Brain tumors in infants and children are relatively uncommon; approximately 1500 new cases are diagnosed across the United States every year. In adults, most primary brain tumors are supratentorial in location and malignant, with malignant glioma/glioblastoma multi-forme as the predominant histology [1]. In children, roughly equal numbers arise above and below the tentorium; there is a near equal incidence of benign and malignant brain tumors and a wide variety of histological subtypes. Astrocytomas form the largest subgroup, and three quarters of these are low-grade. Embryonal CNS tumors comprise the most common group of childhood malignant brain tumors (21%), and consist of medulloblastoma, supratentorial primitive neuroectodermal tumor (PNET), atypical teratoid/rhabdoid tumor, ependymoblastoma and medulloblastoma [2]. This wide histological variety is reflected by a wide range of imaging appearances of the lesions at MRI. Other unique features of pediatric brain tumors include their propensity to disseminate throughout the subarachnoid spaces, often at the time of presentation, and the unique pathology of tumors diagnosed in neonates and young infants [3].

The appearance of most pediatric brain tumors on conventional MR sequences has been well recorded. However the features of pediatric cerebral neoplasms utilizing techniques that provide information about tissue function or physiology (re spectroscopy, perfusion, diffusion) rather than anatomical information are not well characterized. The wide variety of histological types and the low incidence of brain tumors in children (as compared to adults) make it difficult for individual pediatric centers to collect a significant experience for each tumor type. Multi-institutional collaboration that would permit a faster accumulation of knowledge of the functional imaging footprints of pediatric brain tumors is also difficult to perform: most of the functional imaging techniques have not been validated across institutions and across imaging platforms/MRI machine manufacturers. Thus data sharing and comparative analyses have been difficult to perform.

In this chapter, we will review the challenges facing the neuroimaging community in the characterization, staging and prognostication of pediatric brain tumors. The roles of imaging in treatment planning, assessment of treatment response, surveillance and evaluation of long-term effects will follow. The current status of imaging in each of these areas will also be reviewed. First, we will review some of the newer techniques that focus on tissue function/physiology rather than on anatomical features, as these will be central to meeting the challenges facing modern pediatric neuroimaging.

**Functional imaging and neurooncology**

Functional MRI studies focus on cerebral metabolism, perfusion, vascularity and function. These novel imaging techniques include MR spectroscopy, diffusion, cerebral blood volume mapping and cortical activation mapping. The main challenge facing functional imaging techniques involves their validation: the techniques are still in their infancy, with yearly improvements and modifications in technique. Most are used in research rather than clinical settings, and often demand a significant amount of post acquisition processing that can be performed only in departments with qualified physicists and computer scientists. It will thus be some time before these techniques are robust enough to be used in a more widespread, multi-institutional approach necessary for their validation. Such an attempt is currently under way using the imaging center of the Pediatric Brain Tumor Consortium (PBTC)

MR spectroscopy (MRS) provides information about the presence and amount of hydrogen molecules attached to different cerebral molecular compounds [4]. Hydrogen atoms located on different molecular compounds display intrinsic differences in resonant frequencies due to their differing molecular environment. A spectrum can be generated, which corresponds to a scale of resonant frequencies (or chemical shift) vs. amplitude (concentration). The spectrum represents the metabolic composition of the sampled region of interest or volume element (voxel). Each metabolite peak has a different location along the spectrum. The four most relevant molecular compounds identified within cerebral tissue include N-acetyl-aspartate (NAA, a neuronal marker), choline (a marker of membrane-associated compounds), creatine and phosphocreatine (energy metabolites), and lactate (a by-product of cerebral metabolism).

Different metabolites are seen depending on the length of echo time (TE) used during acquisition. The use of a longer TE (135 or 270 ms) results in cleaner data, but it is limited in the number of metabolites that can be clearly identified. Shorter TE (10 or 20 ms) allows for the identification of metabolites such as myoinositol, glutamine, glutamate, and phenylalanine. The shorter TE has a better signal to noise ratio, but requires more complex analysis before quantification may be
determined. Spectroscopy can generate single-voxel or multi-voxel studies. Multi-voxel studies (or chemical shift imaging, CSI) allow a more comprehensive examination of specific areas or regions of interest (Figure 1); single voxel studies demand typically larger volumes of more homogeneous tissue, have faster acquisition times and better spectral resolution. Technically, MRS is difficult to perform in or near areas of magnetic susceptibility, such as the posterior fossa, the floor of the anterior cranial fossa, near the calvarium, and in hemorrhagic lesions.

MRS is useful in characterization of pediatric tumors [4]. Proton MRS of brain tumors consistently demonstrates a reduction or absence of NAA; and an increase in the choline containing compounds, presumably due to altered membrane metabolism during rapid cell growth and neoplasia (Figure 1). Compared to more benign tumors, malignant glial tumors have higher levels of choline and a lower or absent NAA peak. There are exceptions: for example, the juvenile pilocytic astrocytoma (a benign tumor) typically has very high choline to creatine ratio and often demonstrates presence of lactate (Figure 2). Choline elevation in germinoma (a malignant tumor) can be very mild.

Though histological typing with MRS is generally not feasible, MRS has been successfully used to differentiate posterior fossa medulloblastoma, low-grade astrocytomas and ependymomas in children [5]. MRS can differentiate proliferating tumor from necrosis; in necrosis, there is a depression of neuronal (NAA) and membrane (choline) markers, and elevation of lactate and lipid peaks as a result of metabolic acidosis and tissue breakdown. Spectroscopy also allows for non-invasive monitoring of the response of unresected tumor to therapy, as tumor response is associated with decreasing levels of choline. MRS is especially useful in the case of a deep-seated lesion such as brainstem glioma or a diencephalic tumor. These lesions often are not surgically

Figure 1. Axial FLAIR image (a) of an optic pathway glioma with predominant infiltration in the right optic tracts. Choline map (b) from a multivoxel spectroscopy; elevated choline level is most evident in the chiasm and the right optic tracts. Display of metabolite maps (c) of four regions of interest obtained from the multivoxel study reveal marked elevation of choline and reduction in NAA in the chiasm (box 1) and right optic tract (box 2); mild elevation of choline and significant decrease in NAA in the left optic tract (box 3) suggests tumor infiltration despite the near normal FLAIR signal. Normal spectrum from the left occipital lobe is displayed in box 4.