MRS in clinical population. Guidelines for uniform acquisition and preprocessing are need of the hour which would increase the replicability and validity of MRS measures in psychiatry. Finally long term, prospective, longitudinal studies are required in different psychiatric disorders for potential clinical application.

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