MRI and MRS of Neuropsychiatry

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1 INTRODUCTION

MRI and MRS studies are becoming increasingly important in neuropsychiatry. In this chapter, the contributions will be considered of such studies to our understanding of schizophrenia, mood disorders, anxiety disorders, obsessive-compulsive disorder, eating disorders, attention deficit hyperactivity disorder (ADHD), psychoactive substance use, Alzheimer’s disease, Lewy body disease and Binswanger’s disease, Huntington’s disease, autism, electroconvulsive therapy, dyslexia, brain changes following incomplete spinal injury in humans, and drug monitoring.

2 SCHIZOPHRENIA

Many studies using MRI have been carried out on patients with schizophrenia since 1983. In a well-researched critical review of these by Chua and McKenna, it was found that the only well-established structural abnormality in schizophrenia is lateral ventricular enlargement; this is modest and overlaps with ventricular size in the normal population. The authors of the review came to the following conclusions: ‘there is no consistent evidence from MRI studies for a global reduction in brain size in schizophrenia, and only a minority of studies have pointed to a focal reduction in the size of the frontal lobes. However, the numbers of positive and negative replications are approximately equal for the finding of reduced temporal lobe size, and when the hippocampus and amygdala (and perhaps also the parahippocampal gyrus) are specifically considered this turns into a slight majority in favour of reduced size. A reasonable conclusion might therefore be that, while not yet established beyond reasonable doubt, it is likely that any brain substance abnormality in schizophrenia will be found to be localised to the temporal lobe, where it will be predominantly subcortical and perhaps also predominantly left-sided.’

Recently developed techniques of subvoxel registration of high-resolution three-dimensional (3D) serial MR scans and quantification of changes thereby discovered have just started to be applied to various aspects of this disorder. For example, when first-episode schizophrenic patients were classified according to Gruzelier’s syndromal model, it was found that, compared with normal controls, over an 8-month period patients who were ‘withdrawn’ showed progressive ventricular enlargement, with an increase in ventricle-to-brain volume ratio. In contrast a group of ‘active’ patients showed a reduction in ventricle-to-brain volume ratio, with a change that was opposite in sign and smaller in magnitude. These findings suggest that opposite patterns of functional hemispheric activation early in the course of schizophrenia may be associated with strikingly different structural cerebral changes. These techniques have also found application in testing specific predictions of Horrobin’s neuronal membrane phospholipid model of schizophrenia. In the first example of this, it has been found that in a patient with long-standing disease not being treated with conventional medication, sustained remission of positive and negative symptoms of schizophrenia associated with treatment with the omega-3 fatty acid eicosapentaenoic acid (EPA; Kirunal) was accompanied by a reversal of cerebral atrophy (Figure 1).

Using 31P MRS to study the prefrontal cortex in schizophrenia, a number of groups, including Pettingrew and colleagues and Stanley and colleagues, have reported changes in membrane phospholipid metabolism, irrespective of antipsychotic medication status, with reduced levels of phosphomonoesters (precursors of phospholipid biosynthesis) and increased levels of both phosphodiesterphospholipid breakdown products) and intracellular magnesium ions. It has been suggested that these findings may be fundamentally related to the pathophysiology of schizophrenia, with the reduced levels of phosphomonoesters being caused by reduced biosynthesis or altered degradation and the elevated levels of phosphodiesterphospholipid breakdown products being associated with increased activity of phospholipase A2 or A1, or perhaps decreased phosphodiesterase activity. An alternative explanation involves a putative disturbance of metabolic compartmentation of phosphatidylcholine biosynthesis.

Many studies using proton MRS have demonstrated a reduction in the neuronal marker N-acetylaspartate, particularly in the left temporal lobe. In a recent study combining this technique with MRI, the volume of cortical gray matter was found to be reduced in patients with schizophrenia, while the N-acetylaspartate signal intensity from a comparable region was normal; by comparison, the volume of cortical white matter was normal while the N-acetylaspartate signal intensity from a comparable region was reduced. The lack of reduction in gray matter N-acetylaspartate signal intensity suggests that the cortical gray matter deficit involved both neuronal and glial compartments, rather than a neurodegenerative process in which there is a decrease in the neuronal relative to the glial compartment. The reduced white matter N-acetylaspartate signal intensity without a white matter volume deficit may reflect abnormal axonal connections.

3 MOOD DISORDERS

To date there have been relatively few MR studies of mood disorders and the findings are not consistent. For example, ventricular enlargement is an inconsistent finding in depression (using MRI or computed tomography (CT)); when it has been found it has sometimes been shown to be positively correlated with the length of illness. Neither first-episode bipolar disorder nor first-episode major depression appear to be associated with ventricular enlargement, however. Another inconsistent finding is the possibility of an increased frequency of signal hyperintensities on T2-weighted scans in elderly depressed patients, which may be associated with poor cognitive perform-
Figure 1  MRI in a patient with long-term schizophrenia. (a) Transverse image of the brain 12 months prior to commencing treatment with eicosapentaenoic acid (EPA). (b) Transverse image of the brain at baseline (0 months) with respect to EPA treatment. (c) Registered difference image of the baseline scan minus the scan at −12 months ((b) minus (a)). The dark lines around the ventricles are caused by a decrease in brain size. (d) Registered difference image of the scan at 6 months minus the scan at baseline (0 months). The white lines around the ventricles are caused by an increase in brain size. Changes are also seen in the cerebral cortex, with narrowing evident in some sulci and increased volume evident in some gyri.

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ance. Although such hyperintensities may be a marker of underlying pathology, they are by no means specific to depression and indeed may also occur in older normal controls. It has been reported that the presence of such hyperintensities in both the basal ganglia and the pontine reticular formation in patients aged 65 years and over is associated with a poor response to antidepressant monotherapy. It has also been suggested that treatment-resistant chronic unipolar depression is associated with reduced gray matter density in the left temporal cortex, including the hippocampus. Studies using 31P MRS and 1H MRS have indicated possible abnormalities in membrane phospholipid metabolism, high-energy phosphate metabolism, and intracellular pH in mood disorders.

4 ANXIETY DISORDERS

There have been very few MR studies of anxiety disorders, perhaps because anxiety and claustraphobic symptoms constitute a recognized cause of incomplete or cancelled MR examinations. In one 31P MRS study of the frontal lobes in panic disorder, no significant differences were found between patients and controls in 31P metabolite levels, although a significant asymmetry (left greater than right) of phosphocreatine concentration was found in the patients; raised intracellular pH in 2 out of 18 of the patients may have resulted from respiratory alkalosis secondary to hyperventilation in the anxiety state.

5 OBSESSIVE-COMPULSIVE DISORDER

Structural neuroimaging studies indicate that at least a subgroup of patients with obsessive-compulsive disorder may have abnormal basal ganglia development. Although not all such studies demonstrate reduced volumes of these structures, it is noteworthy that a reduced level of the neuronal marker N-acetylaspartate has been found in either the left or right corpus striatum in obsessive-compulsive disorder using proton MRS, even when volumetric MRI studies of the same patients do not show reduced volumes. Hence the inconsistent volumetric findings may reflect the relatively poorer sensitivity of MRI morphometry for detecting neuronal loss compared with proton MRS measurement of N-acetylaspartate.

6 EATING DISORDERS

The CT finding of cerebral atrophy in patients with eating disorders has been replicated using MRI. Female patients with anorexia nervosa and bulimia nervosa have been reported to have smaller pituitary glands than matched controls. In the absence of any other pituitary pathology, this atrophy is likely to be secondary to nutritional or endocrine alterations. Other reported structural abnormalities include enlarged lateral ventricles with dilated cortical and cerebellar sulci and subcortical signal hyperintensities on T2-weighted scans.

In a small cerebral 31P MRS study of anorexia nervosa before treatment, increased levels of phosphodiester were found compared with controls, while decreased phosphomonesters were found that were associated with malnutrition reflected by endocrinological abnormalities. These data suggest that severe malnutrition in patients with anorexia nervosa may result in an abnormality in membrane phospholipid metabolism, which might be related etiologically to the cerebral atrophy of anorexia nervosa. In another study of patients with anorexia nervosa recording proton MR spectra from parieto-occipital white matter immediately following an interval of excessive loss of body mass, higher signal intensity ratios of choline-containing compounds relative to total creatine and lower ratios of N-acetylaspartate relative to choline-containing compounds were found compared with controls, suggesting that starvation may be associated with an abnormal neuronal membrane turnover in the white matter of the brain.

7 ATTENTION DEFICIT HYPERACTIVITY DISORDER

Recent MRI studies have shown that some regions of the frontal lobes (anterior superior and inferior) and basal ganglia (caudate nucleus and globus pallidus) are about 10% smaller in ADHD groups than in control groups of children, with the right caudate nucleus being larger, or left caudate being smaller, in children with ADHD. These findings are consistent with theories implicating frontal-striatal circuit abnormalities in this disorder. Also in harmony with this theory is the fact that the corpus callosum has been found relatively consistently to be smaller in children with ADHD, particularly in the region of the genu and splenium. Recently, the cerebellum has been systematically studied in this disorder; the vermal volume was found to be significantly smaller in a large sample of boys with ADHD than in matched controls. This reduction involved mainly the posterior inferior lobe (lobules VIII to X) but not the posterior superior lobe (lobules VI to VII) and suggests that perhaps cerebello-thalamo-prefrontal circuit dysfunction may subserve the motor control, inhibition, and executive function deficits seen in this disorder.

Advances in genetic studies of ADHD have occurred while these advances in structural neuroimaging have been taking place. An important example of how both of these investigative techniques can complement each other relates to polymorphisms of the D4 dopamine receptor (DRD4). One allele with seven tandem repeats in exon 3 (DRD4*7R) has been associated with ADHD, and when this putative association was investigated by Castellanos and colleagues, it was found that cerebral MRI measures, previously found to discriminate ADHD patients from controls, did not differ significantly between subjects having and those lacking a DRD4*7R allele. Hence the MRI results did not support the reported association between DRD4*7R and the behavioral or brain morphometric phenotype associated with ADHD.

8 PSYCHOACTIVE SUBSTANCE ABUSE

Chronic alcoholism is associated with MRI-detectable atrophic changes in many regions of the brain, including the cerebral cortex, cerebellum, and corpus callosum. Hippocampal volume reduction is proportional to the reduction in volume of the brain as a whole. It has been found that over a 5-year period brain volume shrinkage is exaggerated in the pre-
frontal cortex in normal aging but with additional loss occurring in the anterior superior temporal cortex in alcoholism. This association of cortical gray matter volume reduction with alcohol consumption over time suggests that continued alcohol abuse results in progressive cerebral tissue volume shrinkage.

MRI, but not CT, has been shown to be useful in confirming the diagnosis of acute Wernicke’s encephalopathy. In one recent study, increased T2 signal of the paraventricular regions of the thalamus and the mesencephalic periaqueductal regions was observed in patients with Wernicke’s encephalopathy compared with both controls and asymptomatic chronic alcohol abusers, with the sensitivity of MRI in revealing evidence of this disease being 53% and the specificity 93%. It should be borne in mind, however, that the absence of abnormalities on MRI does not exclude this diagnosis.

With MRI, widespread cerebral atrophy is seen in alcoholic Korsakoff patients; this is largely subcortical and does not develop independently of the diencephalic pathology. It should be noted that while chronic alcohol abuse is associated with mammillary body and cerebellar tissue volume loss, these markers do not distinguish accurately between amnesic and nonamnesic patients; mammillary body atrophy that is detectable on MRI is not necessary for the development of amnesia in alcoholic patients.

It has recently been shown that cerebral MRI may be of use clinically in the differential diagnosis of chronic alcohol abuse and schizophrenia. In this study, patients with both disorders showed widespread cortical gray matter volume deficits compared with controls, but only those with chronic alcoholism showed white matter volume deficits. The patients with schizophrenia had significantly greater volume deficits in prefrontal and anterior superior temporal gray matter than in more posterior cortical regions. By contrast, the deficits in the patients with alcoholism were relatively homogeneous across the cortex. For white matter, the deficits in the patients with alcoholism were greatest in the prefrontal and temporoparietal regions. Although both patient groups had abnormally larger cortical sulci and lateral and third ventricles than the controls, the patients with alcoholism had significantly larger sulcal volumes in the frontal, anterior, and posterior parieto-occipital regions than those with schizophrenia.

Reduced levels of N-acetylaspartate and choline have been found using cerebral proton MRS in chronic alcoholism. The reduction of N-acetylaspartate is consistent with neuronal loss while the reduction in choline may be related to neuronal membrane lipid changes.

In a recent large MRI and proton MRS study comparing asymptomatic abstinent cocaine users with matched controls, it was found that while the ventricle-to-brain ratio and level of white matter lesions did not differ significantly between the two groups, elevated creatine and myo-inositol in the white matter were associated with cocaine use. The N-acetylaspartate level was normal in the cocaine users, suggesting that there was no neuronal loss or damage in the brain regions examined. It was, therefore, concluded that the neurochemical abnormalities observed might result from alterations in non-neuronal brain tissue.

MRI changes associated with chronic toluene abuse include cerebral atrophy, cerebral and cerebellar white matter T2 hyperintensity, T2 hyperintensity involving the middle cerebellar peduncle and the posterior limb of the internal capsule, and T2 hypointensity involving the basal ganglia and thalamus. Chronic solvent abusers who have white matter MRI changes have been found have a lower performance intelligence quotient, as measured by the Weschler Adult Intelligence Scale – Revised, with a particularly low score on the digit symbol subtest.

In polysubstance abusers, there is MRI evidence of reduced volume of the prefrontal cortex (both left and right) consistent with either atrophy or hypoplasia. Ventriculomegaly has not been found to be a feature. Abnormal cerebral metabolism has been found using 31P MRS in male polysubstance abusers during early withdrawal: increased phosphomonoesters and decreased β-nucleotide triphosphates were found in the abusers compared with controls, indicating that cerebral high-energy phosphate and phospholipid metabolite changes result from long-term drug abuse and/or withdrawal.

9 ALZHEIMER’S DISEASE, LEWY BODY DISEASE, AND BINSWANGER’S DISEASE

The first part of this section considers recent studies focusing on the use of MRI in differentiating Alzheimer’s disease from both normal aging and other causes of dementia. While the finding of cortical or subcortical atrophy on MRI or CT is not pathognomonic of Alzheimer’s disease, hippocampal atrophy provides a useful early marker of the disorder, although further longitudinal and neuropathological study is required. CT- and MRI-based measurements of hippocampal atrophy may provide useful diagnostic information for differentiating patients with probable Alzheimer’s disease from normal elderly individuals.

A recent pilot study has indicated that MRI may have a role in assisting with the clinical differentiation between dementia with Lewy bodies and Alzheimer’s disease. Subjects with known or probable Alzheimer’s disease were found to have significantly smaller left temporal lobes and parahippocampal gyri than those with known or probable Lewy body disease. Medial temporal atrophy was present in 9 out of 11 patients with Alzheimer’s disease and absent in six out of nine patients with Lewy body disease. While two patients with neuropathologically confirmed Lewy body disease had severe medial temporal atrophy, in both concurrent Alzheimer’s disease-type pathology was present in the temporal lobe. Therefore, this pilot study supports the hypothesis that a greater burden of pathology centers on the temporal lobes in Alzheimer’s disease compared with Lewy body disease, unless Lewy body disease occurs with concurrent Alzheimer pathology.

Another recent study has suggested that diffusion-weighted MRI may be useful in the differential diagnosis of subcortical arteriosclerotic encephalopathy (vascular dementia of theBinswanger type) and Alzheimer’s disease with white matter lesions. Apparent diffusion coefficients in the anterior and posterior white matter and the genu and splenium of the corpus callosum were significantly higher in patients with both these disorders compared with age-matched controls, with apparent diffusion coefficient values in the groups with Binswanger’s disease and those with Alzheimer’s disease being almost the same. Apparent diffusion coefficient ratios, defined as diffusion-restricted perpendicular to the direction of nerve fibers, were also significantly higher in both groups of patients than in the

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controls. However, there were regional differences in these ratios in the two disorders, with ratios inBinswanger’s disease being higher in the anterior portions of the white matter while ratios in Alzheimer’s disease were higher in the posterior portions.

In vitro and in vivo $^3$P MRS studies of the brain in Alzheimer’s disease show alterations in membrane phospholipid metabolism and high-energy phosphate metabolism: compared with control subjects, mildly demented patients with Alzheimer’s disease have increased levels of phosphomonoesters, decreased levels of phosphocreatine and probably adenosine diphosphate, and an increased oxidative metabolic rate; as the dementia worsens, levels of phosphomonoesters decrease and levels of phosphocreatine and adenosine diphosphate increase. The changes in oxidative metabolic rate suggest that the brain in Alzheimer’s disease is under energetic stress while the phosphomonoester findings implicate basic defects in membrane metabolism in the brain. Thus, in addition to aiding with diagnosis, $^3$P MRS may provide a noninvasive tool to follow both the progression of this disorder and any response to putative therapeutic interventions.

Proton MRS studies of occipital gray matter show that reduced levels of N-acetylaspartate (presumably reflecting neuronal loss) and increased levels of myo-inositol characterize Alzheimer’s disease. Studies using proton MRS to measure cerebral amino acids have tended to demonstrate increased glutamate levels and sometimes reduced γ-aminobutyric acid (GABA); following neuronal loss, the remaining neurons might be exposed to excess glutamate and relatively low levels of GABA, an imbalance that might be neurotoxic.

10 HUNTINGTON’S DISEASE

Initially, structural neuroimaging studies showed atrophy of the caudate and loss of definition between the caudate and the adjacent ventricle as Huntington’s disease progresses; however more recent studies have also shown cortical atrophy, particularly in the frontal lobes. Using proton MRS, Jenkins and colleagues found that lactate concentrations were increased in the occipital cortex of patients with symptomatic Huntington’s disease compared with normal controls, with the lactate level correlating with duration of illness. Several patients in the same study also showed highly elevated lactate levels in the basal ganglia, while basal ganglia levels of N-acetylaspartate were lowered and choline dramatically elevated, relative to creatine, reflecting neuronal loss and gliosis in this brain region. The authors of this study suggested that these findings are consistent with a possible defect in energy metabolism in Huntington’s disease, which could contribute to the pathogenesis of the disease, and that the presence of elevated lactate might provide a simple marker that could be followed over time noninvasively and repeatedly to aid in devising and monitoring possible therapies. A more recent proton MRS study by Taylor-Robinson and colleagues found an elevated ratio of glutamine and glutamate relative to creatine in the striatum compared with healthy controls, suggesting disordered striatal glutamate metabolism and possibly supporting the theory of glutamate excitotoxicity in Huntington’s disease.

Huntington’s disease is now known to result from expanded CAG repeats in a gene on chromosome 4, a possible consequence of which might be progressive impairment of energy metabolism. Jenkins and colleagues have recently extended their previous studies to examine correlations between proton MRS changes and CAG repeat number. The spectra in three presymptomatic gene-positive patients were found to be identical to normal control subjects in cortical regions, but three in eight showed elevated lactate in the striatum. Similar to recently reported increases in task-related activation of the striatum in the dominant hemisphere, they found that striatal lactate levels in patients with Huntington’s disease were markedly asymmetric (left greater than right). Markers of neuronal degeneration, decreased N-acetylaspartate to creatine and increased choline to creatine ratios, were symmetric. Both decreased N-acetylaspartate and increased lactate in the striatum significantly correlated with duration of symptoms. When divided by the patient’s age, an individual’s striatal N-acetylaspartate loss and lactate increase were found to correlate with the subject’s CAG repeat number, with correlation coefficients of 0.8 and 0.7, respectively. Similar correlations were noted between postmortem cell loss and age versus CAG repeat length. Together, these data provide further evidence for an interaction between neuronal activation and a defect in energy metabolism in Huntington’s disease that may extend to pre-symptomatic subjects.

11 AUTISM

MRI studies of individuals with autism have variously and inconsistently shown evidence of hypoplasia of the cerebellum and brainstem with increased size of the fourth ventricle, increased brain volume (though with relative hypofrontality), and smaller size of the body and posterior subregions of the corpus callosum; in addition, previous pneumoencephalographic and CT studies have described lateral ventricular enlargement while MRI studies in general have failed to show abnormality in limbic structures. The degree of cerebellar hypoplasia is significantly correlated with the degree of slowed attentional orienting to visual cues in both children and adults with autism. It should be noted that even in the absence of abnormal MRI findings, autism may be associated with focal areas of decreased perfusion.

The finding that autism is not necessarily associated with MRI abnormalities is consistent with the results of a recent cerebral proton MRS study comparing 28 patients with autism with both 28 age-matched patients with unclassified mental retardation and 25 age-matched healthy children. The ratio of N-acetylaspartate to choline was lower in the nonautistic patients with mental retardation than in the patients with autism and the controls, and, interestingly, there were no significant differences in this ratio between patients with autism and controls.

A $^3$P MRS study of the dorsal prefrontal cortex of 11 high-functioning autistic adolescent and young adult men and 11 matched normal controls found that the autistic group had decreased levels of phosphocreatine, α-ATP, α-ADP, dinucleotides, and diphosphosugars compared with the controls. When the metabolite levels were compared within each subject group with psychological and language test scores, a common pattern of correlations was observed across measures in the

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autistic group, but not in the control group. As test performance declined in the autistic subjects, levels of the most labile high-energy phosphate compound and of membrane-building blocks decreased, and levels of membrane breakdown products increased. No significant correlations were present with age in either group or with IQ in the control group, suggesting that these findings were not the consequence of age or IQ effects. This study provides some evidence of alterations in brain energy and phospholipid metabolism in autism that correlate with psychological and language deficits.

12 ELECTROCONVULSIVE THERAPY

For many years clinicians have been concerned that electroconvulsive therapy may result in acute cerebral structural changes. Indeed, some retrospective imaging studies using MRI and CT have reported an association between a history of electroconvulsive therapy and cerebral change, particularly affecting the lateral ventricles and/or cerebral cortex. However, recently, a prospective MRI study of four electroconvulsive therapy-naïve depressed patients in which they underwent scanning 1 week prior to their first treatment with electroconvulsive therapy and then again following this treatment showed that, using accurate subvoxel registration and subtraction of serial MR images, there was no significant difference in cerebral structure following electroconvulsive therapy, either within 24 h or after 6 weeks (Figure 2). A proton and $^{31}$P MRS study of three patients found no evidence of changes in lactate or in cerebral energy metabolism following electroconvulsive therapy. However, Woods and Chiu have found, using proton MRS, that electroconvulsive therapy reliably induces an elevation in the lipid signal that resonates at approximately 1.2 ppm and observed a similar increase in brain lipids in a patient with temporal lobe epilepsy temporarily off medication, the signal disappearing following restarting medication. This is of interest given that elevations of brain concentrations of arachidonic acid and other free fatty acids have been demonstrated to occur after seizures induced in animals. Large shifts of potassium ions from the intra- to the extracellular space occur during seizure activity, and free fatty acids have a direct effect on membrane potassium ion conductance, suggesting that free fatty acids may play a primary role in seizure evolution in brain tissue.

13 DYSLEXIA

MRI studies have inconsistently shown reversed or diminished asymmetry, compared with normal, in the brain in children with dyslexia, including loss of the usual left greater than right asymmetry of the lateral ventricles and right greater than left asymmetry of the temporal lobes; loss of the normal left greater than right asymmetry of the planum temporale in adolescents, which correlates with the degree of phonological decoding deficits; reversal of the normal left greater than right asymmetry of the angular gyrus in familial dyslexia; and loss

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Figure 2  MRI in patients receiving electroconvulsive therapy. (a) Transverse $T_1$-weighted MR baseline scan showing the anatomy. (b) Difference image obtained by subtracting the baseline scan from the registered follow-up scan showing no evidence of acute structural changes in the brain following electroconvulsive therapy.
of normal right greater than left asymmetry of the frontal cortices and bilaterally smaller size of the frontal cortices. Inconsistent corpus callosum changes have also been reported.\(^7\)

In the first \(^3^P\) MRS study of dyslexia, Richardson and colleagues found elevated phosphomonoesters in the brain in dyslexia compared with that in controls.\(^7^8\) This finding is consistent with the hypothesis that neuronal membrane phospholipid metabolism is abnormal in dyslexia, with reduced incorporation of phospholipids into neuronal membranes occurring.\(^7^9\)

The first proton MRS study of dyslexia showed lateral differences in the ratios of choline to \(N\)-acetylaspartate and of creatine to \(N\)-acetylaspartate in the temporo-parietal region and the cerebellum in dyslexic subjects but not in controls.\(^8^0\)

14 SPINAL INJURY

The first proton MRS study of the human motor cortex following incomplete spinal cord injury showed elevation of \(N\)-acetylaspartate in this part of the brain compared with normal controls.\(^8^1\) The authors suggested that this might reflect neuronal adaptation to injury, the finding being consistent with the hypothesis that dendritic sprouting occurs in the motor cortex following recovery from incomplete spinal injury in humans. Clinically, this finding also suggests that MRS might provide a noninvasive method for monitoring such patients.

15 DRUG MONITORING

It is possible to use \(^7\)Li MRS directly to measure the cerebral concentration of lithium while \(^1^9\)F MRS can be used to measure the cerebral concentrations of psychotropic drugs containing fluorine, for example the selective serotonin reuptake inhibitor fluoxetine and the antipsychotics trifluoperazine and fluphenazine.\(^8^2\)

16 FUTURE DIRECTIONS

As mentioned above, the recently developed MRI techniques of subvoxel registration of high-resolution 3D serial MR scans and quantification of the changes thereby discovered are only just starting to be applied in neuroimaging studies. The sensitivity and accuracy of these techniques hold great promise for neuroimaging applications and the discovery of important new facts concerning the central nervous system.\(^8^3\)\(^8^4\) For example, they have been used recently to show that volumetric change takes place in the lateral ventricles in the human brain following oral glucose loading (Figure 3).\(^8^5\)

Cerebral MRS is currently used primarily as a research tool in neuropsychiatry; in due course it is likely to become more widely used diagnostically and prognostically.

It seems probable that MRI and MRS will interface more often with other disciplines (for instance molecular genetics, as in ADHD) and other investigative tools (such as transcranial magnetic stimulation).

In summary, MRI and MRS are proving to be extremely useful in neuroscientific and neuropsychiatric research. These powerful noninvasive tools are likely to continue to grow in importance in these fields and to gain ever more important clinical applications.

17 RELATED ARTICLES

Brain Infection and Degenerative Disease Studied by Proton MRS; Brain MRS of Human Subjects; Brain Neoplasms in Humans Studied by Phosphorus-31 NMR Spectroscopy; Brain Neoplasms Studied by MRI; Brain Parenchyma Motion Observed by MRI; Hemodynamic Changes owing to Sensory Activation of the Brain Monitored by Echo-Planar Imaging; Central Nervous System Degenerative Disease Observed by MRI; Chemical Shift Imaging; CSF Velocity Imaging; Intracranial Infections; Localization and Registration Issues Important for Serial MRS Studies of Focal Brain Lesions; Magnetic Resonance Imaging of White Matter Disease; Structural and Functional MR in Epilepsy.

18 REFERENCES


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**Biographical Sketch**