

MRI Investigation of the Intracranial Visual System: Standard Approaches and Recent Advances

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INTRODUCTION

The intracranial visual system is made by several grey and white matter structures dedicated to transmission and elaboration of visual signals. Growing evidences have underlined how visual system resulted involved in several brain diseases; for this reason, more and more advanced investigative techniques are required for a reliable detection of its alterations. In this context, MRI represents a very useful set of tools for non-invasive evaluation of intracranial visual system damages. In this chapter a description of advanced MRI approaches suitable for clinical settings as well as some future perspectives are discussed. We started from a brief description of visual system anatomy, in order to provide a didactic basis to understand subsequent topics. Then a synthetic and complete view of clinical implications of visual system involvement is provided. Finally, we described available MRI approaches for investigating each visual system component.

Embryology and Anatomy of the Intracranial Visual System

At the IV week of gestation, it is possible to clearly distinguish the optic peduncle, which connects the optic vesicle (the future eye) with diencephalon [1]. From the optic peduncle both optic nerve (ON) and optic tract (OT) originate. The development of intracranial visual components starts at the V week of gestation; in that period the division of prosencephalon into telencephalon and diencephalon occurs [2]. Regarding thalamic growth, it takes place quickly, assuming its final configuration including several grey matter nuclei among which the lateral geniculate nuclei (LGNs) [2]. Optic radiations (ORs) originate from LGNs approximately at the VI month, allowing the direct connection between these nuclei and occipital visual cortex under development [3]. Cellular differentiation and functional organization is still present before birth; however, their maturation will continue also after birth, by means of endogenous and exogenous stimulation mechanisms, as well as due to the contribution of glial component [4]. It is known that right and left ONs partially decussate at the level of optic chiasm. By this way, homolateral OT will be made by the homolateral ON temporal portion and the contralateral ON nasal one. Along the entire course of intracranial visual system, each structure takes anatomical relationship with several brain ones, which potentially might affect visual system components, e.g. neoplastic mass effects [5]. The direct connection between LGNs and visual cortex is allowed by means of ORs. These two eloquent white matter fiber bundles are conventionally anatomically divided into three different pathways [6]: the anterior one, also called Meyer's loop, which shows the highest variability between subjects [7], the middle and the posterior ones. Unlike the Meyer's loop, the other two portions of ORs did not shown significant variability [8]. The high variability of Meyer's loop is challenging when performing dedicated evaluations in pathological contexts, such as neurosurgery; for this reason advanced sensitive techniques are required for reconstructing this ORs portion. Along their course, ORs take anatomical relationship with several white matter bundles, such as uncinate fasciculus, fronto-occipital fasciculus, superior longitudinal fasciculus and inferior longitudinal fasciculus; moreover, they take relationship also with several brain structures, such as limbic and insular lobes as well as lateral ventricles [9-12]. The most part of ORs' fibers reaches primary and secondary visual areas, as well as an amount is connected with extra-striate cortex [13,14]. The entire visual system shows a high functional complexity, which allows to preserve the retinotopic map as well as the four-quadrants division of the visual field [15,16]. After reaching occipital cortex, visual information is elaborated through the involvement of both striate and extra-striate cortices; moreover, from these areas start connections with parietal and temporal ones in order to perform localization (where) and recognition (what) of the observed object [17].

Clinical aspects of the Intracranial Visual System

Intracranial visual system alterations can be followed by several signs and symptoms; their proper recognition can help in localizing where damage occurs. This is true, for example, for

visual field deficits (Figure 1). An overview of the most common diseases affecting intracranial visual system as well as possible benefits provided by MRI examinations is discussed below.

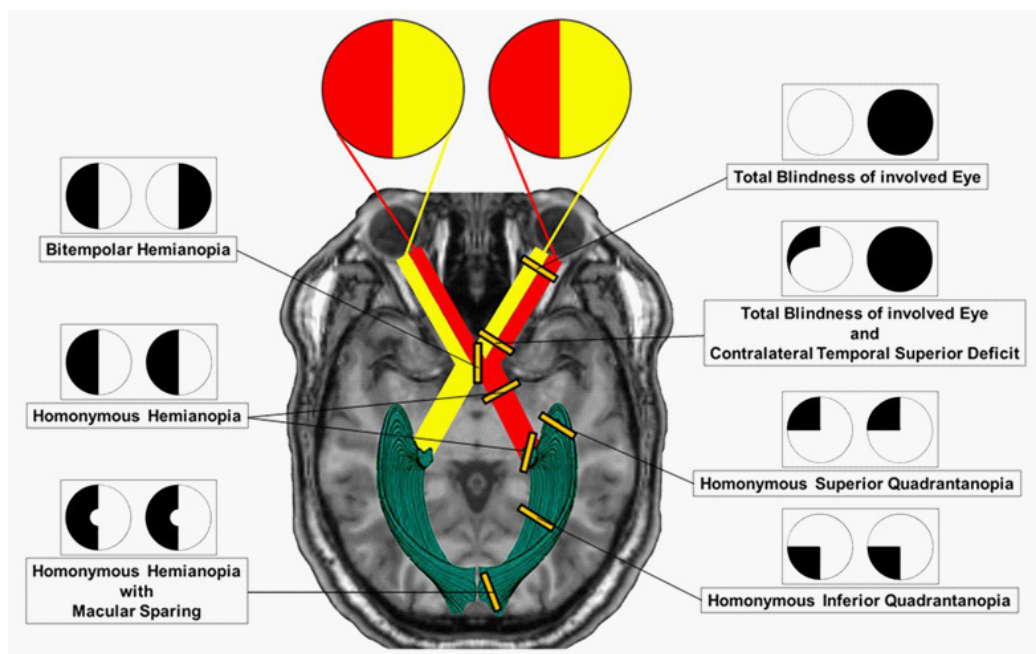


Figure 1: Visual field deficits caused by damages at different levels of the intracranial visual system.

Optic nerve in clinical context

ON can be affected by several pathological conditions; inflammatory, ischemic, traumatic and neoplastic represent the most common ones. The terms optic neuritis and neuromyelitis include a wide spectrum of demyelinating inflammatory disorders commonly characterized by visual acuity loss followed by retrobulbar pain [18]. It is known that these conditions can be associated to an increased risk of development of multiple sclerosis (about 40% of patients) [19]. In this context, the use of MRI approaches have been found to have an impact both for the diagnosis as well as for the prognosis of these patients, providing also useful markers for the evaluation of disease's progression [20]. Moreover, MRI was found to help in distinguishing optic neuritis both in cases of neuromyelitis spectrum disorders and multiple sclerosis [21]. Regarding ON ischemia, diagnosis and follow-up are performed by means of clinical evaluations as well as other imaging techniques (e.g. optic coherence tomography) [22]. In this context, MRI evaluation is required in cases of uncertain findings or to complete diagnostic procedure [23]. A similar kind of use can be required in cases of traumatic injuries [18]. On the other side, MRI is widely required for neoplastic ON disorders; in these cases, it is helpful for the diagnosis of neoplasm (glioma versus meningioma or other uncommon tumors), as well as for their pre-surgical evaluation [18].

Optic chiasm in clinical context

Optic chiasm and OTs can be potentially affected by primitive ON disease, such as inflammatory one, as well as by the same pathological conditions above described. Moving beyond these kinds of alterations, it is known that these structures can often be affected by compressive neoplastic effects coming from surrounding structures [5]. Moreover, both optic chiasm and OTs may undergo to toxic effects of several substances (e.g. ethambutol) as well as radiation-induced alterations [24]. It is worthy to note that, apart from ischemic vascular damages, optic chiasm perfusion deficits can be found both in cases of migraine with or without auras [25]. A more complete summary of chiasmal disorders is reported in Table 1. It should be taken into account that all these pathological conditions may determine more complex visual field alterations, according to the specific chiasmal portion involved, thus requiring often require a specific neuro-ophthalmologic consultation for a reliable interpretation as well as deeper investigations [26].

Table 1: List of main diseases affecting optic chiasm.

Disease	Etiology
Inflammatory	Multiple sclerosis,sarcoidosis,vasculitis, others
Infective	Meningitis, abscess, viruses, others
Neoplastic	Gliomas, meningiomas, metastases, others
Traumatic	Facial and/or skull fractures
Vascular	Artero-venous malformations, ischemic

In all conditions reported, MRI scans, including T1w, T2w, FLAIR, DWI and perfusion acquisitions, are considered fundamental investigations in order to classify chiasmal and retrochiasmal damages as well as to set up the therapeutical protocol.

Optic Radiations in Clinical context

The simplified clinical view of ORs associates their damages to complete homonymous hemianopia or to incomplete ones [27]. Actually, clinical aspects of ORs involvement are more complex. Indeed ORs lesions are associated with abnormalities of pursuit movements as well as conjugate gaze spasticity [28]; they can result also involved in cases of amblyopia [29,30]. Moreover, a recent study reported an LGN involvement in a case of neuro-Behçet syndrome [31], which could reflect its damage also to ORs. The latter study, as well as other reports [32], suggests the importance of neuroimaging evaluations of LGNs and ORs also in systemic inflammatory diseases. Several studies have provided evidences regarding ORs involvement also in glaucomatous patients; indeed, significant ORs alterations of diffusion MRI parameters have been largely demonstrated [33-35], as well as alterations of the metabolic profile of visual pathways, evaluated through spectroscopy approach [36]. Visual pathways involvement was explained through a retrochiasmal trans-neuronal degeneration induced by the primitive retinal one; furthermore, post-mortem studies have demonstrated that a significant glial loss occurs [37,38].

The very strict relationship between glaucoma and visual pathways alterations have induced several authors to suggest a complementary glaucoma classification based on MRI-based evaluations of such alterations, in order to perform a systematic analysis of the entire visual system involvement in this disease [39,40].

ORs resulted significantly involved in multiple sclerosis, both for a primitive localization of plaques on ORs white matter, as well as due to a secondary degeneration induced by optic neuritis [41]. Studies performed in patients affected by optic neuritis have demonstrated similar degenerative ORs MRI findings, suggesting the adoption of such investigative approaches also in this pathological context [42]. In addition, anterograde degenerative processes, starting from primitive ORs involvement and reaching both LGNs and retinas, without the concomitance of optic neuritis, have been also demonstrated [43-46].

Several evidences of ORs involvement in Alzheimer's disease, through a neurodegenerative process directed to these white matter bundles, were also reported; these alterations have been proposed to explain the visual symptomatology found in these patients [47-49]. Moreover, Bien and colleagues have reported that also ORs could be involved for the genesis of visual auras in epileptic patients [50]. Furthermore, significant changes of ORs MRI markers of alterations have been found in schizophrenic patients [51-55].

ORs are often included in neurosurgical and radiosurgical pre-surgical planning, both for brain neoplasms as well as in case of other diseases; their reconstructions, through the combined use of different MRI approaches, is considered fundamental to preserve post-operative visual function as well as to optimize maximal resection margins [56-65].

MRI investigations of the Intracranial Visual System

MRI investigation of Optic Nerve, Optic Chiasm and Optic Tract

MRI investigation of pre-chiasmatic and chiasmatic structures provides fundamental information both in physiological and pathological contexts. Data obtained are different according to the acquisition specifics chosen. It is worthy to note that it is preferable to study these structures by means of MRI scans dedicated to orbital structures instead of entire brain acquisitions. The detailed discussion of all technical aspects of these MRI investigations is beyond the main scope of this chapter; for this reason, a brief description is provided.

T1-weighted, T2-weighted Turbo Spin Echo, fluid-attenuation inversion recovery (FLAIR) as well T1 inversion recovery (STIR) sequences offer very good morphological evaluations of ONs, especially by means of coronal acquisitions [66]. These approaches are commonly used by radiologists to evaluate the presence of inflammation, such as in cases of optic neuritis or neuromyelitis [67], as well as for studying intracranial expansive processes, with the use of contrast agents if needed. These techniques are largely employed for the non-invasive investigation of possible causes of intracranial hypertension in patients showing papilledema

[68,69]. Further improvement for investigating these structures can be reached by diffusion weighted imaging (DWI) based acquisitions. This approach is able to provide useful qualitative information for evaluating different conditions affecting ONs and chiasmatic structures, such as neoplasms, infections, ischemic damages as well as autoimmune processes [70]. Moreover, DWI allows also quantitative evaluations of these alterations, by measuring different parameters, such as apparent diffusion coefficient (ADC), in order to better identify lesion type (e.g. ischemic or inflammatory) and to provide information about its severity [71-73]. Qualitative and quantitative diffusion-based evaluations are considered useful for clinicians, both for diagnosis and follow-up of these pathological conditions.

One common requirement, for all these approaches, is the need of fat signal suppression for a good delineation of ONs with respect to intraorbital fat as well as the suppression of the surrounding CSF [74]. These two components are known to interfere with a reliable detection of ONs as well as of chiasmatic structures. This is particularly challenging if using DWI-based acquisition. Indeed, diffusion signal is known to be affected by fat chemical shift as well as from CSF water; moreover, it suffers from susceptibility artifacts provided by air/tissue interface (Figure 2) [66,70,74,75]. Despite these hurdles, diffusion-based approaches are largely used in clinical settings. The main limitation regards the use of tractographic techniques dedicated for these structures. Indeed, independently from the algorithm used, to date, reliable tractographic reconstructions of ONs and optic chiasm are still missing. This is due to previously described signal interferences as well as to the fibers crossing at chiasmatic level (Figure 2).

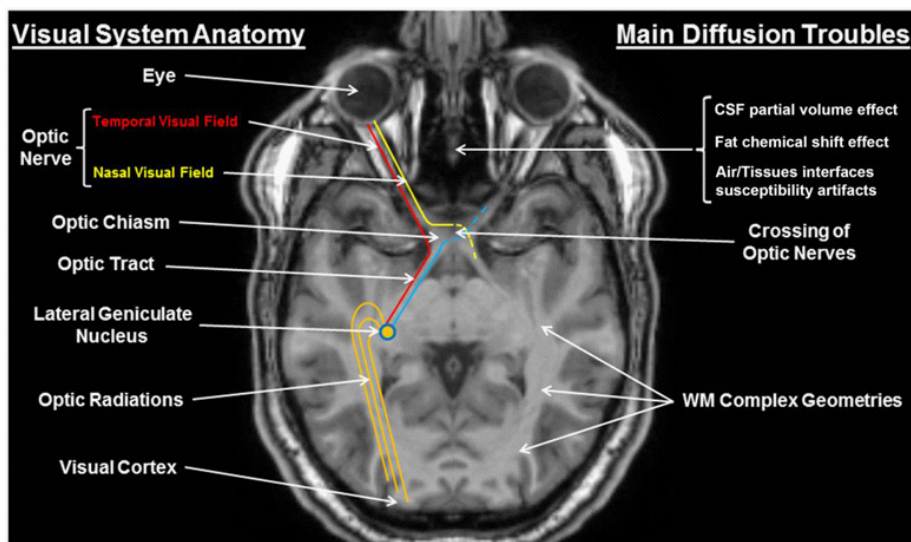


Figure 2: Possible troubles affecting diffusion MRI. Issues shown in the left side of the figure may determine alterations of diffusion signal. In the right side of the figure a schematic representation of the main intracranial visual system components, whose detection may be potentially affected by diffusion troubles, are shown.

Several acquisitions are under study to test their reliability for the evaluation of diffusion signal, e.g. [76,77]; nevertheless, to date, diffusion EPI scan remains the most used in clinical settings. Interesting future perspectives will be the development of more robust diffusion-based post-processing techniques for ONs and optic chiasm as well as of MRI investigation techniques for eye's structures. Indeed, only few studies were conducted in order to assess MRI benefits for investigating the eye [78,79]; this research field is still far from clinical settings, although it might provide further useful evaluations in the next future.

MRI investigation of Optic Radiations

Optic radiations (ORs) are probably the visual structures that have been subject to the larger improvement of investigation techniques based on MRI. Several advanced MRI approaches are suitable for studying ORs; in particular, these white matter bundles can be investigated through morphological approaches, such as Voxel Based Morphometry (VBM), as well as DWI-based ones. VBM is a structural approach providing useful information about grey and white matter changes in the brain [80,81]. By means of this technique, both concentration and volumetric evaluations within each voxel can be performed, respectively adopting unmodulated and modulated approaches; the latter, through a calculation allowing the preservation of local volumes, was found to be less sensitive if compared to the unmodulated one [82]. In particular, Radua and colleagues [82] have underlined how the modulation step causes an increment of variance with a raising of severity if proceeding from low resolution voxels to high resolution ones; the final result is a lack of detection of true altered voxels. The use of unmodulated VBM can provide a more reliable evaluation of ORs both at macroscopic and mesoscopic levels. Moreover, the use of DARTEL tool [83], which is a more advanced registration method able to minimize inter-subject structural variations when warping different structures, can further improve VBM output. In practice, VBM framework is provided by SPM8 package (www.fil.ion.ucl.ac.uk/spm); a possible way for analyzing ORs might be done by following the below described steps. First of all, ORs tractographic reconstructions are performed. Then, these reconstructions are used to obtain a white matter mask for each subject recruited. Finally, all these masks are normalized to MNI coordinates and averaged together in order to obtain a mean OR mask which can be used to detect significant activation clusters obtained by VBM analysis. By this way, it is possible to focus VBM analysis on ORs maintaining the robustness of a whole brain approach. All these steps are shown in Figure 3.

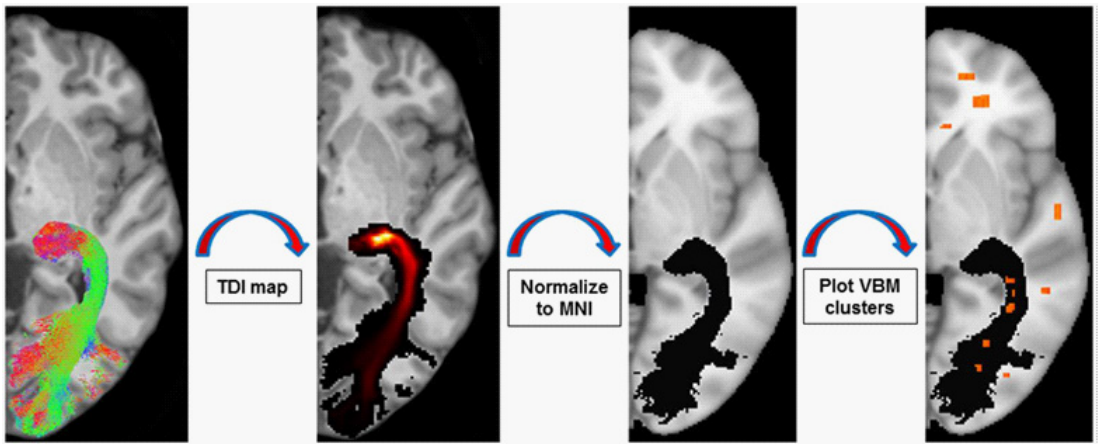


Figure 3: Exemplificative pipeline of VBM evaluation of ORs, obtained from a whole brain VBM analysis. Each ORs tractographic reconstruction, performed in a given group of subjects, is converted into a track-density imaging (TDI) map [84]. All maps are then normalized to MNI coordinates and a global mean map is obtained. Finally, VBM significant clusters are overlapped to the mean white matter map of all subjects and significant clusters, correspondent to ORs voxels, are analyzed.

From a microscopic point of view, of course diffusion-based analysis offers non-invasive reliable tools for structural evaluation of white matter bundles. Starting from a DWI dataset, it is possible to perform qualitative as well as quantitative evaluations of ORs in human brain. Even if a complete description of all technical aspects of diffusion modelling is beyond the scope of this chapter, some key points are discussed below in order to better understand the improvement of ORs evaluation based on DWI scans. It is known that possible outputs of diffusion-based analyses strictly depend on diffusion modelling technique used. Among these, of course diffusion tensor imaging (DTI) is the most known and used approach. DTI output, within each voxel, is represented by the diffusion tensor [85,86], a geometric object that can be considered as a mean of N directional contributes, according to the anisotropic diffusivity of water molecules. By computing tensorial information, a possible application is the qualitative reconstruction of white matter pathways through tractography [87]. Fiber tracking can be performed by deterministic or probabilistic approaches. Although the latter provides more information if compared to deterministic one, and it is a preferable choice for tracking, it should be carefully used due to the possible onset of false positive output.

DTI has been considered a powerful technique for years. Nevertheless, several limitations have been demonstrated to affect DTI data, first of all voxels showing fibers with complex geometries. Indeed, more than 90% of white matter voxels is characterized by fibers with multiple orientations, such as crossing fibers [88]. Since DTI provides a mean of all diffusivity orientations for each voxel, it is not able to resolve complex geometries and consequently it is inadequate to provide reliable evaluation of white matter. For these reasons, several other

techniques have been developed in order to improve white matter analyses; the major ones are High Angular Resolution Diffusion-weighted Imaging (HARDI) and the HARDI-modified Q-ball Imaging (QBI) and Constrained Spherical Deconvolution (CSD) (Figure 4) [89-91]. In particular, CSD has been found to be a very powerful technique if compared to the others for resolving voxels with complex fibers configurations. This technique overcomes the poor angular resolution of QBI [92] as well as it provides very good results with respect of a further modelling technique called Diffusion Spectrum Imaging (DSI) [93], which resulted to be hardly applicable in clinical contexts due to very long acquisition scan time required.

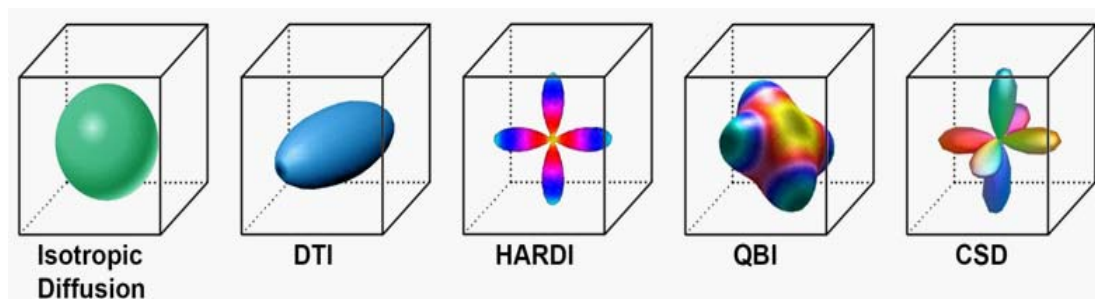


Figure 4: Main diffusion modelling algorithms and their correspondent intra-voxel geometrical representation. A reference isotropic voxel is shown as well.

In practice, when reconstructing ORs by means of DWI-based approaches, several troubles could affect diffusion output (Figure 2). In particular, it is possible to not reliably detect the Meyer's Loop, due to its anatomical course, which could require a high angular resolution of diffusion signal modelling. Moreover, several other white matter bundles might affect ORs tractographic reconstructions, such as uncinate fasciculus, fronto-occipital fasciculus, superior longitudinal fasciculus and inferior longitudinal fasciculus [10,12]. For all these reasons, ORs tractographic reconstruction might be different, according to the sensitivity of the algorithm used (Figure 5). If a reliable ORs detection is important in physiological contexts, in order to perform connectivity analysis as well as other ones, it becomes fundamental for patients examination. Indeed, it is known that ORs are often evaluated in patients with temporo-parieto-occipital brain neoplasms [94] as well as before the temporal lobe resection of epileptic patients [63]. Moreover, it is worth to notice that, in presence of brain neoplasm, DTI-based tractographic reconstruction might also be limited by neoplasia's effects. Indeed, white matter bundles can result dislocated, disrupted and/or infiltrated by neoplasm [95]. Tensorial models are not able to distinguish these conditions, which are all characterized by FA decrease; consequently, DTI can provide only partial tractographic reconstructions. In all these conditions, a detailed pre-surgical planning is required to define ORs anatomical relationships with other structures as well as to preserve or reduce post-surgical visual deficits. For all reasons above described, the use of CSD may help to achieve these goals and consequently to improve patients quality of life.

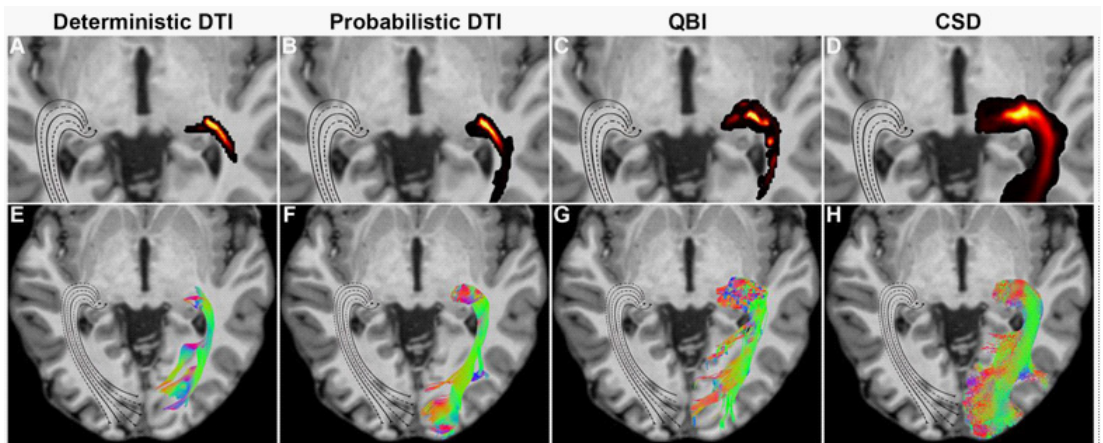


Figure 5: Left ORs tractographic reconstructions obtained by using different diffusion algorithms. A,B,C,D are focused only on Meyer's loop detection; moving from DTI model to CSD one, it is possible to notice an increase of sensitivity in representing this ORs portion. For a better visualization purpose, each Meyer's loop is shown by means of its white matter map. E,F,G,H show the entire ORs tractographic reconstruction. Also in this case, CSD-based one results more complete and reliable, if compared to other models. On the right side of all figures the schematic representation of ORs is shown.

DTI limitations can also affect quantitative evaluation of ORs; indeed, streamlines reconstructed are often evaluated by means of diffusion parameters such as FA and MD, in order to evaluate alterations of axonal structural integrity in several pathological conditions (through a tract-based approach) [96,97]. Since this evaluation represents the mean parameters evaluation of voxels selected by means of ORs streamlines, a partial tractographic reconstruction, like DTI-based one, might affect this kind of evaluation. Indeed, DTI is less sensitive when considering voxels with low FA values [88]; for this reason, it might not provide plausible and reliable information regarding ORs damages. On the other side, the quantitative analysis based on more advanced tractographic outputs, like CSD-based ones, might provide a more detailed analysis of white matter diffusion parameters changes, since it allows to include in calculation voxels showing heterogeneous signals (e.g. complex fibers geometries in physiological condition or edema effect in case of brain neoplasm). Although the quantitative analysis based on these parameters provides useful information regarding the loss of white matter integrity, it still remains less sensitive for a deeper intra-voxel investigation.

Several approaches able to separately analyze intra-axonal from extra- axonal water components, through multi-compartmental models, already exist [98,99]. Since, to date, these approaches need high technical requirements, interesting future perspective will be to make them suitable for application in clinical contexts. These evaluations might provide further information allowing to separately analyze distinct cells types as well as to better characterize microscopic profile of a given damage.

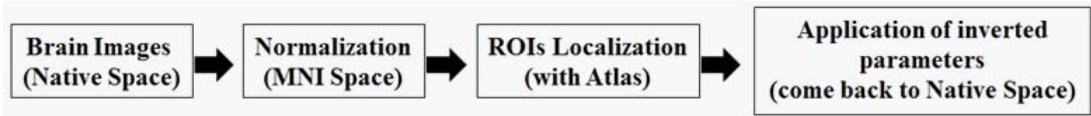
MRI investigation of visual system grey matter

In this paragraph, principal investigation techniques for lateral geniculate nucleus (LGN) and visual cortices are discussed. The first issue to consider when analyzing grey matter structures regards their proper localization. Accurate LGN detection is very important both for morphological evaluations than for performing tractography of ORs. LGN localization and segmentation is challenging due to its small dimension. To achieve this goal, both manual and automated approaches are achievable. The first one requires the involvement of an expert neuroradiologist as well as of high resolution images. LGN can be detected in T1-weighted ones. The automated approach requires the use of brain atlas templates. The most common ones are shown in Table 2.

Table 2: Main brain atlas templates available for the automated LGN localization.

Brain Atlas	Reference
Tailarach Atlas	[100]
MNI Structural Atlas	[101]
Oxford Thalamic Connectivity Atlas	[102]
Juelich Histological Atlas	[103]

In order to localize a specific brain structure, the following pipeline is required:



The rationale of performing analyses in native space is related to the possibility to reduce brain sizes biases as well as other misalignment issues [104]. Although also other approaches have been recently proposed to detect LGN [105], the right choice between automated and manual approach is still challenging. If it is true that manual segmentation might introduce possible operator-related biases for the correct segmentation of brain structures, on the other side also the use of automated approaches is error-prone. Indeed, ROIs might be not perfectly correspondent to anatomical structures; for this reason, supervision and eventually manual correction of an expert operator is always required.

Regarding visual cortices, the same observations can be done. In this case, an automated approach is preferable in order to better distinguish each visual area (V1, V2, V3, V4 and V5). In addition to the abovementioned atlases, cortical parcellation provided by FreeSurfer image analysis suite [106] (<http://surfer.nmr.mgh.harvard.edu/>) is able to perform very accurate detection of visual areas with particular attention in distinguishing sulci and gyri. Furthermore, it provides visual cortices subdivision based on Destrieux Atlas (striate and extrastriate cortices). On the contrary, other atlases allow to separately consider each visual area, from V1 to V5; in particular, if Juelich atlas is used, it is possible to detect them by means of a probabilistic

approach that can be set with different percentages of probability, thus regulating degree of accurateness.

It is worth to notice that a preferable approach for visual areas localization is by means of fMRI [107-109]. By this way, it is possible to perform a subject-specific study avoiding also inter- subjects variability related issues suffered by brain templates. On the other side, since the use of fMRI approach requires specific tasks as well as an increment of acquisition time, this kind of analysis is not always applicable in clinical settings.

Grey matter investigation includes both structural and functional techniques. As previously mentioned, fMRI is able not only to detect visual areas, but also to evaluate eventual damages as well as the preservation of a specific retinotopic map; it is widely used, alone or in combination with other approaches, in several pathological conditions [109-113].

Advanced morphological evaluations include VBM analysis, previously described, as well as evaluation of cortical thickness, through Voxel Based Cortical Thickness (VBCT) approach. This technique is available in Freesurfer image analysis suite [106] and it allows detection of cortical abnormalities between different groups. A fine cortical parcellation is required to clearly distinguish brain sulci and gyri; it is included in Freesurfer pipeline. Once obtained cortical thickness, statistical analyses can be performed. The combined use of VBCT and VBM has been found to be very useful in evaluating grey matter changes; indeed, these two approaches offer structural evaluations from different point of views, thus providing a more robust macroscopic as well as mesoscopic detection of cortical alterations [114].

From a microscopic point of view, grey matter can be investigated by means of diffusion-based approaches. Indeed, by this way, several information regarding grey matter microstructure can be obtained [115]. To achieve this goal, advanced acquisition's specifics are required [116]. Although some papers have been dedicated to this topic, they should be still considered an interesting future perspective more than an already suitable application for clinical contexts.

CONCLUSION

In this chapter, the main MRI investigation techniques for the study of intracranial visual system have been discussed. Moreover, the description of advanced MRI approaches as well as future perspectives has been also provided. MRI of intracranial visual system provides a set of very useful evaluation tools both for diagnosis and follow-up of diseases affecting visual system components. Among these, diffusion-based approaches are promising tools for evaluating the loss of intracranial visual system integrity; their further improvements might provide, in the next future, more detailed microscopic information, which could better delineate degenerative features occurring during onset and progression of brain diseases.

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