Imaging Guidance and Definitions

Frontal lobe: Anterior region of hemisphere; anterior to central sulcus, superior to sylvian fissure

Parietal lobe: Posterior region of hemisphere; posterior to central sulcus, anterior to parietooccipital sulcus

Occipital lobe: Posterior to parietooccipital sulcus

Temporal lobe: Inferior to sylvian fissure, anterior to angular gyrus

Insula: Cortical region hidden within depths of lateral (sylvian) fissure; covered by frontal, temporal, parietal opercula

Basal ganglia: Subcortical nuclear masses in inferior hemispheres excluding thalami

Caudate nucleus: "C-shaped" curved nucleus with large head, tapered body, down-curving tail
- Head forms floor/lateral wall of anterior horn of lateral ventricle
- Body borders, parallels lateral ventricle
- Tail follows curve of inferior horn, lies in ventricular roof

Putamen: Located lateral to globus pallidus, separated by lateral (external) medullary lamina

Globus pallidus: Two segments
- Lateral (external), medial (internal) segments separated by internal medullary lamina
- Higher myelin content than putamen (darker on T2)

Thalamus: Ovoid nucleus, extends from foramen of Monro to quadrigeminal plate of midbrain
- Medially forms lateral walls of third ventricle
- Laterally bordered by internal capsule

Corpus callosum: Largest commissure; links hemispheres
- Four parts: Rostrum, genu, body, splenium
- Rostral fibers extend laterally connecting orbital surfaces of frontal lobes
- Genu fibers curve forward as forceps minor, connect lateral/medial frontal lobes
- Body fibers pass laterally, intersect with projection fibers of corona radiata to connect wide areas of hemispheres
- Most fibers from splenium curve into occipital lobes as forceps major

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Cerebral cortex: The thin layer of gray matter covering the surface of each cerebral hemisphere. Gray matter is comprised of the cell bodies of neurons embedded in neuronal and glial cell projections.

White matter: The conducting portion of the nervous system composed of the long processes of neurons, most of which are myelinated, and glial cells. Its boundaries are the cortex and subcortical gray matter, and it includes the internal capsule. Constitutes the majority of the brain volume, and is divided into zones (subcortical, periventricular and subependymal) and larger named bundles including association fibers which connect one cortical area to another within a hemisphere (e.g., cingulum, arcuate fasciculus), commissural fibers which connect the cortices of two hemispheres (corpus callosum and anterior commissure), and projection fibers which connect cortex to subcortical structures including the basal ganglia, thalamus, brainstem nuclei and spinal cord.

Subcortical: The white matter zone localized immediately beneath the cortex

Periventricular: The white matter zone located around the ventricles, between the subcortical and subependymal white matter

Subependymal: The white matter situated immediately adjacent to the ependyma which is the membranous lining of the ventricles. Note that in some contexts, the white matter situated immediately adjacent to the

ventricles (up to 1 cm) is designated as periventricular white matter and the white matter between the subcortical and periventricular white matter is referred to as the deep white matter.

Cerebellum: The large gray and white matter structure in the posterior fossa attached to the dorsal aspect of the pons and rostral medulla by three white matter peduncles, and which forms the roof of the fourth ventricle. It is composed of a midline portion, or vermis, and two large lateral hemispheres. Each hemisphere is composed of anterior and posterior lobes that are divided by the primary cerebellar fissure.

Vermis: The midline portion of the cerebellum divided into superior (anterior) and inferior (posterior) portions by the primary cerebellar fissure

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T2 signal: T2 weighted imaging is one of the basic pulse sequences in MRI and reflects the differences in the T2 relaxation time of tissues. It relies upon the transverse relaxation of the net magnetization vector. T2 weighting tend to have long TE and TR times. This image weighting is useful for detecting edema and revealing white matter lesions.

Diffusion-Weighted Imaging (DWI): Form of MR imaging based upon the diffusion of water molecules within a voxel. The diffusion-weighted image has an associated T2 weighted part. Acquisition must be repeated with gradients oriented in at least three directions in space. With different b-factors (typically b = 0 and 1000 s/mm^2), it is possible to calculate the apparent diffusion coefficient (ADC). The ADC map is independent of T2 weighting and reflects the diffusion coefficient of water in any given voxel. This information is useful in cases of lesion with T2 hyperintense signal, which can misleadingly produce high signal on the DWI trace maps which are also T2 weighted (i.e., ADC helps in differentiation between T2-shine-through and diffusion restriction).

Enhancement: MR imaging contrast agents alter the relaxation times of atoms within body tissues where they are present after oral or intravenous administration, gadolinium being the common agents in use for brain imaging. Enhancement in neuroimaging refers to pathologically increased signal on a T1 weighted image following the administration of intravenous contrast.

Edema / Swelling: Focal or diffuse increase in volume with accompanying increase in water content, most evident by hyperintense signal on T2 weighted imaging or FLAIR sequence with associated mass effect

Atrophy / Volume loss: Focal or diffuse decrease in expected volume, with or without abnormal signal (i.e., gliosis)

Encephalomalacia / Gliosis: Response to damage to the central nervous system. Encephalomalacia refers to localized softening of the brain substance, due to prior damage (e.g., hemorrhage or inflammation), and can be cystic in nature. Gliosis reflects nonspecific reactive change of glial cells in response to damage to the central nervous system. Encephalomalacia, with or without cystic change, and gliosis can each occur in isolation though, more often than not, occur in combination.

Calcifications: The accumulation of calcium deposits in a body tissue. It normally occurs in the formation of bone, but calcium can be deposited abnormally in soft tissue. Calcifications are more readily apparent on CT imaging where they appear hyperdense. In MR imaging, the T2*weighted gradient-echo or susceptibility weighted (SWI) images are particularly useful in the evaluation for calcification because they are quite sensitive to the magnetic susceptibility changes and local heterogeneity of magnetic fields caused by calcifications*.

Hemosiderin: Chronic breakdown product of hemorrhage and is best detected on MR imaging. The T2*weighted gradient-echo or susceptibility weighted (SWI) images are most sensitive to hemosiderin deposition because they are quite sensitive to the magnetic susceptibility changes and local heterogeneity of magnetic fields caused by hemosiderin*.

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Iron: Iron deficiency and iron excess have been associated with pathophysiology of different brain disorders. Iron accumulation is best demonstrated on MR imaging. The T2*weighted gradient-echo or susceptibility weighted (SWI) images are most sensitive to iron deposition because they are quite sensitive to the magnetic susceptibility changes and local heterogeneity of magnetic fields caused by iron*.

*Differentiation between calcification, hemosiderin, and iron on MR imaging can be difficult. CT imaging plays a complementary role in helping to confirm the presence or absence of calcification.

Malformation of cortical development: Refers to macroscopic or microscopic abnormalities of the cerebrum that occur due to interruption to the normal steps of formation of the cortical plate. The pathogenesis is multifactorial and includes genetic mutations or environmental insults which may be acquired in utero at different stages of brain development, or occur during the perinatal or postnatal period after corticogenesis. This definition encompasses disorders of neuronal precursor proliferation, migration, and organization. Of note, this category includes disorders that occur at a distance from the cortex itself such as gray matter heterotopia.

Partial agenesis: In neuroradiology**,** refers to failure of a structure to develop during embryonic growth due to the absence of primordial tissue. In partial agenesis, there is incomplete development, in complete agenesis, the structure fails to develop.

Complete agenesis: See above

Hypoplasia: Refers to an inadequate or below-normal number of cells and is a congenital condition. Examples in neuroimaging include hypoplasia of the corpus callosum, hypoplasia of the cerebellum, hypoplastic hippocampi, etc.

Polymicrogyria: (PMG) is a developmental malformation of the human brain characterized by an excessive number of small gyri located on the surface of the brain. It may be focal or more generalized. There is a predilection for the perisylvian region which is involved in 80% of patients and bilateral involvement is common (60%). On MRI, Polymicrogyria has signal characteristics similar to normal gray matter. The subjacent white matter is not infrequently hyperintense on T2 weighted images (20-27%) which may relate to dilated perivascular spaces. Occasionally (< 5%), the abnormal cortex demonstrates regions of calcification such as seen in congenital infections.

Heterotopia: Gray matter heterotopias are due to interruption of the normal migration of neurons early in development from the periventricular telencephalic germinal matrix to the cortex. They may be single or multiple and may be due to genetic abnormalities, infection, or trauma. Gray matter heterotopias can be divided macroscopically into the following subcategories, the presence of which may define the underlying condition:

- Nodular heterotopias
    - Subependymal heterotopia: most common
    - Subcortical heterotopia
- Diffuse heterotopias
    - Band heterotopia
    - Lissencephaly: types 1 and 2
    - Laminar heterotopia

On MRI the heterotopic tissue follows the gray matter tissue characteristics on all sequences. The margins of the heterotopia may be indistinct.

Brain myelination begins in utero and continues through the first few years of life. The first structures to myelinate are in the dorsal brainstem with subsequent structures myelinating according to several broad patterns: inferior to superior (i.e., brainstem and posterior fossa before cerebral hemispheres), central to peripheral (i.e., basal ganglia and internal capsule before subcortical white matter), and posterior to anterior

(i.e., occipital lobes before frontal lobes). The normal myelination sequence has long been appreciated histologically and progresses in a highly predictable way on a month-by-month basis in a normally developing brain. It can be assessed accurately and noninvasively by MRI[1]. While advanced imaging techniques such as diffusion tensor imaging can detect changes that parallel brain myelination, stages of myelination are most consistently and easily judged using relative T1 and T2 intensity where T1 and T2 shortening (T1 hyperintense, T2 hypointense signal) indicate appropriate myelination of a brain structure[2].

Normal myelination: Expected pattern of T1 and T2 intensity *for the patient's age at the time of imaging (including corrections for prematurity)*.

- e.g., in a term infant, "normal myelination" would indicate expected T1/T2 shortening of the posterior limb of internal capsule myelination and dorsal brainstem as well as the ventrolateral thalamus and posterior putamen.
- e.g., in a 3 year old, "normal myelination" would indicate a myelination pattern approximating that of an adult.

Conversely, the stage of myelination for a patient less than 2 years of age can be summarized by the approximate age based on the pattern of myelination observed on T1 and T2 imaging. This estimate is requested in the CDE under "myelination," but for patients with a myelination pattern approximating an adult, "mature" may be indicated instead of a specific age estimate. Below is a table of normal myelination milestones on T1-weighted and T2-weighted images:

Ages in which Myelination Appears

Anatomic Region	T1-Weighted Images	T2-Weighted Images
Superior cerebellar peduncle	28 gestational weeks	37 gestational weeks
Median longitudinal fasciculus	25 gestational weeks	29 gestational weeks
Medial lemnisci	27 gestational weeks	30 gestational weeks
Lateral lemnisci	26 gestational weeks	27 gestational weeks
Middle cerebellar peduncle	Birth	Birth to 2 months
Cerebral white matter	Birth to 4 months	3–5 months
Posterior limb internal capsule		
Anterior portion	First months	4–7 months
Posterior portion	36 gestational weeks	40 gestational weeks
Anterior limb internal capsule	2–3 months	7–11 months
Genu corpus callosum	4–6 months	5–8 months
Splenium corpus callosum	3–4 months	4–6 months
Occipital white matter		
Deep	3–5 months	9–14 months
Subcortical	4–7 months	11–15 months
Midfrontal white matter		
Deep	3–6 months	11–16 months
Subcortical	7–11 months	14–18 months
Anterior frontal white matter		
Deep	5–8 months	12–18 months
Subcortical	10–15 months	24–30 months
Centrum semiovale	2–4 months	7–11 months

*Modified from: Barkovich, A.J. and Mukherjee, P. Normal Development of the Neonatal and Infant Brain, Skull, and Spine. In: Barkovich, A.J. and Raybaud, C. Pediatric Neuroimaging, 5th ed. Wolters Kluwer: Philadelphia, PA, 2012.

Delayed myelination: Pattern of myelination which is less advanced than expected for age. In some instances, this delayed myelination may be transient (e.g., profound malnutrition, hypothyroidism such as that associated with *MCT8* mutations). However, once it is clear that the myelination pattern is not merely delayed

but static/arrested, the term **hypomyelination** is applied (e.g., a hypomyelinating leukodystrophy such as Pelizeus-Merzbacher). Defined in this manner, a patient with lagging myelination on an MRI obtained in infancy would be defined as "delayed" rather than "hypomyelination" until follow-up imaging establishes that the findings are static or there is genetic testing that confirms a specific diagnosis known to be static/hypomyelinating. For an individual imaged at an age where myelination would be expected to be mature (e.g., 5 years) an immature pattern may be presumptively classified as hypomyelination.

Demyelination and dysmyelination: Refers to conditions in which there is evidence of a normal brain myelination program but the myelination is not stable. As a result, signal abnormality arises in a background of normal (or previously normal) brain myelination. These conditions of unstable brain myelination are distinguished from delayed myelination in two ways: the signal intensity of the affected white matter is often higher than unmyelinated white matter and the areas of abnormal signal cannot be explained by a simple arrest of the normal myelination sequence (e.g., internal capsule and subcortical white matter appear normally myelinated but the intervening periventricular white matter is not). It should be emphasized that these two terms are used in a confusing manner in the historical and present-day literature. Van der Knaap has proposed that *demyelination* be restricted to disorders that lead to destruction of the myelin membrane itself or the oligodendroglia whereas *dysmyelination* be applied to conditions where the failure to maintain a normal myelination pattern is secondary to a metabolic/neurodegenerative insult that is more extrinsic[3]. By this definition, metachromatic leukodystrophy and multiple sclerosis would both be considered demyelination disorders, but a neurodegenerative condition (e.g., neuronal ceroid lipofuscinosis) would be considered dysmyelination. These definitions can be difficult to apply, especially in cases where a specific diagnosis is uncertain or the underlying histopathology is unknown for a particular disorder. Therefore, it is anticipated that these two terms may require analysis together for any given research project although they are provisionally separated here. These two terms should not be applied to *any* white matter signal abnormality: they should be reserved for pervasive patterns of white matter disease (i.e., symmetric, homogeneous).

White matter tracts: Macroscopic nerve fascicles of sufficient size to be visible on standard (T1,T2) or advanced (diffusion tensor) MR imaging, at least when abnormal. White matter tracts are conspicuously myelinated in a normal participant at maturity, and abnormal signal in white matter tracts can assist with classifying metabolic disorders, including mitochondrial disorders.

- **Corpus callosum**: Side to side commissural fiber linking the cerebral hemispheres. Recognized subdivisions include: the **rostrum, genu, body, isthmus, and splenium** (anterior to posterior).
- **Anterior commissure**: White matter tract linking cerebral hemispheres at the anterior aspect of the third ventricle (lamina terminalis), just below the level of the basal ganglia.
- **Fornix**: Paired C-shaped white matter tracts extending from hippocampus (crus) within the temporal lobe to the lateral ventricle atria where they are suspended from the corpus callosum by the septum pellucidum (body). Anteriorly, the fornices curve inferiorly (pillars, columns) along the margin of the third ventricle before extending through the hypothalamus and terminating at the mammillary bodies located at the posterior aspect of the suprasellar cistern.
- **Hippocampal commissure**: Transverse fibers connecting fibria of fornices along the undersurface of the splenium.
- **Central tegmental tract**: Dorsal midbrain and pontine white matter fibers connecting the red nucleus and inferior olivary nucleus as well as brainstem sensory nuclei and the thalamus. Signal abnormality and particularly restricted diffusion may be seen in Leigh syndrome[4] among other conditions (metabolic and nonmetabolic). Note that isolated central tegmental tract high T2 and DWI signal may be also normally seen as a developmental process in children in the first few years of life.
- **Corticospinal tracts**: Longitudinal white matter tract beginning in primary motor cortex and descending through the ipsilateral internal capsule, cerebral peduncle, and brainstem before decussation just inferior to the medullary pyramids, prominent ventral/anterior bulges of the medulla.
- **Miscellaneous other longitudinal tracts**: **dorsal column, medullary pyramids, medial lemniscus, trigeminal tracts, superior/inferior cerebellar peduncles** are abnormal in leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL, mitochondrial aspartate tRNA synthetase)[5].

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If any longitudinal tract is identified as abnormal (including ones not explicitly listed above), it should be indicated in the free-text box for “white matter tracts” along with the type of signal abnormality (e.g., central tegmental tract, T2/DWI signal hyperintensity).

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