INTRODUCTION

Epilepsy is the fourth most common neurologic disorder in all ages. It is associated with derangement of brain function and predisposition to recurring seizures. It is divided into focal and generalized seizures according to underlying cause ***(Fisher et al., 2014).***

Childhood epilepsy is very common and known to affect cognition and behavior with long lasting adverse effects on lifespan achievement even if the seizures remit and treatment is stopped ***(Lin et al., 2012).*** Partial seizures occur when electrical activity implicates a limited area of the brain. Generalized seizures affect the whole brain ***(Gallagher et al., 2016).***

Precise identification of the epileptogenic zone is critical in presurgical planning as third of patients with focal epilepsy are refractory to medical treatment. Normal structural magnetic resonance imaging (MRI) scans are seen in up to 20-30% of epilepsy patients ***(Duncan, 2010).*** The presurgical assessment of focal epilepsy is particularly challenging in children, the misdiagnosis could lead to epilepsy surgery failures, with a significant impact on neuropsychological development during pediatric age thus a careful presurgical evaluation, may allow tailored resections leading to good seizure control ***(Freri et al., 2017).***

The importance of white matter (WM) in the pathogenesis of focal epilepsy has shown promising growing evidence in recent research work, with WM pathology is being a hallmark feature of the disease process and has been subjected to greater investigations ***(Deleo et al., 2018)*.** WM abnormalities might be a direct consequence of seizures (either acute functional or chronic structural changes). It is also possible that the WM abnormalities represent an underlying predisposing factor in the development of focal epilepsy ***(Concha et al., 2007)*.**

The diagnostic imaging modalities of focal seizures include routine EEG, long-term video-EEG monitoring, and neuroimaging such as MRI, single photon emission computed tomography (SPECT), positron emission tomography (PET), functional MRI (F-MRI) or magneto-encephalography (MEG) tests ***(Rosenow and Luders, 2015).***

MRI plays a pivotal role in the evaluation of patients with focal epilepsy. One of the possible reasons for undetected epileptic lesions in standard outpatient MRI include an unsatisfactory clinical data from the referring neurologists and non-optimized standard head protocols for the spectrum of epileptogenic lesions ***(Bien et al., 2013)*.** MRI epilepsy specific protocol should exist to meet the requirements of both neurologists and radiologists to easily define the spectrum of lesions found in patients with epilepsy. MRI has improved our

ability to non-invasively detect diverse spectrum of epileptogenic lesions, and thus has altered the management of patients particularly with pharmaco-resistant epilepsy to a multidisciplinary approach including radiological and electroclinical correlation ***(Bernasconi and Bernasconi, 2014).*** Fluid attenuated inversion recovery (FLAIR), T2 WI, T1WI, 3-D T1WI and a hemo/calc-sensitive T2*/SWI; are the sequences sufficient to cover the spectrum of diverse epileptogenic lesions. In some patients, examinations including contrast-enhanced T1WI might be necessary to further characterize the underlying lesion, however, this must be an individualized decision by the responsible radiologist beyond the routine protocol ***(Wellmer et al., 2013).***

Diffusion-weighted MRI and its analytical extensions, particularly diffusion tensor imaging (DTI) have been the most widely used technique to image the WM ***(Concha, 2014).*** DTI is a significant innovation that identifies areas of altered diffusivity and may reveal areas of disruption of the microstructural environment. DTI metrics such as fractional anisotropy (FA) reflect underlying neuronal density, fiber orientation, dispersion and degree of myelination ***(Zhang et al., 2012).*** DTI metrics also allows the assessment of the amplitude and the directionality of diffusion within tissue thus, reflecting WM integrity status. Reduced diffusion anisotropy at the expense of increased radial diffusivity is interpreted as reduced axonal density and alteration of myelin architecture ***(Garbelli et al., 2012).***

3-D reconstruction of large WM tracts utilizing the information of directionality of diffusion in each voxel is another application of DTI useful to evaluate direct brain connectivity ***(Judkins et al., 2011).*** The correlation of DTI metrics obtained from WM structures with the age of seizure onset and duration of epilepsy may reflect the burden of disease on the white matter in both the hemisphere with seizure focus as well as the contra-lateral hemisphere as these abnormal changes may extend to the other hemisphere in focal epilepsy patients ***(Diehl et al., 2010).***

WM long association fibers are typically involved in diverse cognitive tasks such as executive functions, attention, memory, learning and emotion processing. The superior longitudinal fasciculus, cingulum and temporal lobe WM are correlated with working memory performance ***(Winston et al., 2013).*** The uncinate, arcuate and inferior fronto-occipital fascicles, as well as temporal cingulum are correlated to verbal memory ***(Diehl et al., 2008; McDonald et al., 2014).*** The alterations of diffusion parameters in the temporal lobe WM is associated with delayed and immediate memory performances ***(Riley et al., 2010).*** WM diffusion characteristics may thus provide valuable information to predict which patients are at higher risk of developing cognitive deficits, such that they can be prevented through more effective treatments and eventually halt further cognitive deterioration ***(Chiang et al., 2016).*** Poor post-surgical outcome can also be a factor associated with progressive WM abnormalities secondary to ongoing seizures ***(Deleo et al., 2018).***

AIM OF THE WORK

The aim of this study is to evaluate the utility and the diagnostic accuracy of applying diffusion tensor imaging and fiber tractography in studying the white matter microstructural alterations in children with focal epilepsy.

Chapter 1

ANATOMY OF WHITE MATTER TRACTS

White matter tracts were classified into four groups including tracts in the brainstem, projection, association, and commissural tracts in the cerebral hemispheres ***(Jellison et al., 2004).***

Tracts in the brainstem

Five major white matter tracts were reconstructed in the brainstem including the superior, middle, and inferior cerebellar peduncles, the corticospinal tract and the medial lemniscus ***(Buttner et al., 2009).***

Projection fibers

I. ***The corona radiata***

The corona radiata is not a specific tract, however it is a name given to the broad fan shaped array of white matter fibers that appear to converge inferiorly into the internal capsule. The fibers of the corona radiata interconnect the cerebral cortex with the thalamus and the brain stem in both directions ***(Mori et al., 2005).***

On imaging, the corona radiata appears as a nearly uniform region of myelinated white matter. On DTI the fibers of the

corona radiata appear as an open fan of blue fibers that course between the corpus callosum and the cingulum bundle medially and the superior longitudinal fasciculus laterally (Fig. 1) ***(Naidich et al., 2013).***

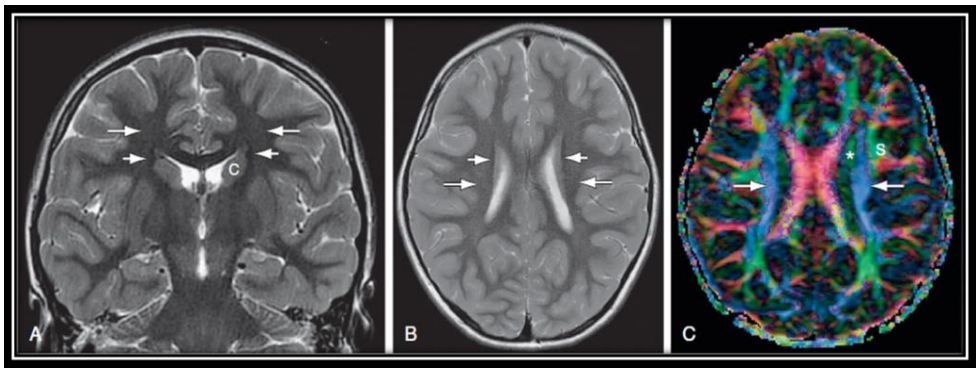

Figure (1): Corona radiata, (long white arrows) are shown in coronal (A) and axial (B) T2W MR images (C) axial DTI color map. The fibers (white arrows) of the coronal radiata are identifiable medial to the fibers of the SLF (s) (***Quoted from Naidich et al., 2013).***

II. The internal capsule

Most connections between the cerebral cortex and subcortical structures travel through the internal capsule. Afferent fibers in the internal capsule largely arise from the thalamus and radiate to all parts of the cortex as the thalamocortical radiation ***(Naidich et al., 2013).***

Efferent fibers in the internal capsule arise from cortical neurons and extend widely to specific portions of the thalamus, brain stem and spinal cord. The fiber tracts passing through the

corona radiata and the internal capsule to interconnect the cortex and the thalamus are designated the thalamic peduncles ***(Naidich et al., 2013).***

It is made up of five parts, **the anterior limb** lies between the head of the caudate nucleus and both the putamen and globus palidus, **genu** lies between the anterior and posterior limbs, **posterior limb** lies between the thalamus and both the putamen and globus palidus, **sublentiform part** lies below the putamen and globus palidus and **retrolentiform part** lies behind the putamen and globus palidus (Fig. 2) ***(Buttner et al., 2009).***

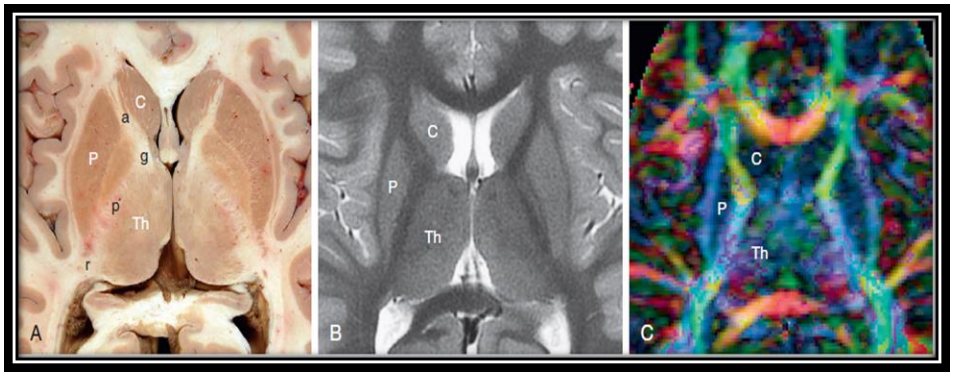

Figure (2): Internal capsule different parts. (A) Axial anatomic section and (B) T2WI MRI: The anterior limb (a), genu (g), posterior limb (p) and retrolenticular (r) portion of the internal capsule course between the caudate nucleus (C) and thalamus (Th) medially. P, putamen. (C) DTI color map the blue coloration in the posterior limb indicates that the fibers are oriented vertically, while the fibers in the anterior limb, genu and retrolenticular portion of the internal capsule course obliquely ***(Quoted from Naidich et al., 2013).***

III. Corticospinal and corticobulbar tracts

The corticospinal and corticobulbar tracts are major efferent projection fibers that connect motor cortex to the brain stem and spinal cord. Corticospinal fibers converge into the corona radiate and continue through the posterior limb of the internal capsule to the cerebral peduncle. Corticobulbar fibers converge into the corona radiata and continue through the genu of the internal capsule to the cerebral peduncle ***(Jellison et al., 2004).***

The corticospinal tract is the predominant pathway for the relay of impulses for voluntary skilled movements of the upper extremities, trunk, and lower extremities.

On imaging the corticospinal tract is readily displayed in the posterior limb of the internal capsule as a focal hypointensity on TI W images and a focal hyperintensity on T2 WI, FLAIR and DWI. DTI displays the corticospinal tract as a blue colored very compact fiber bundle passing craniocaudally from the region of the precentral gyrus through the posterior limb of the internal capsule and the midportion of the cerebral peduncle into the ventral brain stem (Fig. 3) ***(Naidich et al., 2013).***

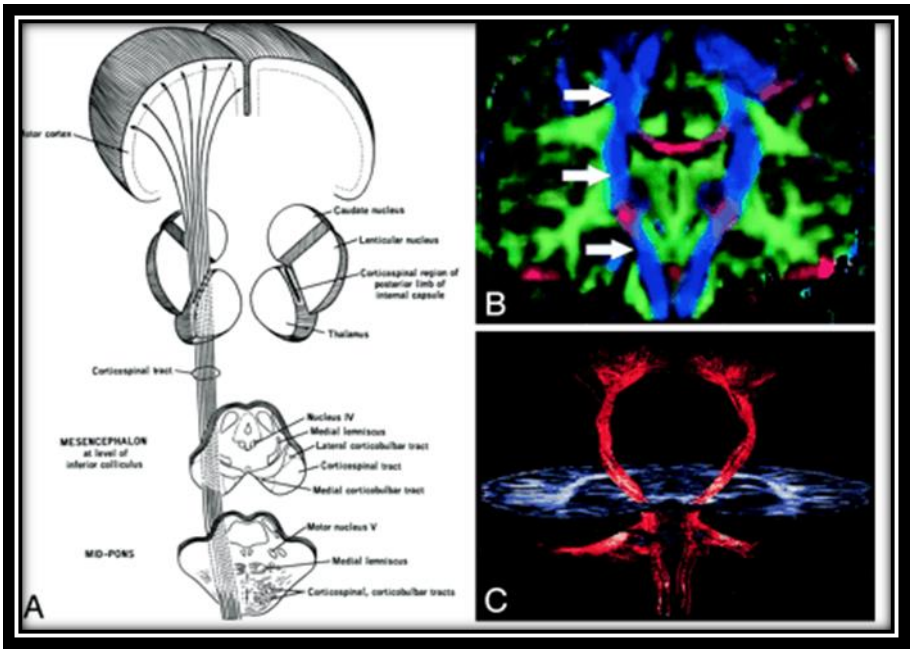

Figure (3): (A) Illustration showing the corticospinal fibers originating along the motor cortex converge through the corona radiata and posterior limb of the internal capsule on their way to the lateral funiculus of the spinal cord. (B) Coronal DTI map: Corticospinal fibers (arrows) are identified in blue. The fibers take on a more violet hue as they turn medially to enter the cerebral peduncles, then become blue again as they descend through the brain stem. C, represents a virtual tractogram ***(Quoted from; Jellison et. al., 2004***).

Association fibers

Association fibers connect different areas of the same hemisphere together and are classified into short and long association fibers. Short association fibers course within the cortex or in the most superficial layer of the adjacent white matter to interconnect adjacent gyri of the same or adjacent lobes, they resemble the letter U and are designated as the subcortical U-fibers. The long association fibers connect different lobes

together, forming prominent fiber bundles that interconnect different lobes within the same hemisphere over long distances; some fiber bundles contain mixed short and long association fibers (Fig. 4) ***(Naidich et al., 2013).***

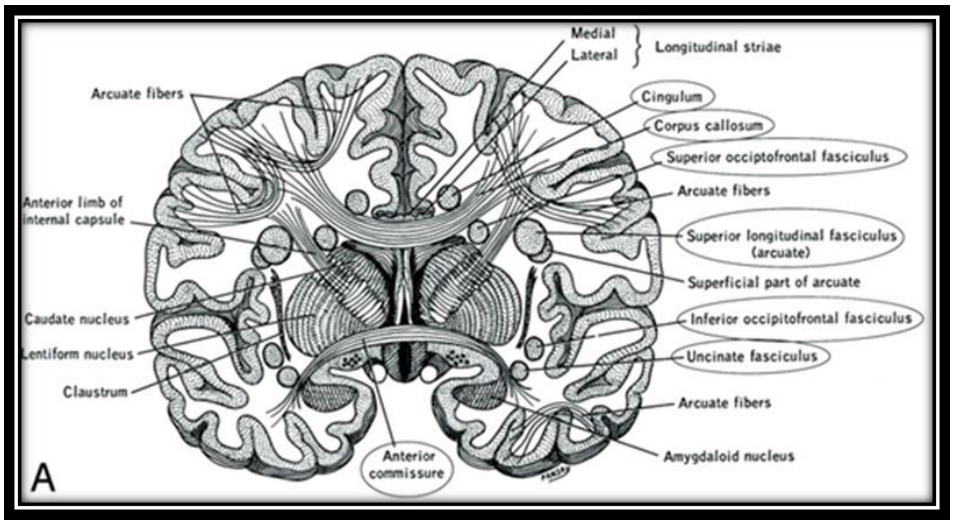

Figure (4): Illustration shows the anatomic relationships of several WM fiber tracts in the coronal plane. The superior longitudinal fasciculus sweeps along the superior margin of the claustrum in a great arc. The inferior occipitofrontal fasciculus lies along the inferolateral edge of the claustrum. The corpus callosum is seen "sandwiched" between the cingulum superomedially and the superior occipitofrontal fasciculus inferolaterally ***(Quoted from Jellison et al., 2004).***

They include the superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), superior fronto-occipital fasciculus (SFOF), inferior fronto-occipital fasciculus (IFOF), and uncinate fasciculus (UNC) as well as three major association fibers connecting the limbic system, namely the cingulum (CG), fornix (FX), and stria terminalis (ST) ***(Naidich et al., 2013).***

I. SLF

This tract is one of the long association fibers related to the parietal lobe, it is located at the supero-lateral side of the putamen. It forms a large arc, sending branches into the frontal, parietal, occipital, and temporal lobes ***(Naidich et al., 2013).***

Several subcomponents of the SLF have been described. The temporal component of SLF is known to be the arcuate fasciculus which consists of direct and indirect components. The direct component interconnects the temporal cortex and the prefrontal cortex together ***(Zhang et al., 2010).***

On DTI the SLF appears as an intense green triangle in color coded FA maps coronal images. Fiber tractography (FT) reveals a "spiked crescent" with a smooth concave inferior border that curves around the sylvian fissure and a highly serrate convex superior border that arches through the frontal, parietal and temporal lobes (Fig. 5 and 6) ***(Naidich et al., 2013).***

The SLF is responsible for the initiation of motor activity and the higher order control of body centered action and involved in working memory. The arcuate fasciculus provides for the ability to recognize language and respond to it appropriately through connecting Broca's and Wernicke's area in the brain. The arcuate fasiculus provides for the ability to recognize language and respond to it appropriately ***(Naidich et al., 2013).***

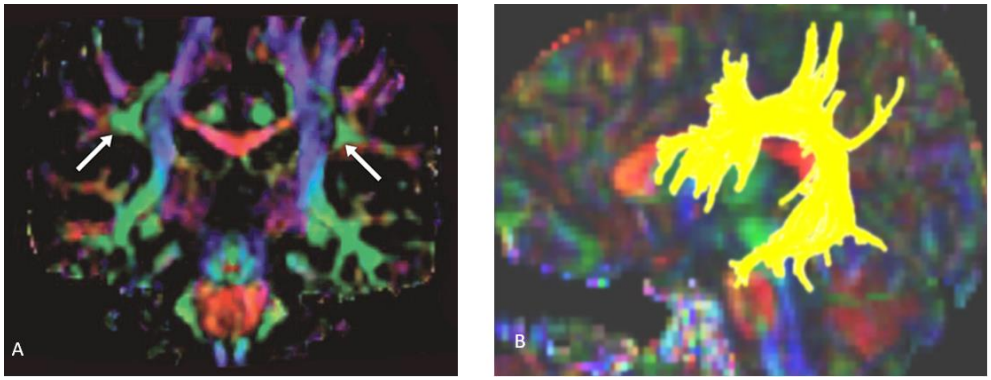

Figure (5): DTI map Coronal view and corresponding tractography of SLF of a 7-year-old normal control female subject included in our study showing: Normal appearance of the superior longitudinal fasciculus (arrows) defined at this level as triangular green shapes lateral to the blue descending fibers of the corticospinal tract, on tractography the SLF appears as a "spiked crescent".

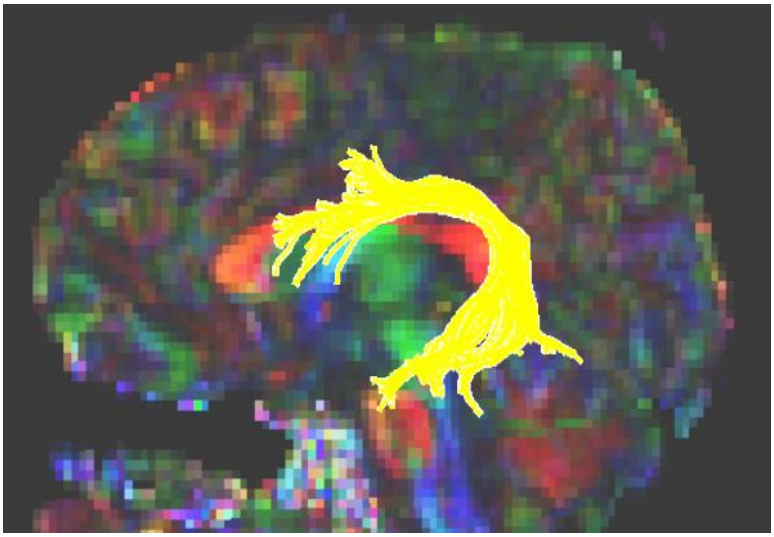

Figure (6): Virtual construction of the arcuate fasciculus of a 7-year-old normal control female subject included in our study.

II. IFOF

This is one of the long association fiber tracts, it connects the occipital and frontal lobes passing through the temporal lobe

but is far inferior in position compared with the superior fronto-occipital fasiculus ***(Jellison et al., 2004).***

On sagittal DTI, the IFOF has a symmetric "bow tie" shape with a characteristic central narrowing along the floor of the extreme capsule (Fig. 7).

This fasciculus may be a major component of the ventral subcortical "what" pathway important for object recognition and discrimination ***(Naidich et al., 2013).***

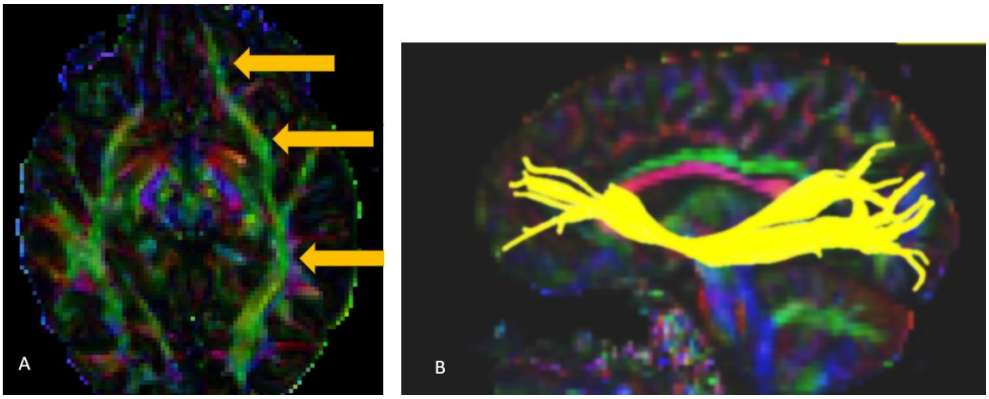

Figure (7): IFOF (yellow arrows) on axial directional map and FT of a 10-year-old normal control male subject included in our study. The IFOF lies in a roughly axial plane and is easily identified in green; tractography shows its connection with frontal and occipital lobes at the level of the midbrain.

III. ILF

This is a long association fiber tract situated contiguous to the lateral aspect of the inferior horn of the lateral ventricle, in the temporo-occipital lobe. It extends from the occipital to the temporal pole ***(Tamraz and Comair, 2005).***

On sagittal DTI, the ILF lies in approximately the same position as the IFOF but it lies slightly more inferior and lateral, and it has a more uniform ribbon shape. On axial DTI images, the ILF lies more lateral in position and shows a greater lateral convexity than the IFOF (Fig. 8) ***(Naidich et al., 2013).***

The ILF plays a role in the ventral visual stream for object recognition, discrimination and memory. Face recognition probably depends on the ILF as well ***(Naidich et al., 2013).***

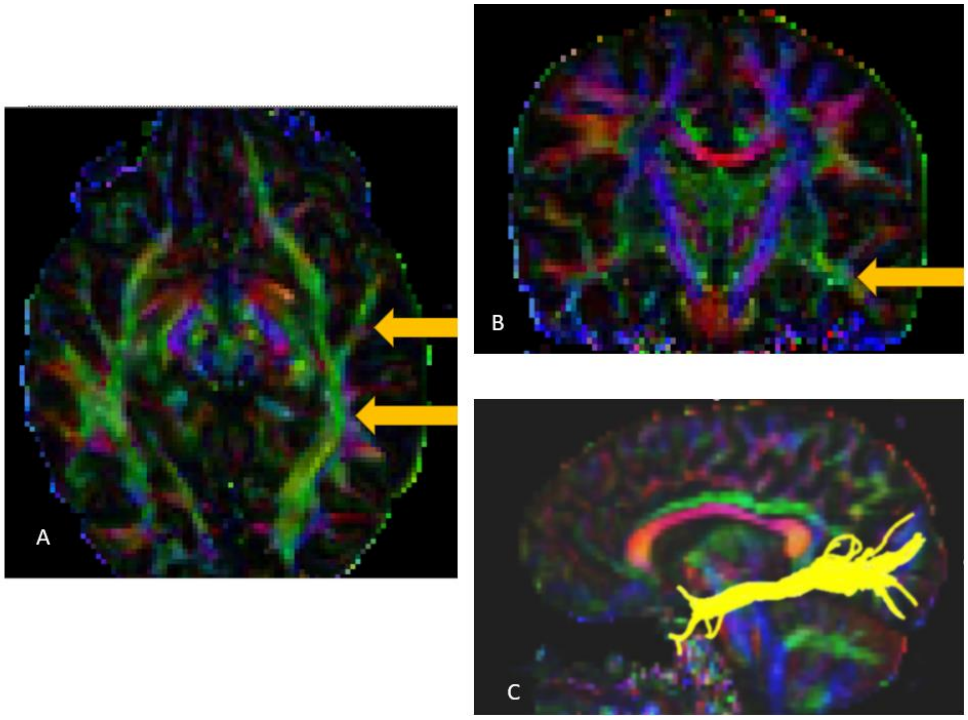

Figure (8): axial (a) coronal (b) and sagittal (c) Color coded directional maps of a 7-year-old normal control female subject included in our study, showing the ILF trajectory as uniform ribbon shape on FT with more lateral convexity that IFOF on axial image (arrow).